

**Cardiovascular Responses to Isometric Resistance Training
in Individuals with Hypertension,
to aid in Blood Pressure Management.**

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BHSc, BSc (Hons1), University of New England, 2017

A thesis submitted for the degree of Doctor of Philosophy

to the

School of Science and Technology

University of New England

Armidale NSW Australia

December 2017

Statement of Original Authorship

I certify that the substance of this thesis has not already been submitted for any degree and is not currently being submitted for any other degree or qualification.

I certify that any help received in preparing this thesis and all sources used have been acknowledged in this thesis.

Signature

A black rectangular box redacting the signature of the author.

Date: 29 November 2017

Acknowledgements

First and foremost, I need to acknowledge and thank my extremely understanding partner Anthony Bennett for his unending love, support and encouragement throughout the entire journey of my PhD. I would never have considered undertaking a PhD if he had not encouraged me and convinced me that I could do it in the first place. There have been many early mornings and late nights at university when I was conducting my research and had deadlines to meet, where he has cooked me breakfast before I left in the morning, and had dinner on the table when I got home to make sure that I ate. He has made sure that everything was taken care of at home so that I could focus on my studies and achieve this amazing goal. Every time I wanted to go to a conference to promote my research he always encouraged me and helped me budget how we were going to afford to go. He came with me to every conference to support me, helped me hang up every poster, and constantly told me how proud he was of what I was achieving. This has been an amazing journey and I am so glad that we have shared it together.

Most importantly thank you to all my supervisors who have guided me throughout my PhD, you are an amazing team and I feel blessed to have been part of that team. Thank you, Professor Neil Smart, for initially talking me into doing honours and my PhD, I had never met you but after talking to you on the phone for about 30 minutes you convinced me that anything was possible. You were always available whenever I needed to discuss anything with you, even if it was a quick email or text at night or over the weekend. You constantly listened to my ideas, even when at times you looked at me as if they were a bit crazy, but you could see the merit of what I was endeavouring to achieve and helped me find a way to make it work. Thank you for believing in me and pushing me to have the confidence to go to conferences, especially the ACRM symposium which was an amazing experience.

Thank you Associate Professor Gudrun Dieberg, you were an inspiration to me during my undergraduate degree, and have been a wonderful mentor throughout my honours and PhD. I always thought that I was pedantic, but have now learnt to take that to a whole new level, your constructive criticism and proof reading of all my work has made me a much better writer. Over the years you have always steered me back on track if I started to wander off it, and have always prompted me to look at things from different aspects to make sure that I have the whole picture, which I fully appreciate. Your

wonderful caring nature has made it possible for me to feel that I could come to you whenever I needed to discuss anything affecting my PhD, and I have always walked away feeling stronger and more confident.

Thank you, Professor Jim McFarlane, for your knowledge and insight over the years, and your can-do attitude. You provided some excellent input into my research protocols and always looked at things from a pragmatic aspect which helped me to fine tune my research. I am forever grateful for your support and guidance in helping me to increase my depth of knowledge of the statistical analyses required for my PhD.

I would also like to acknowledge the support provided by the Australian Commonwealth Government in funding my research project through an RTP scholarship (formerly - Australian Postgraduate Scholarship) throughout my candidature, which contributed to the success of this research. Thank you also to the Keith and Dorothy Mackay Postgraduate Travelling Scholarship which aided in me attending my first international conference, the ACRM annual conference in Dallas, Texas, USA.

An overwhelming thank you to Craig Lawlor and Michael Price for helping me with all of the technical issues that occurred throughout my research. The technical knowledge and experience that you both have shared with me, which helped me design my research was phenomenal. Especially to Craig who came up with the lightbox concept of how to blind the participants while providing them with visual feedback to ensure that they were working at the correct intensity. Thank you both for helping me every time that I needed help to set up equipment, and for calibrating it all for me to ensure the accuracy of my data collection.

Thank you to all of my wonderful family and friends for all of your love, support, encouragement and helping me to maintain my sanity over the past three and a half years. Importantly I need to thank my mother Flo and my stepfather Mel for answering the phone every time I called when I was driving home from university, even when it was late at night, to help me stay awake on the drive home, and listen to me vent. Thank you to my children Christopher and Kayla, and my brother Steven, for providing me with respite whenever I needed to get away and not think about my PhD for a couple of days. To my uncle Leigh, who has constantly told me how proud he is of me, and how proud my dad would be, and for being there when I needed you the most, I will be forever in your debt. To my friends

Annette, Kelly, and Shanisse for always answering the phone when I needed to talk to someone, and for being there when I needed you; and to Peter and everyone in the Armidale Division of St John Ambulance for all of your patience and understanding.

Thank you also to my fellow PhD students and colleagues, who are too numerous to name individually, for all your stimulating conversations, morning teas and lunches. Particularly to Liza and Dane; we have shared our journey throughout our honours year, graduated honours together, and shared our ups and downs of PhD life, and I treasure your friendship. Also Nicole Hess for your collaboration, insightful conversations, coffee breaks and friendship.

Thank you to Jodie, Suresh, Dougal, Aimee and Tony who helped as research assistants by supervising participants when I needed extra hands. Also for keeping my research going whenever I was sick or unable to be at the lab with participants. Your conversations, feedback and brain storming were always constructive and helpful.

Lastly, and importantly, thank you to all the wonderful people who participated in my research, this would not be possible without you. I have met some very incredible people throughout this journey and had some very interesting conversations with you all. Thank you.

Preface

This thesis is by publication. The thesis is composed of an abstract summarising the publications, and an introduction which is a literature review detailing the relevance and necessity of the research conducted during my candidature. The main body is composed of five manuscripts which have either been published, or are submitted and under review at a journal. The author's contribution and statement of originality are provided for each publication. The concluding chapter links the manuscripts, addressing the safety and efficacy of the research, and discusses future research direction. All work cited in each chapter is referenced at the end of the relevant chapter.



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(http://www.austlii.edu.au/au/legis/cth/consol_act/ca1968133/s200ab.html)

The chapters that have been published are available from:

Chapter 2:

Inder, J., Carlson, D., Dieberg, G., McFarlane, J., Hess, N., & Smart, N. (2015). Isometric exercise training for blood pressure management: a systematic review and meta-analysis to optimize benefit. *Hypertension Research*, 39(2), 88-94. doi: 10.1038/hr.2015.111

Chapter 3:

Carlson, D., Inder, J., Palanisamy, S., McFarlane, J., Dieberg, G., & Smart, N. (2016). The efficacy of isometric resistance training utilizing handgrip exercise for blood pressure management. *Medicine*, 95(52), e5791. doi: 10.1097/md.0000000000005791

Chapter 5:

Carlson, D., McFarlane, J., Dieberg, G., & Smart, N. (2017). Rate Pressure Product Responses During An Acute Session Of Isometric Resistance Training: A Randomized Trial. *Journal Of Hypertension And Cardiology*, 2(3), 1-11. doi: 10.14302/issn.2329-9487.jhc-17-1428

No Proof of publication could be located for the following chapters:

Chapter 4:

“A randomized controlled trial on the effects of isometric handgrip exercise, followed by detraining, on 24-h ambulatory blood pressure.”

Chapter 6:

“Blood pressure measurements in research – suitability of sphygmomanometer, beat-to-beat and ambulatory blood pressure measurements”

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List of Abbreviations

ABP	Ambulatory Blood Pressure
ABPM	Ambulatory Blood Pressure Monitoring
ABS	Australian Bureau of Statistics
ACE	Angiotensin Converting Enzyme
ACEI	Angiotensin Converting Enzyme Inhibitor
ADA	American Diabetes Association
AHA	American Heart Association
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AOBP	Automated Office Blood Pressure
ARB	Angiotensin Receptor Blocker
BP	Blood Pressure
BPM	Beats per Minute
CCB	Calcium Channel Blocker
CHEP	Canadian Hypertension Education Program
CI	Confidence Interval
CKD	Chronic Kidney Disease
Cl ⁻	Chlorine
CO	Cardiac Output
CV	Cardiovascular
CVD	Cardiovascular Disease
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic Blood Pressure
DF	Degrees of Freedom

DHPCCB	Dihydropyridine Calcium Channel Blocker
ECG	Electrocardiograph
EMG	Electromyography
ESC	European Society of Cardiology
ESH	European Society of Hypertension
FMD	Flow-Mediated Dilation
HBPM	Home Blood Pressure Monitoring
HBPRCA	High Blood Pressure Research Council of Australia
HCO ³	Bicarbonate
HR	Heart Rate
HRV	Heart Rate Variability
IHG	Isometric Handgrip
IRT	Isometric Resistance Training
ISH	International Society of Hypertension
ISHIB	International Society for Hypertension in Blacks
JNC	Joint National Committee
JNC7	7 th Joint National Committee
JNC8	8 th Joint National Committee
K ⁺	Potassium
KDIGO	Kidney Disease Improving Global Outcome
LBNP	Lower Body Negative Pressure
LOCF	Last Outcome Carried Forward
MANOVA	Multivariate Analysis of Variance
MAP	Mean Arterial Pressure
MD	Mean Difference
MVC	Maximum Voluntary Contraction

Na ⁺	Sodium
NHF	National Heart Foundation of Australia
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Clinical Excellence
OD	Organ Damage
PWV	Pulse Wave Velocity
RF	Risk Factor
RPP	Rate Pressure Product
SA	Sinoatrial
SBP	Systolic Blood Pressure
SD	Standard Deviation
SNS	Sympathetic Nervous System
SV	Stroke Volume
SVR	Systemic Vascular Resistance
TPR	Total Peripheral Resistance
VO ₂	Volume of Oxygen
WHO	World Health Organisation

List of Publications

Original Manuscripts

Carlson, D.J., Dieberg, G., Hess, N.C., Millar, P.J. and Smart, N.A. (2014). Isometric exercise training for blood pressure management: A systematic review and meta-analysis. *Mayo Clinic Proceedings*, 89(3), 327-334. <http://dx.doi.org/10.1016/j.mayocp.2013.10.030>

Inder, J.D., **Carlson, D.J.**, Dieberg, G. McFarlane, J.R. and Smart N.A. (2016). Isometric exercise training for blood pressure management: a systematic review and meta-analysis to optimize benefit. *Hypertension Research*, 39(2), 88-94. doi:10.1038/hr.2015.111

Hess, N.C.L., **Carlson, D.J.**, Inder, J.D., Jesulola, E., McFarlane, J.R. and Smart, N.A. (2016). Clinically meaningful blood pressure reductions with low intensity isometric handgrip exercise. A randomized trial. *Physiological Research*, 65(3), 461-468.

Carlson, D.J., Inder, J., Palanisamy, S.K.A., McFarlane, J.R., Dieberg, D. and Smart, N.A. (2016). The efficacy of isometric resistance training utilizing handgrip exercise for blood pressure management. A randomized trial. *Medicine*, 95(52), e5791, 1-7. <http://dx.doi.org/10.1097/MD.0000000000005791>.

Carlson, D.J., McFarlane, J.R., Dieberg, G. and Smart, N.A. (2017). Rate pressure product responses during an acute session of isometric resistance training: A randomized trial. *Journal of Hypertension and Cardiology*, 2(3), 1-11. doi:10.14302/issn.2329-9487.jhc-17-1428.

Carlson, D.J., Dieberg, G., McFarlane, J.R. and Smart, N.A. A randomized controlled trial on the effects of isometric handgrip exercise, followed by detraining, on 24-h ambulatory blood pressure. Submitted to *Medicine*, 20/9/2017, currently under review.

Carlson, D.J., Dieberg, G., McFarlane, J.R. and Smart, N.A. Blood pressure measurements in research – suitability of sphygmomanometer, beat-to-beat and ambulatory blood pressure measurements. Submitted to *Blood Pressure Monitoring*, 17/10/2017, currently under review.

Conference Presentations

Carlson, D.J., McFarlane, J.R., Dieberg, G. and Smart, N.A. (2015). Isometric handgrip exercise to reduce hypertension for stroke prevention and recovery. *Archives of Physical Medicine and Rehabilitation*, 96(12), p.e25. doi: 10.1016/j.apmr.2015.10.070

Carlson, D.J., Inder, J., McFarlane, J.R., Dieberg, G. and Smart, N.A. (2016). Blood pressure management – isometric handgrip exercise reduces hypertension. *Hypertension*, 67(5), E9

Carlson, D.J., Hess, N.C.L., Inder, J.D., Palanisamy, S.K.A., McFarlane, J.R., Dieberg, G. and Smart, N.A. (2016). Rate pressure product in healthy individuals during an acute bout of isometric handgrip exercise. *Exercise and Sport Science Australia Research to Practice*. Poster 321.

Carlson, D. J., Dieberg, G., McFarlane, J. R. & Smart, N. A. (2017). Isometric handgrip exercise reduces 24hr ambulatory blood pressure. *Circulation*. 136: A17175. Printed online, Retrieved from http://circ.ahajournals.org/content/136/Suppl_1/A17175

Abstract

Background

Hypertension is a major risk factor contributing to cardiovascular disease; including coronary artery disease, stroke and heart failure. The recent U.S. National Health and Nutrition Examination Survey indicates that >50% of cardiovascular deaths in the US occurred in individuals with hypertension. Antihypertensive medications are effective in controlling blood pressure and have minimal side effects; however, only half the people with hypertension reach treatment goals. Current first line treatment for hypertension is non-pharmacological lifestyle modification including healthy eating, smoking cessation and increasing physical activity. Recent research indicates that isometric resistance training may elicit blood pressure reductions greater than those seen with dynamic aerobic and resistance exercise.

Methods

In order to determine our research direction, a meta-analysis was conducted of previous isometric studies. The meta-analysis in chapter 2 was conducted to determine characteristics of patients conducting isometric resistance training (IRT) and the current protocols being utilised. The systematic review conducted for the meta-analysis indicated gaps in the literature pertaining to study sample sizes, with the largest study having 36 participants; and duration, as the majority of studies were for 8 weeks. The meta-analysis also indicated that, although 2 studies utilised a low intensity group, either a sedentary control or no control group was used for all studies.

Based on this, we initially conducted an IRT study using high and sham/low intensity groups for eight weeks to look at the efficacy of IRT in blood pressure management. The primary aim of this study was to address the gap in the literature relating to the use of a sham low intensity group as a working control. Previous studies had predominantly had participants who were either < 35 years or > 60 years, there were a few studies that had participants aged between 45 and 60 years; we recruited participants aged between 35 and 65 to address this gap in the literature.

A second study was conducted with a duration of 12 weeks, the longest published study to date. At the time of conducting my research there were no published IRT studies which had utilised 24 hour ambulatory blood pressure monitoring, so this used to address the gap in the literature. No studies had

determined the detraining effect of IRT so I had participants return 12 weeks after completing the exercise protocol to determine the detraining effect.

Another randomized trial was conducted to determine hypertensive responses, including peak rate pressure product (RPP) during isometric handgrip exercise. Concerns had been raised by cardiologists and other researchers at a conference I was presenting at about the hypertensive effect during IRT. Research indicated that there had been no published research conducted into the hypertensive responses during IRT, so I addressed this gap in the literature.

To determine suitability of blood pressure measuring devices utilized in research, I conducted a comparison of the commonly used devices. Reviewer responses from the journal article in Chapter 2 over the reliability of the Finometer, and the lack of research validating the Finometer incited addressing this gap in the literature.

Results

Our meta-analysis indicated reductions in systolic blood pressure (SBP) of -5.2mmHg , $p<0.01$. Similar results were seen at 30% maximum voluntary contraction (MVC) in the first and second studies with reductions of SBP -7mmHg , $p=0.04$ (8wks) and -7mmHg , $p=0.02$ (12wks). Diastolic blood pressure (DBP) showed significant reductions in the meta-analysis of -3.91mmHg , $p<0.01$. Our 8 and 12 week studies saw similar reductions of DBP at 30% MVC -4mmHg , $p=0.04$ and -5mmHg , $p<0.01$, respectively. As expected, RPP peak values during exercise were significantly higher than baseline in all IRT intensities assessed, all $p\leq 0.01$.

Comparison of blood pressure measurement devices indicated no difference between sphygmomanometer and beat-to-beat SBP (0.23mmHg , $p=0.87$); however, DBP had a difference of 4.82mmHg , $p<0.01$. Ambulatory blood pressure was higher than both sphygmomanometer and beat-to-beat measurements for both SBP and DBP with $p<0.001$ for all measures.

Conclusion

There is a positive linear relationship between blood pressure and IRT intensity, this research indicates that cardiovascular responses during IRT are within safe limits. Isometric resistance training is effective at lowering systolic and diastolic blood pressure, and utilization of a 5% MVC group is suitable as a working control.

Chapter 1: Literature Review

This thesis is by publication and focuses on the effect of isometric resistance training (IRT) on hypertension. Hypertension is a major modifiable risk factor for cardiovascular disease, which is the number one cause of death globally (WHO, 2017). The current first line treatment for hypertension is lifestyle modifications, including exercise. There has been no clear optimal exercise prescription for blood pressure management, and approximately only half of the individuals with hypertension conduct the current recommended exercise prescription (Cornelissen and Smart, 2013; National Center for Health Statistics, 2014). There is an increasing body of evidence on the effectiveness of IRT, indicating that blood pressure reductions are comparable to those seen in aerobic exercise (Millar et al., 2014). This thesis explores and clarifies the efficacy of conducting IRT for blood pressure management.

A literature search was conducted of databases which contained journal articles relating to hypertension and exercise including PubMed, CINAHL, Cochrane and SPORTDiscus. Websites including World Health Organisation, U.S. Centers for Disease Control and Prevention, Australian Bureau of Statistics and the National Heart Foundation of Australia were searched for the most current and up-to-date statistics and data. Search terms included “hypertension”, “blood pressure”, “cardiovascular disease”, “exercise”, “isometric exercise” and “isometric resistance training”.

The literature review explores and discusses:

- 1.1 Hypertension
- 1.2 Isometric resistance training
- 1.3 Blood pressure measurement devices
- 1.4 Summary outlining the research questions

1.1 Hypertension

Hypertension has been defined as resting blood pressure consistently equal to or greater than 140mmHg systolic (SBP) and/or 90mmHg diastolic (DBP) for over 10 years (Chobanian et al., 2003; Head et al., 2012). In November 2017, a review of the high blood pressure clinical practice guideline was released which lowered hypertensive blood pressure measurements to 130mmHg SBP or 80mmHg DBP (Whelton et al., 2017). Hypertension is the major risk factor that contributes to cardiovascular disease; including coronary artery disease, stroke, chronic heart failure, chronic kidney disease and their progression (Mancia et al., 2013; Whelton et al., 2017). Globally,

hypertension is responsible for 45% of cardiovascular deaths due to heart disease and 51% due to stroke (WHO, 2013).

1.1.1 Hypertension Prevalence

Hypertension affects approximately 1.13 billion people globally. In 2015, 24.1% of males and 20.1% of females over 18 years of age had hypertension, these levels are almost identical to those seen yearly since 2007, which was 25.4% and 21.5%, respectively (WHO, 2017a and b; Merai et al., 2016). Prevalence of hypertension has increased in low and middle-income countries, and remained steady or decreased in high income countries since 2000 (Mills et al., 2016). Middle aged groups, between 40-59 years, in low and middle-income countries have the highest burden of hypertension. Compared to low and middle-income countries, there was twice as much hypertension awareness and treatment in high income countries in 2010 (Mills et al., 2016).

In 2011/12, 4.6 million Australians (31.6% of the adult population) had hypertension; more recently in 2015 the World Health Organization (WHO) reported that 18% of males and 12.3% of females over 18 years in Australia had hypertension (ABS, 2014; WHO, 2017c). The recent U.S. National Health and Nutrition Examination Survey (NHANES) indicates that >50% of cardiovascular deaths in the U.S. occurred in individuals with hypertension (Whelton et al., 2017). Most population surveys, such as NHANES, rely on averaging blood pressure measurements at one single visit, which may overestimate hypertensive prevalence compared to measurements taken on two or more visits (Whelton et al., 2017). Hypertension awareness, treatment and control are possibly underestimated by surveys such as the NHANES, due to the definition of control excluding lifestyle modification or nonpharmacological intervention. Prevalence of hypertension increases with age and varies in relation to ethnicity; with control rates in the U.S. lower in individuals ≥ 75 years of age, and those below the poverty line (Whelton et al., 2017). Antihypertensive medications are effective at controlling blood pressure and have minimal side effects; however, there are increasing economic health costs, and only half the people with hypertension reach treatment goals. (CDC, 2016; Cornelissen & Smart, 2013; Nuckols et al., 2011). In 2014, hypertension affected almost 78 million adults in the U.S. According to NHANES during 2007 and 2010, 81.5% of people with hypertension were aware of having it, 74.9% were being treated, but only 52.5% had their hypertension controlled at treatment goals. (Go et al., 2014).

1.1.2 Hypertension Definition and Classification

Until recently, hypertension was classified as blood pressure with systolic pressure ≥ 140 mmHg and /or diastolic pressure ≥ 90 mmHg, generally measured on three separate occasions (Garg et al., 2014). The 7th Report of the Joint National Committee (JNC7) on prevention, detection and evaluation and treatment of high blood pressure classified blood pressure as normal, prehypertension, and Stage 1 or Stage 2 hypertension, as shown in Table 1; this has been the recommended guideline since 2003 (Chobanian et al., 2003).

Table 1: The JNC7 Classification and management of blood pressure for adults

BP Classification	SBP (mmHg)	DBP (mmHg)	Lifestyle modification	Initial drug therapy	
				Without compelling indication*	With compelling indication*
Normal	< 120	And < 80	Encourage	No	Drugs for compelling indications
Prehypertension	120-139	Or 80-89	Yes	antihypertensive drug indicated	Drugs for compelling indications.
Stage 1 Hypertension	140-159	Or 90-99	Yes	Antihypertensive drugs indicated	Other antihypertensive drugs as needed
Stage 2 Hypertension	≥ 160	Or ≥ 100	Yes	Antihypertensive drugs indicated. Two-drug combination for most.	

Adapted from Chobanian et al. (2003) 'The seventh report of the Joint National committee on prevention, detection and evaluation and treatment of high blood pressure. JAMA 289, 2560-2572.

SBP - systolic blood pressure; DBP - diastolic blood pressure

*Compelling indications are high-risk conditions including heart failure, ischaemic heart disease, chronic kidney disease, and stroke.

The Australian position statement by Head et al. (2012) classified hypertension thresholds into 140/90mmHg as Grade 1 mild, 160/100mmHg as Grade 2 moderate, and 180/110mmHg as Grade 3 severe. There has been recent controversy over blood pressure goals; the 8th Joint National Committee (JNC8) has recommended that systolic blood pressure goals for people over 60 years of age should be 150mmHg instead of 140mmHg, and diastolic below 90mmHg (Chobanian, 2017; James et al., 2014). The JNC8 also recommend that blood pressure goals for people younger than 60 years should remain at 140/90 mmHg (James et al., 2014). Blood pressure recommendations by the 2007 European Society of Hypertension / European Society of Cardiology (ESH/ESC) guidelines

are <140/90mmHg for low to moderate risk hypertensives, and <130/80mmHg for high risk hypertensives with diabetes, cerebrovascular, cardiovascular or renal disease (Mancia et al., 2013). The 2016 National Heart Foundation of Australia guidelines for categorising hypertension which also followed the guidelines of the ESH/ESC are listed in Table 2.

Table 2: 2016 National Heart Foundation of Australia and 2013 ESH/ESC Classification of blood pressure levels

Diagnostic Category *	Systolic (mmHg)		Diastolic (mmHg)
Optimal	< 120	and	< 80
Normal	120-129	and/or	80-84
High-Normal	130-139	and/or	85-89
Grade 1 (mild) hypertension	140-159	and/or	90-99
Grade 2 (moderate) hypertension	160-179	and/or	100-109
Grade 3 (severe) hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 140	and	< 90

*When a systolic and diastolic blood pressure levels fall into different categories, the higher diagnostic category and recommended actions apply. Isolated systolic hypertension should be graded 1, 2 or 3 according to systolic BP values in the ranges indicated. National heart foundation of Australia. Guidelines for the diagnosis and management of hypertension in adults – 2016. (2016). Melbourne, National heart foundation of Australia. Retrieved on 24/9/2017 from https://www.heartfoundation.org.au/images/uploads/publications/PRO-167_Hypertension-guideline-2016_WEB.pdf Mancia et al. (2013). ESH/ESC guidelines for the management of arterial hypertension. European heart journal: 34 (28); 2159-2219. doi:10.1093/eurheartj/eh151

Table 3: Current 2017 High Blood Pressure Clinical Practice Guideline. Blood Pressure Categories in Adults

Blood Pressure Category	Systolic Blood Pressure		Diastolic Blood Pressure
Normal	< 120 mmHg	and	< 80 mmHg
Elevated	120 – 129 mmHg	and	< 80 mmHg
Hypertension			
Stage 1	130 – 139 mmHg	or	80 – 89 mmHg
Stage 2	≥ 140 mmHg	or	≥ 90 mmHg

Adapted from Whelton et al., 2017(2017). 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension, 00:e000-e000.

In November 2017, the American College of Cardiology/American Heart Association task force on clinical practice guidelines recommended new categories of blood pressure in adults, which are

outlined in Table 3. Classification of blood pressure status should be based on an average of at least two careful measurements taken on two or more occasions; individuals with systolic blood pressure (SBP) and diastolic blood pressure (DBP) in two different categories should be designated to the higher blood pressure category. (Whelton et al., 2017).

1.1.3. Etiology and Risk Factors

Arterial blood pressure is determined by cardiac output (calculated by multiplying heart rate and stroke volume) and peripheral resistance. Cardiac output is affected by sodium intake, renal function and mineralocorticoids, while peripheral resistance is dependent upon the sympathetic nervous system, humoral factors and local autoregulation (Hamrahian et al., 2017). Neurohumoral activation of the heart or increased blood volume are generally responsible for increasing cardiac output, and increased sympathetic activation or circulating vasoconstrictors such as angiotensin II are responsible for increasing systemic vascular resistance (Klabunde, 2012a).

Primary risk factors for hypertension include age (men > 45 years and women > 65 years of age), race, family history, obesity, physical inactivity, high sodium intake, smoking, alcohol and stress (Mayo Clinic, 2014; Contractor & Gordon, 2009). Insulin resistance, low potassium, low calcium and genetic factors (inherited blood pressure) are also factors which may increase blood pressure (Carretero and Oparil, 2000). Hypertension can be a result of pre-eclampsia/eclampsia, or malignancy; however, is more often essential or secondary. Pre-eclampsia/eclampsia occurs during pregnancy, and malignant hypertension is elevated blood pressure due to papilloedema (Contractor & Gordon, 2009). Papilloedema is swelling of the optic disc due to intracranial pressure from an intracranial mass or lesion. Approximately 95% of people with hypertension have essential hypertension (Carretero and Oparil, 2000). Essential hypertension is often referred to as primary or idiopathic hypertension, and there is generally no known specific cause for the individual's hypertension. Secondary causes of hypertension such as renal disease and aldosteronism are not seen in individuals with essential hypertension. (Carretero and Oparil, 2000).

Secondary hypertension is caused by an underlying condition such as kidney problems, adrenal gland tumours, thyroid problems, medications including birth control pills and decongestants, illegal drugs, and alcoholism (Mayo Clinic, 2014). Increased cardiac output and/or systemic vascular resistance elevates arterial pressure resulting in secondary hypertension (Klabunde, 2012a).

Secondary hypertension occurs in a small percentage of cases, it can often be improved or cured by surgery or medical intervention, and is predominantly renal or endocrine hypertension. According to Klabunde (2012a) the main causes of secondary hypertension are renal artery stenosis, renal artery disease, primary hyperaldosteronism, stress, sleep apnoea, hyper- or hypothyroidism, high levels of circulating catecholamines, and narrowing of the aorta. Renal hypertension generally results from an imbalance of sodium and fluids leading to volume expansion or an alteration in renal secretion resulting in a change in arteriolar tone (Contractor & Gordon, 2009). Secondary hypertension often appears suddenly causing higher blood pressure than essential hypertension; if the underlying condition is controlled, blood pressure will generally reduce to near-normal levels (Bullock, Hales, & Babey, 2013). Approximately 10% of hypertensive patients have secondary hypertension, which can lead to cardiovascular complications, or complications of other underlying conditions if undiagnosed and untreated (Puar et al., 2016).

1.1.4 Pathophysiology of Hypertension

The pathophysiology of hypertension is unclear but it appears to involve vascular smooth muscle hypertrophy, vessel wall inflammation and loss of vessel integrity (Bullock et al., 2013). The four main theories of hypertension pathophysiology relate to excess sympathetic activity, an overactive renin-angiotensin-aldosterone system, altered neurohormonal control, or a metabolic disturbance (Bullock et al., 2013). Hypertension is likely due to an interaction between the sympathetic nervous system (SNS), the renin-angiotensin system, sodium, circulating blood volume and hormones, specifically catecholamines and mineralocorticoid release (Beevers, Lip & O'Brien, 2001). The SNS and the renin-angiotensin-aldosterone system both control vascular tone (the extent of vasoconstriction or vasodilation at any given moment), and blood volume (Beevers et al., 2001). Communications with the alpha-adrenergic receptors on vascular smooth muscle from the adrenal medulla to maintain tissue perfusion, and cardiac output regulation by the heart are both controlled by the SNS. Angiotensin II is a potent vasoconstrictor which contributes to aldosterone release; increased levels of aldosterone promote sodium and water retention, thus increasing blood volume and blood pressure. Aldosterone also promotes myocardial hypertrophy which can contribute to heart failure due to the aggravated burden on the heart from enduring hypertension (Bullock et al., 2013).

In the central nervous system angiotensin II enhances sympathetic outflow which alters the hormones released affecting blood volume, sodium levels, vascular, renal and cardiac regulation, and modulation of inflammatory processes (Young and Davisson, 2015). Angiotensin II increases sodium transport causing sodium retention, this reduces urine volume and water loss, resulting in an increase in blood volume. Increased blood volume increases arterial pressure, renal perfusion and glomerular filtration rate (Klabunde, 2012a). Circulating angiotensin II is generally too large to cross the blood brain barrier; however, hypertension disrupts the blood brain barrier enabling angiotensin II to access parts of the brain which it normally cannot affect (Young and Davisson, 2015). The pathogenesis of hypertension also involves angiotensin II-induced reactive oxygen species production in the brain, which activates voltage-gated calcium channels; this increases neuronal firing, and subsequently promotes hypertension. Alterations in cellular redox status and calcium levels due to prolonged periods of cell stress induced by angiotensin II, lead to an accumulation of unfolded/misfolded endoplasmic reticulum proteins (Young and Davisson, 2015). Endoplasmic reticulum stress from angiotensin II induced hypertension can lead to cardiac damage, endothelial dysfunction and aortic stiffening; triggering isolated systolic hypertension which is associated with increased risk of cardiovascular morbidity and mortality. Recent research indicates that brain inflammation may also contribute to hypertensive actions of angiotensin II (Young and Davisson, 2015).

Neurohormonal compounds including atrial natriuretic peptide, brain natriuretic peptide and adrenomedullin, promote sodium excretion (natriuresis) and mediate vasodilation in response to changes in blood pressure (Bullock et al., 2013). Metabolic syndrome refers to insulin resistance in people without diabetes that have high blood pressure, which is lowered with diabetic medication (Bullock et al., 2013). 'Increased sympathetic tone, elevated angiotensin II activity, reduced endothelial cell-mediated vasodilation and altered renal function' (Bullock et al., 2013) are all associated with a loss of insulin sensitivity.

Hypertension damages the endothelium and often leads to atherosclerosis, particularly in the presence of hyperlipidaemia. Atherosclerosis is a fatty porridge-like substance that fills and hardens arteries, resulting in plaques that can be complicated by thrombi, and is responsible for ischaemic heart disease (Bullock et al., 2013). Lipoproteins are transported around the body via the blood to wherever they are needed. Low-density lipoproteins have low levels of protein, high levels of fat

and cholesterol, and are often referred to as bad cholesterol. Low-density lipoproteins are less likely to be taken up by cells, often resulting in high levels 'found freely circulating in the bloodstream' (Bullock et al., 2013), thus providing the building blocks for atherosclerotic plaques.

Atherosclerotic plaques develop deep to the endothelial cells inside the blood vessel wall, damaging the endothelial cells. Endothelial cells 'maintain the local vasodilation-vasoconstriction balance of the blood vessels' (Bullock et al., 2013) and control formation and dissolution of thrombi which occur as a result of wear and tear on blood vessels. Vasoconstriction is influenced by the brain; vasomotor neurones release noradrenaline which acts on alpha-adrenergic receptors; local oxygen availability, and endothelin-1 (released from the endothelial cells) (Bullock et al., 2013). The vasodilatory compounds of nitric oxide, adenosine and prostaglandins are released by endothelial cells to increase local blood flow when required (Bullock et al., 2013). Nitric oxide release from endothelial cells opposes vascular tone causing vascular smooth muscles to relax, promoting vasodilation and reducing blood pressure (Li, Yon & Cai, 2015). Synthesis of angiotensin II by angiotensin-converting-enzyme decreases nitric oxide and prostaglandin levels, and stimulates release of endothelin (ET-1), which increases blood pressure (Klabunde, 2012a).

1.1.5 Clinical Features of Hypertension

Hypertension has various clinical features based on the differing characteristics present during blood pressure measurement:

- Resistant hypertension
- White coat hypertension
- Masked hypertension

Resistant hypertension is defined as blood pressure which remains high despite appropriate doses of antihypertensive medications from three classes (including a diuretic), treatment adherence, and appropriate lifestyle modification management (Head et al., 2012; Fagard, 2012; Boolani, Sinha and Randall, 2013). Between 2005-2008, 11.8% of American adults with hypertension had resistant hypertension (Pimenta & Calhoun, 2012). Recent research by Sheppard and colleagues (2017) indicates that the prevalence of resistant hypertension among various study participants is between 8.8% and 18%. Apparent or pseudo-resistant hypertension occurs when patients do not adhere to lifestyle measures, medication adherence or intolerance, when a physician is not

following the guidelines for hypertension management, or poor clinic blood measurement technique (Fagard, 2012; Sheppard, Martin and McManus, 2017). Patients sometimes discontinue medication due to side effects, cost, lack of consistent or primary care, poor understanding of instructions, social and cultural barriers, or not enough support from their physician (Fagard, 2012). It is important for doctors to provide motivation, as well as consistent and continuous care to their patients to aid in adherence (Fagard, 2012). True resistant hypertension can be the result of an unsuspected specific and potentially curable secondary cause of hypertension, obstructive sleep apnoea, volume overload, drug induced hypertension, or lifestyle conditions such as weight gain, obesity or excessive alcohol intake (Fagard, 2012). Accurate estimates of resistant hypertension prevalence are hard to establish because accurate diagnosis of true resistant hypertension is difficult (Sheppard et al., 2017).

Clinical blood pressure measurements are generally higher when taken by a doctor than when taken by trained nonmedical staff or at home, these higher readings are commonly referred to as the white-coat effect and can result in white-coat hypertension in untreated individuals (Head et al., 2012; Wang et al., 2017). Approximately 15-30% of patients with elevated blood pressure when taken in the medical practitioner's office have white-coat hypertension (Franklin et al., 2013). The 2017 high blood pressure clinical practice guideline suggest that patients with blood pressure \geq 5-10mmHg above goal on three or more medications should be screened for white coat hypertension. (Whelton et al., 2017). Individuals with white-coat hypertension, that is elevated in the clinic but not elevated when measured using home or ambulatory blood pressure monitoring, are classified as having a decreased risk of cardiovascular disease (Wang et al., 2017).

Masked hypertension is blood pressure that is not elevated in a clinical setting; however, is elevated when measured away from a clinical setting, preferably with an ambulatory monitor (Wang et al., 2017). Masked hypertension occurs when blood pressure measurements taken in the clinic are lower than those taken at home or using an ambulatory blood pressure monitor, and is seen in approximately 10% of patients (Head et al., 2012; Rizzoni, 2016). In contrast, Booth et al. (2016) indicate that the prevalence of masked hypertension is as high as 15 to 30%. Individuals with masked hypertension have an increased risk of developing cardiovascular disease, target organ damage, and higher mortality (Rizzoni, 2016; Booth, 2016; Wang, et al., 2017). Clinic blood pressure measurements also do not provide information about a patient's circadian pattern which can be

influenced by ambient temperature, humidity, physical activity, alcohol consumption, caffeine, food, emotional states, and sleep-wake routine (Head et al., 2012).

1.1.6 Hypertension Treatment and Management

First line treatment for hypertension is lifestyle changes as per Table 4 below; if no improvement is seen then pharmacological intervention will generally be commenced. Treatment guidelines include restricting salt intake, moderation of alcohol consumption, dietary changes, weight reduction, smoking cessation, and regular exercise (Mancia et al., 2013; Whelton et al., 2017). The 2017 High Blood Pressure Clinical Practice Guideline states that non-pharmacological intervention strategies should be focused on targeting both the general population, as well as a targeted approach in adults with the greatest risk of developing blood pressure related cardiovascular disease (Whelton et al., 2017). Those at greatest risk include people with hypertension, adults who are overweight, are physically inactive, consume excessive amounts of sodium or who have a high alcohol intake (Whelton et al., 2017).

Table 4: Blood pressure treatment guidelines

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130-139 Or DBP 85-89	Grade 1 HT SBP 140-159 Or DBP 90-99	Grade 2 HT SBP 160-179 Or DBP 100-109	Grade 3 HT SBP ≥ 180 Or DBP ≥ 110
No other RF	• No BP intervention	• Lifestyle changes for several months • Then add BP drugs targeting < 140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting < 140/90	• Lifestyle changes • Immediate BP drugs targeting < 140/90
1-2 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting < 140/90	• Lifestyle changes for several weeks • Then add BP drugs targeting < 140/90	• Lifestyle changes • Immediate BP drugs targeting < 140/90
≥ 3 RF	• Lifestyle changes • No BP intervention	• Lifestyle changes for several weeks • Then add BP drugs targeting < 140/90	• Lifestyle changes • BP drugs targeting < 140/90	• Lifestyle changes • Immediate BP drugs targeting < 140/90
OD, CKD stage 3 or diabetes	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting < 140/90	• Lifestyle changes • BP drugs targeting < 140/90	• Lifestyle changes • Immediate BP drugs targeting < 140/90
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RF's	• Lifestyle changes • No BP intervention	• Lifestyle changes • BP drugs targeting < 140/90	• Lifestyle changes • BP drugs targeting < 140/90	• Lifestyle changes • Immediate BP drugs targeting < 140/90

BP - blood pressure; CKD - chronic kidney disease; CV - cardiovascular; CVD - cardiovascular disease; DBP - diastolic blood pressure; HT - hypertension; OD - organ damage; RF - risk factor; SBP - systolic blood pressure.

Adapted from Mancia et al. (2013) ESH/ESC guidelines for the management of arterial hypertension. *European heart journal*: 34; 2159-2219.

doi:10.1093/eurheartj/eh1151

The colours in the table are indicative of the class of recommendation: green – class I, yellow – class IIa, orange – class IIb, red – class III.

Management of hypertension should focus on the overall health of the patient, with an intention of reducing the risk of future adverse cardiovascular outcomes (Whelton et al., 2017).

Antihypertensive medication should be implemented in individuals who have a combination of increased blood pressure level and absolute cardiovascular risk. Nonpharmacological and pharmacological strategies should be integrated, and blood pressure management should be intensified with increased risk of future cardiovascular events (Whelton et al., 2017). The guidelines from ESH/ESC (Mancia et al., 2013) which outlines blood pressure treatment guidelines based on hypertensive status are listed in Table 4.

1.1.7 Medications

A patient's age, the presence of any associated clinical conditions or end organ damage, potential interaction with other medications, as well as any possible concerns regarding adherence, cost and the patient's medication choice should be considered when antihypertensive medications are prescribed by a health care provider (National Heart Foundation of Australia (NHF), 2016).

Antihypertensive drug therapy should be implemented when patients do not reach target blood pressure levels, with regular follow-up and review of the patient's treatment (Glynn, Murphy, Smith, Schroeder, & Fahey, 2010). Blood pressure goals are achieved in only 25 to 40% of people taking antihypertensive medication, approximately 54% of American adults and 32% of Australian adults with hypertension have their condition under control (Glynn et al., 2010; CDC, 2016; NHF, 2016). Inadequate blood pressure control has been associated with poor follow-up, no primary care physician, ineffective management and inadequate practice organisation (clinical inertia), patient characteristics (gender, age) and lack of adherence (Glynn et al., 2010).

Scientific evidence indicates that reducing blood pressure with the use of medications reduces death, stroke, and heart disease (Heran, Wong, Heran & Wright, 2008a; Ettehad et al., 2016). There is also evidence suggesting that the blood pressure lowering effects of antihypertensive medications does not always reflect reductions in mortality or cardiovascular disease, nor does it explain better health outcomes (Heran et al., 2008a). A recent systematic review and meta-analysis conducted by Ettehad and colleagues (2016) indicates that every 10mmHg reduction in systolic blood pressure significantly reduces the risk of coronary heart disease, stroke and heart failure; as well as a 13% reduction in all cause mortality.

Deciding which medication, and dosage, to prescribe to a patient is one of the main difficulties of managing hypertension. There is generally more than one mechanism contributing to hypertension so treatment with monotherapy medication to modify one physiologic system may trigger compensatory responses from other systems (Chen, Heran & Wright, 2009). The use of two or more medications which affect different pathways, can neutralise or minimise counter-regulatory mechanisms triggered by the other, improving blood pressure reductions (Chen et al., 2009). There are eight classifications of antihypertensive medications available: α -adrenergic blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, antiadrenergic agents, β -adrenergic blockers, calcium channel blockers, diuretics and vasodilators (Chen & Yang, 2013). Comorbidities such as heart failure and chronic kidney disease should be considered when prescribing antihypertensive medications (Whelton et al., 2017). Studies indicate the possibility that a 10mmHg reduction of blood pressure in medicated heart failure patients may have an increased risk of developing renal failure (Ettehad, 2017).

Medications currently recommended as first-line treatment for uncomplicated hypertension are angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonist, calcium channel blocker or thiazide diuretics (NHF, 2016). If the target blood pressure is not reached by use of one of these medications then a combination of ACE inhibitor (or angiotensin II receptor antagonist) plus either a calcium channel blocker or low-dose thiazide diuretic should be used. The three are then all used in combination with each other if blood pressure targets are still not reached. Beta blockers can increase the risk of developing diabetes and are no longer recommended as a first-line treatment for uncomplicated hypertension (NHF, 2016). Each of the medications has side effects which may affect the patient, and could prevent them from being compliant with taking their medication. According to Diao, Wright, Cundiff and Gueyffier (2012) approximately 9% of people treated for mild hypertension with medication discontinue treatment due to adverse side effects.

1.1.7.1 ACE Inhibitor

Angiotensin converting enzyme (ACE) works by converting angiotensin I into angiotensin II resulting in vasoconstriction, vascular growth, and aldosterone release (Ritter, 2011). Blocking ACE prevents the conversion of angiotensin I into angiotensin II, decreasing synthesis and therefore the availability of angiotensin II (Ritter, 2011). Blocking ACE enables the smooth muscle of blood vessels

to relax which promotes excretion of sodium ions and potassium retention; this then reduces cardiac preload and afterload, resulting in lower blood pressure (Brozovich et al., 2016). When the renin-angiotensin pathway is activated the effects of ACE inhibition are enhanced (Prescriber, 2010a). Kinins, including bradykinin, are accumulated during ACE inhibition and aid in promoting arterial and venous vasodilation, contributing to overall effectiveness of ACE inhibitors (Klabunde, 2012b). A plateau is reached fairly quickly with ACE inhibitors, increased dosage prolongs the duration of action not peak blood pressure (Prescriber, 2010a). There is no change in heart rate with ACE inhibition so there is no concerns of it causing tachycardia.

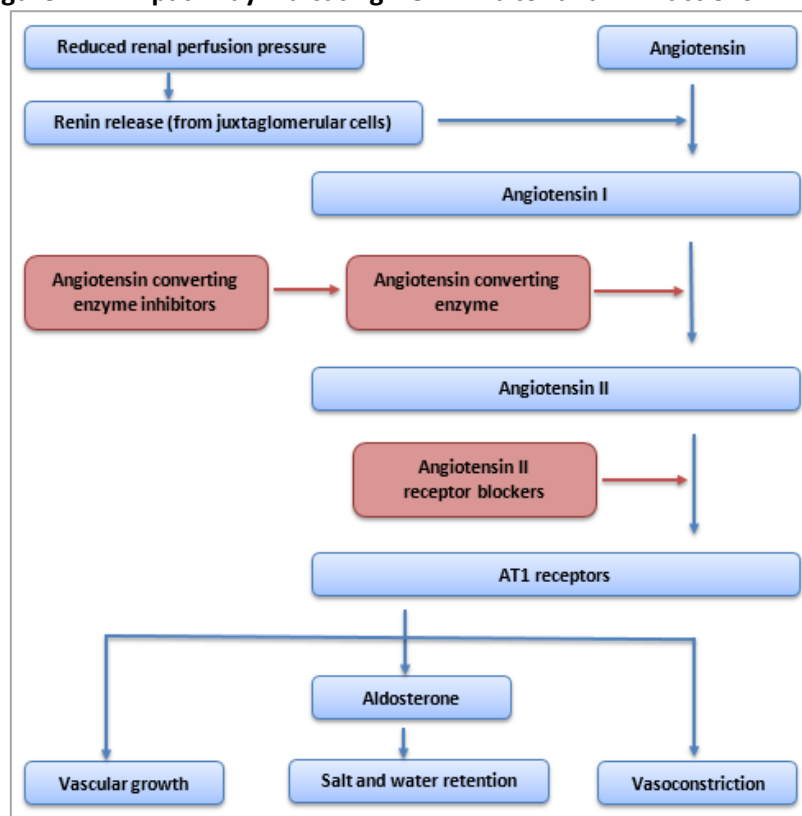
Angiotensin converting enzyme (ACE) inhibitors are vasodilators and have been widely used for hypertension and heart failure (Foex and Sear, 2004; Heran et al., 2008a). Recent research indicates that some ACE inhibitors are not as efficacious in preventing heart failure and stroke as calcium channel blockers or thiazide diuretics (Whelton et al., 2017). A main side effect of ACE inhibitors is a dry hacking cough, seen in 4-30% of patients, this can result in some people discontinuing treatment, angiotensin II receptor blockers may be better tolerated than ACE inhibitors in these patients (Ritter, 2011). A review of 92 ACE inhibitor trials, looking at 14 different ACE inhibitors, in 12,954 participants over 6 weeks, conducted by Heran et al. (2008a), indicated that there was little variation in the blood pressure lowering effects of the various medications. Heran et al. (2008a) also found that approximately 70% of the blood pressure lowering effect of ACE inhibitors can be achieved with the lowest recommended dose of the drugs.

1.1.7.2 Angiotensin II Receptor Blocker

Angiotensin II receptor blockers (ARBs) block AT1 receptors that are responsible for vasoconstriction, hypertrophy, inflammation, cellular growth and proliferation, as well as modulating noradrenalin release (Abramov and Carson, 2012). Blocking the binding of angiotensin II to the AT1 receptor leads to inhibition of renin release which subsequently reduces aldosterone release, as well as reducing the negative effects associated with AT1 stimulation (Abramov & Carson, 2012). Angiotensin II is also mediated by the AT2 receptor which induces vasodilation, inhibition of cell growth, and production of nitric oxide; however, the AT2 receptor is not affected by ARBs (Carey, Wang & Siragy, 2000). The AT1 receptor promotes increases in blood pressure, and the AT2 receptor incites counterregulatory vasodilation to prevent blood pressure increases (Carey

et al., 2000). Angiotensin II receptor blockers (ARBs) are used for hypertension, heart failure and isolated systolic hypertension (Foex and Sear, 2004; Heran, Wong, Heran & Wright, 2008b). Side effects from ARBs include hypotension (usually with the first dose), dizziness, headache, insomnia, muscle cramps, electrolyte disturbances, angioedema and sexual dysfunction. Figure 1 illustrates the effect of renin release on the formation of angiotensin II and the subsequent vasoconstriction which increases blood pressure.

Figure 1: RAA pathway indicating ACE inhibitor and ARB actions



Ritter, J.M. (2011). Angiotensin converting enzyme inhibitors and angiotensin receptor blockers in hypertension. *BMJ*; 342:d1673, 8 pages. doi: 10.1136/bmj.d1673

1.1.7.3 Calcium Channel Blocker

Movement of calcium ions into vascular and cardiac muscle is necessary for muscle contraction. The mechanism of action of calcium channel blockers (CCBs) is that they block voltage-gated calcium channels to decrease calcium influx into the cells and vascular smooth muscle (Prescriber, 2010b). Decreasing calcium influx reduces smooth muscle contraction and vasoconstriction (Jackson, 2000). As a result, the amount of cardiac work and the demand on the heart is decreased, reducing blood pressure (Simonetti and Mohaupt, 2007). Lowering blood pressure reduces afterload, which decreases the force required to overcome diastolic blood pressure and eject stroke

volume. Optimising stroke volume ejection reduces the cardiac workload, and aids in restoring the supply/demand imbalance from the heart (Bullock and Manias, 2014).

Calcium channel blockers have differing structural and functional distinctions. Dihydropyridine derivatives are peripheral vasodilators with an intense cardiac stimulation which can overcome direct effects on the heart; while phenylalkylamine and benzothiazepine derivatives, are both rate limiting CCBs with noticeable effects on the heart including reducing heart rate (Prescriber, 2010b). The mechanism of action of cardioselective agents blocks voltage-gated calcium channels, decreasing calcium influx into the sinoatrial (SA) node and cardiomyocytes (Prescriber, 2010b). At the SA node this delays rapid depolarisation to prolong the duration of the action potential to reduce heart rate, decrease heart work, optimise ejection fraction and reduce blood pressure (Bullock & Manias, 2014). At the cardiomyocytes it reduces liberation of calcium from intracellular sarcoplasmic reticulum stores reducing contraction force and optimising ejection to alleviate the symptoms of angina.

Calcium channel blockers can be effective in elderly patients, and those with Raynaud's phenomenon, peripheral vascular disease or asthma; however, some CCBs are contraindicated in heart failure (Foex and Sear, 2004). The recent 2017 High Blood Pressure Clinical Practice Guideline indicates that some CCBs may be more effective in lowering blood pressure, stroke prevention and heart failure than ACE inhibitors and are a suitable choice for initial therapy if thiazide diuretics are not tolerated by patients (Whelton et al., 2017).

1.1.7.4 Diuretic

Loop diuretics and thiazides are effective as both a first-line and second-line medication for lowering blood pressure (Chen et al., 2009). The mechanism of action of loop diuretics are to inhibit $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ symporter in the thick ascending limb of the loop of Henle in the nephron of the kidney to prevent reabsorption (Bullock & Manias, 2014). Preventing the reabsorption of sodium prevents water from being retained in the body and promotes urination. Increased urination decreases blood volume and the loss of $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ ions, but will not affect the HCO_3^- or the uric acid, causing a slight increase in vasodilation of the veins aiding cardiac output and reduction of blood pressure (Bullock & Manias, 2014).

Loop diuretics inhibit the sodium-potassium-chloride cotransporter in the thick ascending limb of the loop of Henle (Klabunde, 2012b). Inhibition of this pump increases the concentration of sodium at the distal tubule which reduces hypertonicity of the interstitium and water reabsorption in the collecting duct, resulting in diuresis (increased water loss) and natriuresis (increased sodium loss) (Klabunde, 2012b). Loop diuretics are used for heart failure; side effects include hypovolaemia (dehydration), hypotension, dizziness, dyslipidaemia, electrolyte disturbances and metabolic alkalosis (Klabunde, 2012b). Some side effects can be combatted by placing the patient on a different medication, or by using another medication in conjunction with their current treatment (Bullock & Manias, 2014). Loop diuretics are not a first-line treatment for hypertension; however, reducing oedema in hypertensive patients, particularly those with chronic kidney disease, can aid in reducing their blood pressure (Malha & Mann, 2016).

The mechanism of action of thiazide diuretics is dependent on renal prostaglandin production (Klabunde, 2012b). Thiazide diuretics inhibit the sodium-chloride transporter in the distal convoluted tubule of the nephron, and are less effective than loop diuretics in generating diuresis and natriuresis (Klabunde, 2012b; Duarte & Cooper-DeHoff, 2010). Thiazide and thiazide-like diuretics such as hydrochlorothiazide are used for hypertension and heart failure; side effects include hypovolaemia, hypotension, dizziness, weakness, muscle cramps, electrolyte disturbances and metabolic alkalosis (Klabunde, 2012b). Thiazide and thiazide-like diuretics inhibit Na^+/Cl^- symporter in the distal convoluted tubule (Bullock & Manias, 2014). Thiazide diuretics block the chloride binding site and inhibit sodium reabsorption as well as promoting potassium, magnesium, and hydrogen excretion, but not calcium (Sniecinski, Wright & Levy, 2007). The exact mechanism for blood pressure lowering with thiazide diuretics is unknown; however, studies indicate electrolyte balance plays a role, and acid-base disorders are common with diuretic use (Bullock & Manias, 2014; Greenberg, 2000). According to Wright and Musini (2009) thiazides are the best first choice for hypertension with low-dose thiazides having better health outcomes and reduced mortality and morbidity. The 2017 High Blood Pressure Clinical Practice Guidelines indicate that thiazide diuretics are superior to CCBs and ACE inhibitors in preventing heart failure, lowering blood pressure and stroke prevention and are the best initial choice for single drug therapy (Whelton et al., 2017).

Potassium-sparing diuretics are an aldosterone-blocking diuretic that function at the distal segment of the distal tubule and the collecting duct to inhibit sodium and potassium exchange (Prescriber, 2011). Increased levels of sodium and water pass into the collecting duct for excretion; however, less potassium and hydrogen exchange occurs. Less potassium and hydrogen are lost in the urine which prevents hypokalaemia, which is often seen in loop and thiazide diuretics (Klabunde, 2012b). Potassium-sparing diuretics which work to reduce the loss of potassium in the kidney help lower blood pressure by inducing mild natriuresis and plasma volume reduction (Heran, Chen, Wang and Wright, 2012). Due to their relatively weak effects on overall sodium balance, they are often used in conjunction with thiazide or loop diuretics to help prevent hypokalaemia (Klabunde, 2012b). Potassium-sparing diuretics which block the epithelial sodium channel are prescribed as a second-line drug in patients taking other diuretics such as thiazide diuretics (Heran et al., 2012).

The effects of diuretics on sodium and water balance decrease blood volume and venous pressure, decreasing preload which via the Frank-Starling mechanism decreases stroke volume and cardiac output, reducing arterial pressure (Klabunde, 2012b). Decreased venous pressure reduces capillary hydrostatic pressure, decreasing capillary fluid filtration which promotes capillary fluid reabsorption and reduces oedema. Long-term diuretic use can cause reduced systemic vascular resistance which helps to sustain arterial blood pressure reductions (Klabunde, 2012b). Most patients with hypertension are effectively treated with diuretics, mostly with thiazide diuretics.

1.1.7.5 Beta Blocker

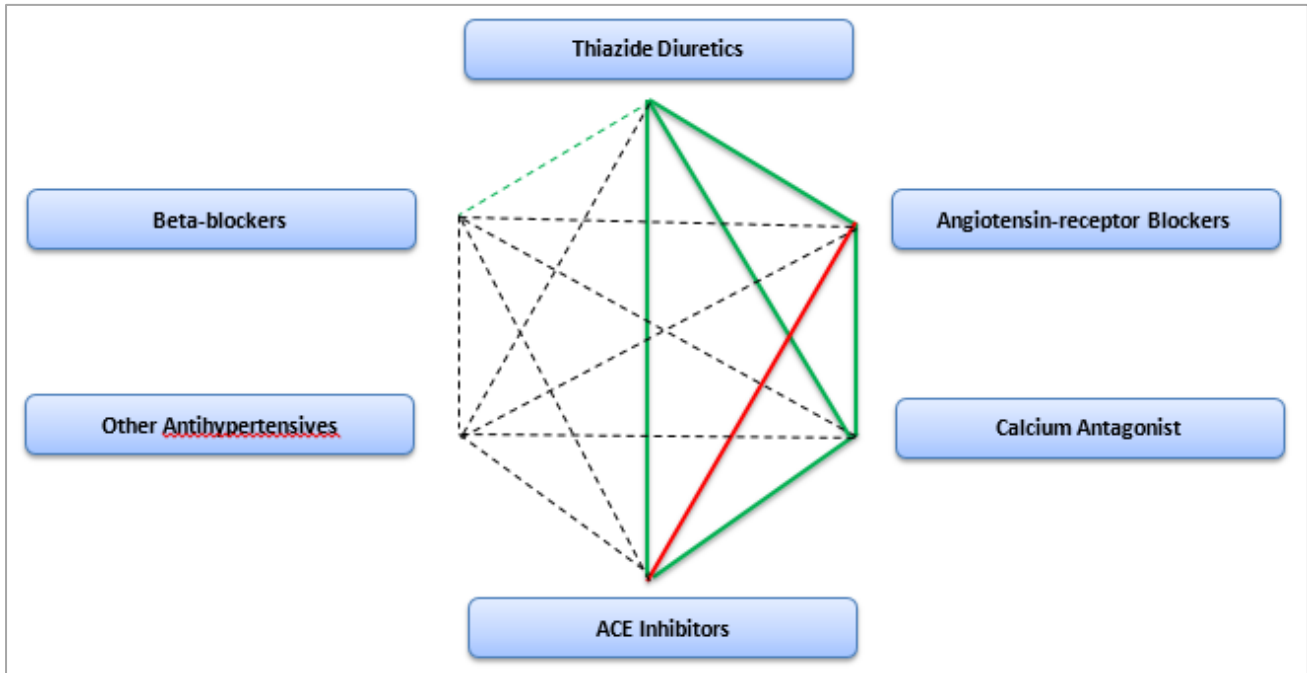
Beta-adrenergic blockers (β -blockers) are used in the treatment of high blood pressure, angina pectoris, arrhythmia, hypertrophic cardiomyopathy, heart failure; and are often used in the treatment of glaucoma and migraine headaches (Frishman, 2003). Catecholamines, adrenalin and noradrenalin, are released from nerve endings of the sympathetic nervous system (SNS) and the adrenal medulla to stimulate adrenergic receptors on cell surfaces, and increase cell activity (Frishman, 2003). Stimulation of β -adrenergic receptors increases heart rate, heart muscle contraction, blood pressure, and relaxation of the bronchial tube smooth muscle enabling lung expansion making it easier to exercise (Frishman, 2003). The use of β -blocking medications blocks the access of the catecholamines to their receptors reducing heart rate, blood pressure, and the oxygen needs of the heart (Frishman, 2003). β -blockers are most effective with high catecholamine

levels and receptor numbers during intense exercise; they also assist with modifying the heart's response to stress. β -blockers are beneficial in the long term treatment of high blood pressure, and are able to be used in conjunction with other blood pressure lowering medications (Frishman, 2003).

Beta-adrenergic blockers are classified as either β_1 -selective or nonselective, according to their antagonistic ability (Frishman, 2013). At low doses ' β_1 -selective blocking drugs inhibit cardiac β_1 receptors but have less influence on β_2 -receptors in bronchial and vascular locations' (Frishman, 2013). At high doses β_1 -selective blocking drugs also block β_2 -receptors. Chobanian et al. (2003) considered β -blockers to be the first line treatment for hypertension. Frishman (2013) mentions that although atenolol is less efficacious than other hypertensive drugs, β -blockers still remain important first-line treatments for people with hypertension and angina pectoris, myocardial infarction or congestive heart failure. According to (Ram, 2010) traditional β -blockers lower brachial blood pressure, but are less effective in reducing central aortic pressure when compared to other classes of antihypertensive medications.

It has been suggested that a high incidence of stroke in people taking β -blockers has been due to blood pressure variability (Cahan, Ben-dov and Bursztyn, 2012), possibly due to bradycardia induced by the medication. Cahan et al. (2012) suggest that an underestimation of systolic blood pressure, bradycardia and under treatment of hypertension, may have an effect on the poorer outcomes of patients taking β -blockers. The 2017 High Blood Pressure Clinical Practice Guideline indicate that β -blockers may be less effective in cardiovascular disease and stroke prevention than diuretics (Whelton et al., 2017). Treatment often requires pharmacological intervention requiring more than one medication to obtain treatment goals (Whelton et al., 2017). There are numerous combination medications currently available for patients; however, not all medications are able to be used in combination with each other, as demonstrated in Figure 2.

Figure 2: Possible combinations of classes of antihypertensive drugs



ACE= angiotensin-converting enzyme

Green continuous lines: preferred combinations; green dashed line: useful combination (with some limitation); black dashed line: possible but less well-tested combinations; red continuous line: not recommended combination.

Mancia et al. (2013). ESH/ESC guidelines for the management of arterial hypertension. *European heart journal*: 34 (28); 2159-2219. doi:10.1093/eurheartj/eh151

1.1.7.6 Treatment Guidelines

Guidelines for pharmacological intervention to treat hypertension have changed over the years with continued research. The 2007 ESH/ESC guidelines indicated that antihypertensive medication should commence when a patient has Grade 1 hypertension, even without other risk factors, if non-pharmacological intervention was unsuccessful (Mancia et al., 2013). The 2013 ESH/ESC guidelines have modified initiation of pharmacological intervention in relation to cardiovascular disease, chronic kidney disease, organ damage and risk factors, Table 4 and Table 5. The 2017 High Blood Pressure Clinical Practice Guideline indicates that health care practitioners should focus on overall patient health in reducing the risk of future cardiovascular outcomes by integrating pharmacological and nonpharmacological strategies (Whelton et al., 2017).

Table 5: ESH/ESC Initiation of antihypertensive drug treatment guideline

Recommendations	Class ^a	Level ^b
Prompt initiation of drug treatment is recommended in individuals with grade 2 and 3 hypertension with any level of CV risk, a few weeks after or simultaneously with initiation of lifestyle changes.	I	A
Lowering BP with drugs is also recommended when total CV risk is high because of OD, diabetes, CVD or CKD, even when hypertension is in the grade 1 range.	I	B
Initiation of antihypertensive drug treatment should also be considered in grade 1 hypertensive patients at low to moderate risk, when BP is within this range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle measures.	IIa	B
In elderly hypertensive patients drug treatment is recommended when SBP is ≥ 160 mmHg.	I	A
Antihypertensive drug treatment may also be considered in the elderly (at least when younger than 80 years) when SBP is in the 140-159mmHg range, provided that antihypertensive treatment is well tolerated.	IIb	C
Unless the necessary evidence is obtained it is not recommended to initiate antihypertensive drug therapy at high normal BP.	III	A
Lack of evidence does also not allow recommending to initiate antihypertensive drug therapy in young individuals with isolated elevation of brachial SBP, but these individuals should be followed closely with lifestyle recommendations.	III	A

BP - blood pressure; CKD - chronic kidney disease; CV - cardiovascular; CVD - cardiovascular disease; OD - organ damage; SBP - systolic blood pressure.

^aClass of recommendation; ^bLevel of evidence.

Mancia et al. (2013) ESH/ESC guidelines for the management of arterial hypertension. *European heart journal*: 34; 2159-2219. doi:10.1093/eurheartj/eh151

The JNC8 specifies that the primary goal of pharmacological intervention is to attain and maintain optimal blood pressure (James et al., 2014). Blood pressure goal should be reached within a month of commencing pharmacological treatment; if not then either the dose of the initial medication should be increased, or another added. When adding another drug, it should be a thiazide-type diuretic, calcium channel blocker, ACE inhibitor, or Angiotensin II receptor blocker (ARB) (James et al., 2014). If blood pressure goals are not reached with two medications then a third should be introduced, ensuring that ACE inhibitors and ARB's are not prescribed together in the same patient. There are varying recommendations of hypertension guidelines from some organisations which can be confusing for practitioners, the main recommended treatment guidelines are listed in Table 6.

Table 6: JNC 8 guideline comparisons of goal BP and initial drug therapy for adults with hypertension

Guideline	Population	Goal BP (mmHg)	Initial drug treatment options
2014 Hypertension guideline (U.S.A.)	General ≥ 60 yrs	< 150/90	Nonblack: thiazide-type diuretic, ACEI, ARB or CCB. Black: thiazide-type diuretic or CCB
	General < 60 yrs	< 140/90	
	Diabetes	< 140/90	ACEI or ARB
	CKD	< 140/90	
ESH/ESC 2013 (Europe)	General non-elderly	< 140/90	Diuretic, β-blocker, CCB, ACEI or ARB
	General elderly < 80 yrs	< 150/90	
	General elderly ≥ 80 yrs	< 150/90	
	Diabetes	< 140/85	ACEI or ARB
	CKD no proteinuria	< 140/90	
	CKD + proteinuria	< 130/90	
CHEP 2013 (Canada)	General elderly < 80 yrs	< 140/90	Thiazide, β-blocker (age <60yr), ACEI (non-black) or ARB
	General elderly ≥ 80 yrs	< 150/90	
	Diabetes		ACEI or ARB with additional CVD risk. ACEI, ARB, thiazide or DHPCCB without additional CVD risk
	CKD		ACEI or ARB
ADA 2013 (U.S.A.)	Diabetes	< 140/80	ACEI or ARB
KDIGO 2012 (U.S.A. / Belgium)	CKD no proteinuria	≤ 140/90	ACEI or ARB
	CKD + proteinuria	≤ 130/80	
NICE 2011 (U.K.)	General < 80 yrs	< 140/90	< 55yrs: ACEI or ARB
	General ≥ 80 yrs	< 150/90	≥ 55 yrs or black: CCB
ISHIB 2010 (U.S.A.)	Black, lower risk	< 135/85	Diuretic or CCB
	Target organ damage or CVD risk	< 130/80	

Abbreviations: ADA - American Diabetes Association; ACEI - angiotensin converting enzyme inhibitor; ARB - angiotensin receptor blocker; CCB - calcium channel blocker; CHEP - Canadian Hypertension Education Program; CKD - Chronic kidney disease; CVD - Cardiovascular disease; DHPCCB - Dihydropyridine calcium channel blocker; ESC - European Society of Cardiology; ESH - European Society of Hypertension; ISHIB - International Society for hypertension in blacks; JNC - Joint National Committee; KDIGO - Kidney disease improving global outcome; NICE - National Institute for Health and Clinical Excellence.

James et al. (2014). Evidence-based guideline for the management of high blood pressure in adults. Report from the panel members appointed to the eighth joint national committee (JNC8). *JAMA*: 311(5); 507-520. Doi:10.1001/jama.2013.284427.

1.1.8 Lifestyle Modification

Lifestyle modifications including exercise, diet, reducing weight, alcohol consumption and sodium intake are often recommended for people with hypertension (James et al., 2014). The 2017 High Blood Pressure Clinical Practice Guideline recently added the use of isometric resistance training as a lifestyle modification to aid in blood pressure management (Whelton et al., 2017). Brook, Jackson, Giorgini, and McGowan (2015) suggest that health risks related to high blood pressure can begin within the prehypertensive range of > 115/75 mmHg. To prevent future development of target organ disease (e.g. left ventricular hypertrophy, chronic kidney disease) and the onset of more

severe hypertension stages, treatment should be implemented during the prehypertensive and mild (stage 1) stages (Brook et al., 2015). The American Heart Association's, Health Campaign for Life's Simple 7, emphasises that individuals should avoid smoking, engage in daily physical activity, eat a healthy diet, maintain a healthy weight, and healthy cholesterol, blood pressure, and glucose levels (Benjamin et al., 2017). A 3 to 12 month trial of lifestyle modification including a low sodium diet, a Dietary Approaches to Stop Hypertension (DASH) eating plan, weight loss, aerobic exercise, and alcohol restriction, as demonstrated in Table 7 is suitable for people who are validated as low risk (Go et al., 2014). Individuals who are low risk, do not have target organ damage, cardiovascular disease (e.g. myocardial infarction, stroke, aortic aneurysm, heart failure), or diabetes (Brook et al., 2015).

Table 7: Recommended lifestyle modifications

Modification	Recommendation	Approximate SBP Reduction (range) **
Reduce weight	Maintain normal body weight (body mass index 18.5 - 24.9 kg/m ²)	5 - 20 mmHg / 10kg
Adopt DASH* eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8 - 14 mmHg
Lower sodium intake	a. Consume no more than 2,400 mg of sodium / day b. Further reduction of sodium intake to 1,500 mg / day is desirable since it is associated with even greater reduction in blood pressure c. Reduce intake by at least 1,000 mg / day since that will lower blood pressure, even if the desired daily sodium intake is not achieved	2 - 8 mmHg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 mins per day, most days of the week)	4 - 9 mmHg
Moderation of alcohol consumption	Limit consumption to no more than 2 standard drinks per day in most men and no more than 1 drink per day in women and lighter weight persons.	2 - 4 mmHg

Adapted from Go et al. 2014.

* DASH, dietary approaches to stop hypertension

** The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals.

Alternative therapies which may be appropriate for low risk individuals with mild hypertension include slow breathing, transcendental meditation, aerobic, resistance, and isometric handgrip

exercises; these can reduce blood pressure by approximately 5 mmHg (Brook et al., 2015). According to Brook et al. (2015) if blood pressure remains elevated after the trial of alternative therapies then individuals should consider pharmacological intervention. Adults with pre-hypertension, patients with well-controlled hypertension attempting to reduce medication, and individuals with multiple drug side effects or resistant hypertension (for whom other options have been exhausted) may also benefit from alternative approaches to lower their blood pressure (Brook et al., 2015).

Class 1 level B evidence suggests that 150 minutes of exercise each week offers an alternative that may be used to complement antihypertensive medication (Carlson et al., 2014; Cornelissen & Smart, 2013). The American College of Sports Medicine recommends 30 minutes of dynamic aerobic exercise daily as the preferred exercise modality for blood pressure management (Pescatello et al., 2004). Currently there is no clear optimal exercise training prescription for blood pressure management (Cornelissen & Smart, 2013). The effects of exercise training may differ depending upon which exercise modality is used, program length, session duration, frequency and exercise intensity. There is conflicting evidence for the appropriate exercise prescription for people with hypertension. Sharman and Stowasser (2009) recommend a combination of aerobic and resistance training; while Cornelissen and Smart (2013) suggest that endurance, dynamic and isometric resistance training all lower both SBP and DBP, and that combined training only lowers DBP.

The recommended exercise prescription is regularly being modified with growing research into the effects of exercise on blood pressure. The ESH/ESC 2013 guidelines state that people with hypertension should perform at least 30 minutes of moderate intensity aerobic exercise (walking, jogging, cycling or swimming) 5-7 days each week (Mancia et al., 2013). There are also indications that regular lower intensity physical exercise is also associated with approximately a 20% decrease in mortality (Mancia et al., 2013). In 2014 the American Heart Association (AHA) exercise recommendations to aid in controlling hypertension were a minimum 30 minutes per day, at least 5 days per week, of physical activity (Go et al., 2014). According to Brook (2015) the first line approach to alternative therapies should be 150 minutes of moderate intensity aerobic exercise each week, due to its blood pressure lowering efficacy, as it has been proven to reduce overall cardiovascular risk. In the AHA update of Heart Disease and Stroke Statistics, Mozaffarian et al.

(2015) recommended that adults should conduct at least 150 minutes of moderate intensity aerobic exercise, or 75 minutes of vigorous intensity aerobic exercise, or an equivalent combination of both each week, plus at least two days of muscle strengthening weekly.

Recent AHA guidelines indicate that adults should conduct a minimum of 150 mins of moderate or 75 mins of vigorous exercise (or a combination of both) each week, as well as a minimum of 2 days of muscle strengthening, for ideal cardiovascular health (Benjamin et al., 2017). According to the U.S. NHANES 2014, only 50% of adults over 18 years of age with hypertension met the recommended aerobic activity guidelines, with only 21.4% meeting the guidelines for both aerobic activity and muscle strengthening (National Center for Health Statistics, 2014). Recent analyses suggest that isometric resistance training (IRT) may elicit blood pressure reductions greater than those seen with dynamic aerobic and resistance exercise (Cornelissen and Smart, 2013; Carlson et al., 2014; Millar et al., 2014). The new 2017 High Blood Pressure Clinical Practice Guidelines recommend physical activity of either 90-150 min/wk of aerobic exercise, 90-150 min/wk of dynamic resistance exercise, or IRT 3 times/wk for 8-10 weeks (Whelton et al., 2017).

1.1.9 Summary

Hypertension is a major risk factor for cardiovascular disease and affects approximately 1.13 billion people worldwide. Hypertension classification has changed over the past 15 years, and Stage 1 hypertension is currently classified as blood pressure of SBP between 130-139mmHg or DBP between 80-89mmHg. More than 95% of people with hypertension have essential hypertension, with no known cause of their hypertension. The main theories of hypertension pathophysiology are excess sympathetic activity, overactive renin-angiotensin-aldosterone system, altered neurohormonal control, or a metabolic disturbance. The clinical features of hypertension are resistant hypertension, white coat hypertension, and masked hypertension.

First line treatment for hypertension is lifestyle changes including restricting salt intake, moderate alcohol consumption, dietary changes, maintaining optimal weight, avoid smoking, and conducting regular exercise. No improvement in blood pressure will require pharmacological intervention with either an ACE inhibitor, angiotensin II receptor antagonist, calcium channel blocker, diuretic, beta blocker or a combination of these depending on responsiveness to treatment. Although exercise guidelines are constantly being reviewed, it is currently recommended that people with

hypertension should conduct either 90-150 min/wk of aerobic exercise, 90-150 min/wk of dynamic resistance exercise, or isometric resistance training 3 times/wk to aid in their blood pressure management.

1.2 Isometric Resistance Training

Isometric exercise consists of sustained contractions against an immovable load or resistance with no, or minimal change, in length of the muscle group (Garg et al., 2014). During isometric exercise the joint remains static (stable) and does not move. This stability makes isometric exercise beneficial for assisting with stabilisation of a joint, and maintaining muscle strength during recovery after an injury (Garg et al., 2014). There has been increasing research into the effect of isometric exercise as a method of blood pressure management. Research has particularly looked at long-term isometric resistance training for a minimum of four weeks, with some starting to look at the effects after 12 weeks; notably Pagonas et al. (2017), and the current research detailed in Chapter 5 of this thesis. Recent meta-analyses indicate reductions of resting blood pressure of approximately 5/4mmHg, with hypertensive participants having larger reductions than their normotensive counterparts (McGowan et al., 2017; Whelton et al., 2017).

In order to retain the health benefits of exercise, individuals need to remain physically active throughout their life (Toraman, 2005). Adaptations from training are often lost after ceasing training, which can include a decline in cardiovascular function (Toraman, 2005; Neufer, 1989). Wiley et al. (1992) looked at the detraining effect in participants after completing a five week IRT protocol, which indicates that after five weeks of detraining, SBP and DBP had both returned to baseline measurement.

Participant blood pressure measurement have predominantly been conducted at rest in IRT studies. Recently studies have started utilising ambulatory blood pressure measurements to determine the effects of IRT on SBP and DBP over time. Stiller-Moldovan (2012) and Somani et al. (2017) measured blood pressure using 24 hour ambulatory monitoring, which was recorded every 30 minutes during the day, and hourly at night. Ash et al. (2017) utilised 24 hour ambulatory monitoring which measured blood pressure over four 15 minute intervals in the laboratory, and then hourly at home. Pagonas et al. (2017) recorded blood pressure every 20 minutes during the day and every 30 minutes at night. As only a few studies have utilised 24 hour ambulatory monitoring with IRT there is currently no set measurement protocol.

1.2.1 Protocols and Risk

Isometric resistance training protocols are time efficient and can last for as little as 12 minutes, are well tolerated by participants, have high compliance rates, and appear to be low risk with no published reports of adverse events (McGowan et al., 2017). Millar et al. (2014) noted that some studies reported that SBP, DBP and heart rate responses to a single isometric contraction were equivalent, or lower, than those seen at equivalent dynamic aerobic exercise. This indicates that rate pressure product (RPP) calculated as (SBP x heart rate) may be lower after isometric exercise compared to treadmill exercise. Due to minimal evidence of the safety and efficacy of IRT many professionals are reluctant to recommend it to patients with hypertension (Ghadieh & Saab, 2015). Determining the peak cardiovascular responses, including RPP, during IRT would address the safety issues.

There is currently no set standard protocol for the use of isometric exercise in reducing blood pressure. Various studies which have investigated the use of isometric exercise for reducing blood pressure have often utilised different protocols. Generally, isometric exercises with the intention of reducing blood pressure are either conducted as handgrip exercises or bilateral leg exercises (Carlson et al., 2014; Millar et al., 2013). Isometric handgrip exercise involves the use of a hand dynamometer, most commonly by the non-dominant hand, or bilaterally. When conducting isometric exercise it is recommended that participants maintain their elbow flexed at 90°, with the dynamometer held firmly in their hand, and squeezing with their fingers (Hisdal et al., 2004). It is important to ensure that the person squeezing is maintaining normal breathing to prevent initiating a valsalva reaction (Hisdal et al., 2004).

Most studies have performed isometric handgrip exercise at 30% of participants' maximum voluntary contraction, which is determined at each session (McGowan et al., 2007; Stiller-Moldovan et al., 2012). Maximum voluntary contraction is generally determined by having the participant perform at least one, to a maximum of five, contractions at maximum force, each separated by a 1-minute rest period (Howden et al., 2002). An average of the contractions at maximum force is then used to calculate intensity required for training.

There has also been a wide variety of hand dynamometers used in various isometric handgrip studies. Wiley et al. (1992) used a direct-reading voltage display meter connected to the dynamometer to supply feedback to their participants enabling them to maintain the appropriate tension when exercising. Numerous researchers have utilised a computer programmable handgrip device (McGowan et al., 2006; Miller et al., 2009; Badrov et al., 2013a and b; Goessler et al., 2016) which can be quite expensive while others have utilised inexpensive hand dynamometers (Millar et al., 2008). Some of the available hand dynamometers are designed so that the individual can read the intensity of their contraction which can make it difficult to blind participants in a research setting.

An early study into isometric handgrip exercise conducted by Wiley et al. (1992) had participants training by performing four 2-minute isometric contractions with 3-minute rests between contractions using their dominant arm. This protocol has since been adopted by other handgrip studies, with variations on which hand is used and the percentage of contraction intensity performed by participants. The length of studies has varied from acute one day training, up to longer 10 week studies, with one recent study of 12 weeks duration. There are also variations of how many days per week participants trained. Wiley et al. (1992) conducted two studies one with participants exercising 3 days per week, and the other for 5 days per week; the majority of studies use 3 days per week. McGowan et al. (2017) have determined that performing four 2-minute isometric handgrip contractions with a brief 1-minute rest period between, conducted three to five times a week for up to ten weeks is the most common isometric resistance training protocol. Due to the varying protocols utilised, isometric handgrip study protocols are detailed in Table 8.

Table 8: Isometric Handgrip Study Protocols (in chronological order)

Study	Duration	Participants Age (years)	Frequency	Exercise Protocol	Exercise Training	Outcomes Measured	HTN	Fasting
Aoki et al. (1983) Japan	1 acute bout	68 - All male 18 normotensive Age: 40 ± 3 50 hypertensive Age: 41 ± 4	Once	30% MVC No control	3 x 3 min right hand IHG, 2 min rest	SBP, DBP, HR	Yes, went 4 wks without meds	Not specified
Wiley et al. (1992) USA	8 weeks	18 Age: 20-35	3 days / week	30% MVC Sedentary control	4 x 2 min dominant arm IHG, 3 min rest	SBP, DBP, HR	No	Maintain diet, exercise, alcohol habits
Wiley et al. (1992) USA	5 weeks	10 Age: 29-52	5 days / week	50% MVC No control	4 x 45 sec alternating IHG, 1 min rest	SBP, DBP, HR	No	Maintain diet, exercise, alcohol habits
Howden et al. (2002) USA	5 weeks	8 M:6; F:2 Age: 21.0 ± 1.4	3 days / week	30% MVC (3 groups inc. legs)	4 x 2 min IHG, 3 min rest	SBP, DBP, HR, LBNP, ECG, EMG	No	Not specified
Taylor et al. (2003) Canada	10 weeks	17 M:10; F:7 Age: 60-80 \bar{x} = 67.5	3 days / week	30% MVC Sedentary control	4 x 2 min alternating IHG, 1 min rest	SBP, DBP, HR, HRV, MAP	Yes, some on meds	Not specified
Hisdal et al. (2004) Norway	3 separate protocols of 1 bout	16 M:8; F:8 Age: 24.2 ± 3.7	Once for each protocol	40% MVC No control	2 min right hand IHG	MAP, HR, SV, CO, TPR, LPR Doppler, ECG, Finometer®	No	Food – 2hr Caffeine – none during the day Ex – 2hr
McGowan et al. (2006) Canada	8 weeks	17 Age: 66.9 ± 5.8	3 days / week	30% MVC No control	4 x 2 min non- dominant hand IHG, 4 min rest	Artery diameter, HR, MAP	Yes, all on meds	Food – 4hr Caffeine – 12hr Ex – 24hr
McGowan et al. (2007a) Canada	8 weeks	Unilateral M:7; F:2 Age: 66.1 ± 6.3 Bilateral M:5; F:2 Age: 61.7 ± 4.2	3 days / week	30% MVC	4 x 2 min IHG Unilateral: non- dominant hand, 4 min rest Bilateral: alternating, 1 min rest	Brachial FMD Fasting lipids SBP, DBP	Yes, all on meds	Food – 4hr Caffeine – 12hr Exercise – 24hr

Study	Duration	Participants Age (years)	Frequency	Exercise Protocol	Exercise Training	Outcomes Measured	HTN	Fasting
McGowan et al. (2007) Canada	8 weeks	11 M:8; F:3 Age: 27.5 ± 14.2	3 days / week	30% MVC No control	4 x 2 min non-dominant hand IHG, 4 min rest	BP, FMD	No	Food – 4hr Caffeine – 12hr Ex – 24hr
Bakke et al. (2007) Norway	1 acute bout	33 PAD - M:5; F:6 Age: 66.8 ± 9.3 Control 1 M:4; F:7 Age: 24.2 ± 5.1 Control 2 M:7; F:4 Age: 62.7 ± 3.3	Once	40% MVCs Same for control	1 x 2 min right hand IHG	Finometer® SBP, DBP, MAP, HR, SV, CO, TPR	No	Food – 2hr Caffeine – 2hr Ex – 2hr
Millar et al. (2008) Canada	8 weeks	49 M:21; F:28 Age: 66.4 ± 0.9	3 days / week	30-40% MVC Sedentary control	4 x 2 min alternating bilateral IHG, 1 minute rest	SBP, DBP	Yes, no meds	Ex – 24hr Alcohol – 24hr
Millar et al. (2009) Canada	1 acute bout	18 M:9; F:9 Age: 70 ± 5	Once	30% MVC Crossover	4 x 2 min bilateral IHG, 1 min rest	SBP, DBP, HR	No	Similar meals each visit Caffeine – 12hr Ex – 24hr Alcohol – 12hr
Mortimer & McKune (2011) South Africa	5 days	18 All female Age: 47.88 ± 1.8	5 consecutive days	30% MVC Sedentary control	4 x 45 sec bilateral IHG, 1 min rest	SBP, DBP, HR	No	Normal daily routine
Stiller-Moldovan et al. (2012) Canada	8 weeks	20 M:10; F:10 Age: 60.0 ± 8.5 Control: 62.7 ± 6.1	3 days / week	30% MVC Sedentary control	4 x 2 min alternating IHG, 1 min rest	SBP, DBP, HR	Yes, meds	Light breakfast Caffeine – 12hr Ex – 24hr Alcohol – 24hr
Millar et al. (2013) Canada	8 weeks	23 All female IHG: 13 Age: 65 ± 6 Control: 10 Age: 67 ± 6	3 days / week	30% MVC Sedentary control	4 x 2 min left hand (non-dominant) IHG, 4 min rest	SBD, DBP, MAP, HRV	Yes, all on meds	Food – 4hr Caffeine – 12hr Ex – 24hr

Study	Duration	Participants Age (years)	Frequency	Exercise Protocol	Exercise Training	Outcomes Measured	HTN	Fasting
Badrov et al. (2013a) Canada	10 weeks	24 M:13; F:11 Age: 65 ± 7 Control: 63 ± 9	3 days / week	30% MVC sedentary Control	4 x 2 min bilateral IHG, 1 min rest	SBP, DBP, MAP, HR	Yes, meds	Light meal Caffeine – 12hr Ex – 24hr Alcohol – 24hr
Badrov et al. (2013b) Canada (blind randomisation)	8 weeks	32 All females 3x: 23(4) 5x: 27(6) Control: 24(8)	3 or 5 days / week	30% MVC Sedentary control	4 x 2 min non-dominant hand IHG, 4 min rest	SBP, DBP, HRV, FMD (resistance vessel endothelial function)	No	Food – 4hr Caffeine – 12hr Ex – 24hr Alcohol – 24hr
Badrov et al. (2016) Canada	8 weeks	20 M: 9; 21 ± 2 F: 11; 23 ± 4	3 days / week	30% MVC No control, study compared males vs females	4 x 2 min non-dominant hand IHG, 4 min rest	SBP, DBP, MAP, HR, FMD	No	Food – 4hr Caffeine – 12hr Ex – 24hr Alcohol – 24hr
Ash et al. (2017) USA	Acute: crossover	27 M:23; F:4 40.6 ± 2	Once	30% MVC Crossover	4 x 2 min bilateral IHG, 1 min rest	19hr ambulatory SBP, DBP, PWV	Yes	Standard breakfast – 2-3hr Caffeine – 6hr
Ash et al. (2017) USA	8 weeks	5 M:4; F:1 43.4 ± 5.3	3 days / week	30% MVC Aerobic exercise	4 x 2 min bilateral IHG, 1 min rest	19hr ambulatory SBP, DBP, PWV	Yes	Standard breakfast – 2-3hr Caffeine – 6hr
Pagonas et al. (2017) Germany	12 weeks	75 – all female 25: 28.8 ± 10.6 Sham-25: 62.1 ± 7.1 Aerobic-25: 60.7 ± 9.3	5 days / week 60 sessions in 12 weeks unsupervised	30% MVC 5% MVC/sham Aerobic	4 x 2 min bilateral IHG, 1 min rest	24hr ambulatory and office SBP, DBP, PWV, SVR	Yes	Not mentioned

ECG – electrocardiograph; EMG – electromyography; CO – cardiac output; DBP – diastolic blood pressure; FMD – flow-mediated dilation; HR – heart rate; HRV – heart rate variability; IHG – isometric handgrip; LBNP – lower body negative pressure; MAP – mean arterial pressure; MVC – maximum voluntary contraction; PWV – pulse wave velocity; SBP – systolic blood pressure; SV – stroke volume; SVR – systemic vascular resistance; TPR – total peripheral resistance.

1.2.2 Early Systematic Reviews and Meta-analyses

Systematic reviews and meta-analyses summarise the results of published primary treatment studies and diagnostic test accuracy studies (Debray et al., 2017). Combining information from multiple studies enables estimation of probability or risk that a specific condition will occur in the future (Debray et al., 2017). Review papers and meta-analyses on the efficacy of IRT and its effects on blood pressure in both normotensive and hypertensive populations have aided in guiding research.

Owen, Wiles and Swain (2010) conducted a meta-analysis which included five studies from Medline and SPORTDiscus databases with a total of 122 participants; three of the studies utilised isometric handgrip exercise, the other two studies were double-leg extension exercises. The studies used in the meta-analysis were all small, were less than 10 week duration, and utilised three exercise sessions a week with four bouts of isometric exercise each session with varying rest periods between bouts (Owen et al., 2010). Among the five studies which Owen et al. (2010) analysed; only one had participants who were hypertensive, and one was not randomised. All of the studies used in the meta-analysis saw significant reductions in SBP and DBP; the meta-analysis determined an overall mean reduction of -10mmHg in SBP and -6.65mmHg in DBP (Owen et al., 2010).

Kelley and Kelley (2010) conducted a meta-analysis of randomised controlled trials which were retrieved from Pubmed, Cochrane Central Register of Controlled Clinical Trials, CINAHL, SPORTDiscus and Dissertation abstracts international). Their inclusion requirement was randomised controlled trials which utilised isometric handgrip exercise conducted by adults 18 years and over for at least four weeks. After an initial search of 287 potential studies the meta-analysis contained only three studies with a total of 81 participants, with exercise in two of the studies being conducted for eight weeks, and the third study having a ten week duration (Kelley and Kelley, 2010). Overall reductions in SBP of -13.4mmHg in a random effects model and -13.8mmHg in fixed effects model, as well as reductions in DBP of -7.8mmHg with random effects and -6.1mmHg with fixed effects were determined by Kelley and Kelley (2010).

Cornelissen and Smart (2013) conducted a systematic review and meta-analysis of studies involving dynamic endurance aerobic, dynamic resistance, combined and IRT from Medicine (Ovid),

Embase.com and SPORTDiscus. The inclusion requirements were randomised controlled parallel-design studies of exercise training for four weeks or longer with participants aged 18 years or older without cardiovascular or other diseases. There were only four IRT studies included in the meta-analysis, comprising 114 participants, three studies utilised handgrip exercise and one study used leg exercise, all were for a minimum of eight weeks. The meta-analysis indicated significant reductions in SBP for endurance, resistance and isometric exercise, but not combined training, while significant reductions were seen in DBP in each of the training protocols (Cornelissen and Smart, 2013). Larger reductions were seen in IRT than all of the other studies examined by Cornelissen and Smart (2013) with SBP -10.9mmHg and DBP -6.2mmHg.

On close examination of the meta-analyses by Owen et al. (2010), Kelley and Kelley (2010) and Cornelissen and Smart (2013), each of them used the same three studies in their analysis. Kelley and Kelly (2010) added the additional study by Howden et al. (2002) which incorporated isometric leg exercise into the meta-analysis by Owen et al. (2010); while Cornelissen and Smart (2013) incorporated an extra study from Wiles et al. (2010) which utilised isometric leg extension. Due to the similarity of the studies used in the various meta-analyses, it is likely that this influences the similar results seen by the authors.

1.2.3 Systematic Review and Meta-analysis by Carlson et al. 2014

Up until 2013 the earlier meta-analyses published all contained the same studies with only one extra study being added. Due to the growing interest into the effect of isometric exercise on blood pressure and increased studies available, a new systematic review and meta-analysis to update earlier data was conducted (Carlson et al., 2014). This systematic review and meta-analysis focused on the effect of IRT to quantify its effects on the change in systolic, diastolic and mean arterial pressure in sub-clinical populations. It also examined whether magnitude of change in SBP and DBP was different with respect to blood pressure classification (Carlson et al., 2014). A systematic search was conducted using PubMed, CINAHL and the Cochrane Controlled Trials Registry between 1966 and July 31st 2013. The search strategy included the key concepts of hypertension, blood pressure, isometric exercise, isometric resistance training, physical training and exercise training. These were combined with a sensitive search strategy to identify randomized controlled- and crossover- trials (Carlson et al., 2014). Included studies were randomized, controlled trials and cross-over studies

containing adults who conducted isometric exercise training; animal studies, review papers, acute exercise studies, and non-randomized controlled trials were excluded.

Nine studies were included in the analysis, totalling 211 patients. Systolic blood pressure (SBP) was significantly reduced in all participants mean difference (MD) -6.77 mmHg (95% CI -7.93 to -5.62, $p < 0.00001$). However, hypertensive participants demonstrated a smaller reduction in SBP MD -4.31 mmHg (95% CI -6.32 to -2.21, $p < 0.0001$) than normotensive participants MD -7.83 mmHg (95% CI -9.21 to -6.45, $p < 0.00001$) (Carlson et al., 2014). Diastolic blood pressure (DBP) was significantly reduced MD -3.96 mmHg (95% CI -4.80 to -3.12, $p < 0.00001$). However, hypertensive participants demonstrated a larger reduction in DBP MD -5.48 mmHg (95% CI -7.93 to -3.03, $p < 0.0001$) than normotensive participants MD -3.08 mmHg (95% CI -3.88 to -2.27, $p < 0.00001$) (Carlson et al., 2014). Mean arterial blood pressure (MAP) was reduced MD -3.94 mmHg (95% CI -4.73 to -3.16, $p < 0.00001$) with hypertensive participants demonstrating a larger reduction in MAP MD -6.01 mmHg (95% CI -8.04 to -3.97, $p < 0.00001$) than normotensive participants MD -3.58 mmHg (95% CI -4.43 to -2.73, $p < 0.00001$). Resting heart rate was slightly reduced with MD -0.79 beats.min⁻¹ (95% CI -1.23 to -0.36, $p = 0.0003$) (Carlson et al., 2014).

Reductions in SBP of almost -7 mmHg were similar to those seen by previous meta-analyses of -10 mmHg, indicating that IRT is comparable to dynamic aerobic or resistance training for reducing SBP. To investigate these reductions further, a follow up meta-analysis was conducted which performed sub-analyses on eleven studies, included in Chapter 2 of this thesis. The meta-analysis by Inder et al. (2016) confirmed that IRT lowers SBP, DBP and MAP, with a large effect in hypertensive males aged 45 years and over using unilateral isometric handgrip exercise for eight weeks or longer.

1.2.4 Responses to Isometric Resistance Training and Potential Mechanisms of Action

A few researchers have published review papers which have examined and compared published IRT studies, some in conjunction with their own research, which provide valuable insight into the effect of isometric resistance training on blood pressure. Studies indicate that IRT of eight weeks or longer promotes significant reductions in SBP and MAP with minimal changes in DBP and HR (Wiley et al., 1992; Taylor et al., 2003; Millar et al., 2013). There is minimal research into the cardiovascular

effects during IRT; however, an early study by Bakke et al. (2007) indicates increases in SBP, MAP and HR but not BP during IRT.

Chrysant (2010) performed a Medline search between 2000 and 2009 and reported on 6 studies which included normotensive and hypertensive participants. Chrysant (2010) noted that heart rate, blood pressure and cardiac output increased immediately in response to isometric exercise in normotensive and hypertensive participants, with no increase in peripheral vascular resistance, which he attributes to vagal withdrawal. Increases in blood pressure returned to baseline levels quickly after completion of isometric exercise, suggesting that repetitive isometric exercise may lead to baroreceptor resetting, lowering blood pressure, and enhancing antihypertensive medication actions (Chrysant, 2010).

Acute cardiovascular and cardiac autonomic responses with IRT in healthy participants vary according to IRT intensities and rest period frequency and duration; however, SBP recovery appeared to not be affected by intensity and rest periods (Millar, MacDonald & McCartney, 2011). Stiller-Moldovan et al. (2012) found that eight weeks of IRT did not lower resting or ambulatory blood pressure, or improve heart rate variability, in hypertensive participants who were medicated with baseline blood pressure $\leq 120/80$ mmHg. Millar et al. (2014) conducted a PubMed search and identified 16 studies which investigated isometric resistance training with normotensive, pre-hypertensive and hypertensive participants, utilising either handgrip or leg exercises. Reductions in blood pressure were greater in hypertensive participants, with a larger magnitude of change in those with higher baseline blood pressure (Millar et al., 2014).

A more recent updated review was conducted by Farah et al. (2017) which looked at the acute response immediately following a bout of IRT, and the chronic effects of isometric handgrip exercise on cardiovascular measures in people with hypertension. A search was conducted in the PubMed/Medline (National Library of Medicine) database of isometric handgrip studies that contained only hypertensive participants, and that evaluated at least one cardiovascular parameter (Farah et al., 2017). Farah et al. (2017) looked at two acute studies containing a total of 62 participants, and five chronic studies containing 111 participants that conducted isometric handgrip exercise for six weeks or longer. The acute studies reported varying results with one indicating that there was no post hypotension, while the other study reported increases after 60 minutes. The

study protocol was the same for four of the chronic studies and utilised 4x2min alternating isometric handgrip exercises at 30% maximum voluntary contraction, the fifth study performed 4x45sec exercises at 50% maximum voluntary contraction. The four chronic studies which performed 4x2min exercises all saw significant reductions in SBP ranging from 5-19mmHg; however, only the 4x45sec study saw a reduction in DBP. Variation in results seen by Farah et al. (2017) indicates that there are still gaps in the literature which should be explored to determine optimal exercise prescription for blood pressure management.

Kelly and Kelly (2010) mention that there were no exact mechanisms which explain the reductions in SBP and DBP from isometric handgrip exercise. Various researchers have proposed that oxidative stress and ischaemic reperfusion, sympathetic nerve activity, neurohormonal vagal control, increased systemic shear stress from increased blood pressure and cardiac output, and a possible genetic component may each affect isometric exercise impact on blood pressure (Kelly and Kelly, 2010). According to Millar et al. (2014) the mechanisms for blood pressure reductions have not been fully determined, possibly due to the small sample sizes of current studies. Either cardiac output or total peripheral resistance (or both), which affect MAP may be mechanically involved in the blood pressure reductions seen in IRT studies (Millar et al., 2014). Studies monitoring heart rate variability indicate that IRT may elicit cardiac neural adaptations in some individuals depending upon hypertension and medication status (Millar et al., 2014). Nitric oxide dependent dilatation adaptations have been observed in participants with hypertension, but not healthy participants, suggesting that improving resistance vessel function may be a possible mechanism in reducing blood pressure (Millar et al., 2014).

Heart rate variability/neural cardiac control, arterial compliance, vascular function, reduced sympathetic outflow and/or an enhanced oxidative capacity may possibly be responsible for the blood pressure lowering mechanisms of IRT (McGowan et al., 2017). Higher baseline SBP elicits the greatest reductions in blood pressure from IRT; however the effect of gender is currently unclear due to sample sizes (McGowan et al., 2017). Farah et al. (2017) suggest that future studies should look at cardiac baroreflex sensitivity, flow mediated dilation, shear stress, blood flow, arterial stiffness, ventricular function, oxidative stress and inflammatory markers in order to clarify the potential mechanisms of action of IRT.

There are concerns over participants not being blinded in isometric resistance training studies, due to do participants knowing that they are obviously not exercising if they are in a sedentary control group (Millar et al., 2014). Isometric handgrip exercise studies have predominantly used a sedentary control; however, some isometric bilateral leg exercise studies have utilised a low intensity group. Wiles et al. (2010) utilised a low intensity (approximately 10%) group in healthy participants that conducted bilateral leg exercise for 8 weeks, which saw a significant reduction in SBP and DBP. Baross et al. (2012) utilised an 8% low intensity group which saw no significant reduction in SBP, DBP or MAP after 8 weeks of bilateral leg exercises.

Research by Hess et al. (2016) looked at the effect of low intensity isometric resistance training on blood pressure to determine if a low intensity sham group would be suitable as a working control in future studies. Hess et al. (2016) utilised a 4x2min isometric handgrip exercise protocol, with participants exercising at either 5% or 10% of maximum voluntary contraction three times a week for six weeks. After six weeks of low intensity isometric resistance training there was no significant changes in SBP, DBP or heart rate for either the 5% or 10% intensity group. The research by Hess et al. (2016) indicates that a low intensity sham group may be suitable as a working control to address concerns over participant blinding and the placebo effect among participants.

There have been two recent studies published which have looked at comparison of aerobic exercise versus isometric handgrip exercise. Ash et al. (2017) recruited 11 participants, aged between 18-55 years, with pre-hypertension or stage 1 hypertension. Six of the participants conducted aerobic exercise for 45 minutes a day at 60% $VO_{2\text{ peak}}$ (peak oxygen uptake) for eight weeks, and five who conducted isometric handgrip exercise, 4x2-min at 30% MVC three days a week for eight weeks. Blood pressure measurements were conducted using ambulatory monitoring 48 hours after completing training (Ash et al., 2017). According to Ash et al. (2017) aerobic exercise reduced daytime SBP by -7.6mmHg but not DBP; however, isometric handgrip exercise saw no change in SBP but DBP increased by 5mmHg during daytime and 7mmHg during nighttime.

Pagonas et al. (2017) recruited participants aged between 41-76 years who had stage 1 hypertension, and conducted a randomised controlled trial comparing dynamic aerobic exercise, isometric handgrip training and a sham isometric handgrip training group, over 12 weeks. The aerobic exercise consisted of walking, jogging, cycling or swimming with choice of exercise left up to

the discretion of the individual participant, three to five times a week; the exercise was not structured or supervised (Pagonas et al., 2017). Isometric handgrip exercise was conducted at either 30% maximum voluntary contraction, or 5% for the sham group using a bilateral 2x2-min protocol five times a week. There is no indication in the article as to whether or not the isometric handgrip protocol was supervised. Twenty four participants performed isometric handgrip exercise, 23 performed sham handgrip exercise, and 19 performed aerobic exercise. Reported blood pressure results were measured with an ambulatory monitor; however, there is no indication as to how soon after completion of training the measurements were performed. According to Pagonas et al. (2017) there was a 1.5mmHg increase in SBP for the 30% group and a -0.6mmHg reduction in DBP, the 5% sham group saw a -1.1mmHg reduction of SBP and a -1.4mmHg reduction in DBP; none of which was significant. Aerobic exercise saw a significant reduction of -4.9mmHg in SBP and a non-significant reduction of -1.9mmHg in DBP (Pagonas et al., 2017).

The studies by Ash et al. (2017) and Pagonas et al. (2017) both utilised ambulatory blood pressure monitoring which is the current gold standard, and have explored important concepts; however there are flaws in both studies. The low numbers in the study by Ash et al. (2017) may not be a true reflection of the population, and larger participant numbers may have yielded different results. The study by Pagonas et al. (2017) needed more clarification of measurement and a supervised standardisation of participants. There is no indication of how active the participants were prior to commencement of the study, or monitoring of the isometric handgrip training. A study looking at the aspects of both of these studies, with high participant numbers and structured supervised aerobic and isometric exercise is needed to clarify the differences between modalities.

1.2.5 Inferences from Meta-analyses and Review papers

According to Owen et al. (2010) the reductions of SBP and DBP seen in their meta-analysis are comparable to those achieved by a single pharmacological intervention, and larger than those seen with regular dynamic or resistance exercise. Concerns were also raised by Owen et al. (2010) regarding muscle fatigue, publication bias due to no available studies showing no effect, possibility of the placebo effect and adherence to longer programs. There have been recent studies showing no significant changes in blood pressure, although some have seen clinically meaningful reductions of approximately 3mmHg and 4mmHg in SBP (Stiller-Moldovan et al., 2012; Pagonas et al., 2017).

The meta-analysis conducted by Inder et al. (2016) indicated that unpublished data would not change their findings of isometric resistance exercising reducing SBP, DBP and MAP.

Kelley and Kelley (2010) noted that post-IRT changes in blood pressure were clinically meaningful, with a -5mmHg reduction in SBP being associated with a decreased risk in mortality from coronary heart disease, stroke and all-causes. Kelley and Kelley (2010) indicate that further isometric exercise studies would benefit from comprising isometric, aerobic and dynamic resistance training with a control group containing sedentary participants. Cornelissen and Smart (2013) noted that there was no heterogeneity among the five isometric training groups in their meta-analysis, they also expressed concerns over participants being aware of group allocation in exercise studies, and a possible lack of follow-up in control group participants.

There is no consistency between the last exercise session and post intervention blood pressure measurements, with most being conducted between two and seven days after completing training (Millar et al. 2014). Approximately only 50% of the studies which Millar et al. (2014) looked at conducted either a randomised or cross-over design, with only one having a sham control group and no blinding of exercisers or investigators. There is a need for researchers to refine the protocols for isometric resistance training in order to develop an effective and affordable way to transition the multitude of research into general practice, which McGowan et al. (2017) are endeavouring to achieve.

1.2.6 Summary

Isometric resistance training is emerging as a potential alternative exercise in blood pressure management for people unable to conduct aerobic exercise. The growing body of evidence suggests that clinically significant reductions in blood pressure, particularly SBP, are possible with IRT. Although studies have noted that neural cardiac modulation of heart rate variability, nitric oxide adaptations, arterial compliance, vascular function and reduced sympathetic outflow are probable mechanism for these blood pressure changes, evidence suggests that more research still needs to be conducted in this area.

1.3 Blood Pressure Measurement Devices

Blood pressure measurement was traditionally conducted using a mercury sphygmomanometer, recently the use of aneroid, oscillometric and ambulatory devices have become more commonplace. The current Canadian recommended guidelines for blood pressure measurement state that the preferred method is the use of automated office blood pressure, non-automated office blood pressure, home blood pressure monitoring and ambulatory blood pressure monitoring (Leung et al., 2017). The 2017 High Blood Pressure Clinical Practice Guideline mention that auscultatory methods using a column of mercury have been superseded by oscillometric devices (Whelton et al., 2017).

Aneroid sphygmomanometers use mechanical parts to transmit the information regarding pressure in the cuff to the dial (Buchanan, Orris and Karliner, 2011). Oscillometric sphygmomanometers are automated with the cuff inflating and deflating electronically, then displaying a digital blood pressure readout (Buchanan et al., 2011). Ambulatory blood pressure devices, which employ oscillometry, are small, relatively quiet and can take blood pressure readings while individuals conduct their normal activities (Ogedegbe and Pickering, 2010). Ambulatory blood pressure monitoring is discussed in detail in the section 1.3.2.

Research into blood pressure monitoring has refined measurement procedures; however, there have been concerns over how best to assess blood pressure, particularly in relation to the accuracy of measurement and blood pressure fluctuations which occur as part of daily life (Stergiou and Parati, 2011). Every single blood pressure value indicates an index of risk; however, patterns of blood pressure over time increase the prognostic ability of blood pressure levels. Refining blood pressure measurement requires taking the aspects which may affect accurate blood pressure measurement, as listed in Table 9, into account when planning on measuring blood pressure. Standardising methods of blood pressure measurement is needed in an aim to develop multiple approaches to quantify blood pressure for more precise risk prediction (Stergiou and Parati, 2011).

Table 9: Aspects of blood pressure measurement that may influence assessment

Aspect	Different approaches affecting blood pressure measurement
Setting	Office, work, ambulatory, home
Time	Daytime, night-time, nocturnal dip, morning, evening, morning surge, postprandial
Observer	Doctor, nurse, technician, relative, self-measurement, automated
Device	Mercury, aneroid, hybrid, oscillometric
Posture	Basal, lying, seated, standing, exercise
Reading	First reading, first day, first visit, several measurements
Calculation	Average, variability, reactivity, maximum

Stergiou, G. S. and Parati, G. (2011). How to best assess blood pressure? The ongoing debate on the clinical value of blood pressure average and variability. *Hypertension*, 57, 1041-1042. Doi: 10.1161/HYPERTENSIONAHA.111.172924

Blood pressure measurement is generally taken at the brachial artery; however, monitors are available that take measurements at the wrist and finger. Systolic and diastolic pressures vary throughout the arterial tree; with systolic increasing and diastolic decreasing the more distal they are to the heart (Ogedegbe & Pickering, 2010). The mercury sphygmomanometer was widely regarded as the gold standard for office blood pressure measurement and has been used for over 100 years (Ogedegbe & Pickering, 2010; Buchanan et al., 2011). Recent concerns over the toxicity of mercury have contributed to the development of aneroid and oscillometric blood pressure devices, with the use of mercury devices diminishing and slowly being phased out (Buchanan et al., 2011; Drawz et al., 2012).

Accurate blood pressure measurements are vital to patient care, so it is imperative that measurements taken with alternative devices are correct. Mercury devices can be up to 28% inaccurate if not regularly calibrated, newer aneroid devices that undergo regular calibration are generally equally or more accurate than mercury devices (Buchanan et al., 2011). Oscillometric devices are popular for home use; however, many are not validated by the manufacturers so it is important for people to ensure that they purchase a validated device (Buchanan et al., 2011). Errors relating to defective devices, improper techniques, and observer bias can result in an overestimation or underestimation of a person's true blood pressure (Head et al., 2012). Automated blood pressure monitors, which also employ oscillometry, are now available that can be programmed to measure blood pressure at intervals, allowing several readings to be taken whilst

the observer leaves the room to minimise white coat effect during clinic measurement (Drawz, et al., 2012; Myers, 2014).

1.3.1 Sphygmomanometry and Oscillometry

The most common blood pressure measurement was by auscultation using a mercury sphygmomanometer and stethoscope listening for Korotkoff sounds, the common alternatives to these are aneroid and oscillometric devices (Buchanan et al., 2011). Aneroid sphygmomanometers have mechanical parts which transmit pressure in the cuff to a dial, while the observer manually inflates and deflates the cuff and uses auscultatory techniques to determine systolic and diastolic pressures (Buchanan et al., 2011). Korotkoff sounds are used to detect the values of SBP and DBP by noting when they appear and disappear, respectively; generally by listening to the turbulence of blood flow at the brachial artery through a stethoscope while an inflated sphygmomanometer cuff is being deflated (Ramakrishnan, 2016).

Oscillometric devices are automatic, inflate and deflate the cuff electronically, calculating the systolic and diastolic pressure using an algorithm (Buchanan et al., 2011). The algorithms used in an automated oscillometric device can provide questionable SBP and DBP estimates because they are sensitive to differences in pulse pressure and artery stiffness (Babbs, 2012). Automated oscillometric sphygmomanometers such as the BpTRU are validated for accuracy by the manufacturer, have been specifically designed for recording office blood pressure, and are able to record multiple readings at one minute intervals while patients rest quietly on their own (Myers, 2014).

Williams, Brown and Conlin (2009) suggests that to enable accurate auscultatory measurement the room used should be quiet, a comfortable ambient temperature, and the patient should not have exercised, used tobacco, ingested caffeine or eaten within 30mins prior to blood pressure measurement. The patient should be seated with their feet on the ground and legs uncrossed, the arm used for measurement should be bare, supported and at heart level (Williams et al., 2009). Correct cuff size and positioning are imperative for accurate measurement, the cuff should be approximately 2cm above the elbow crease with the midline over the brachial artery, and the cuff should be snug but able to slide two fingers underneath it (Williams et al., 2009).

A constant deflation rate of 2mmHg/sec is the current recommended guideline when measuring blood pressure (Cahan et al., 2012). Cahan et al. (2012) note that there is a maximal error when measuring systolic blood pressure (SBP) of -1.5mmHg at heart rate (HR) of 120 beats per minute (bpm), and -4.3mmHg at HR of 40bpm. Diastolic measurements have a maximal error of +1.4mmHg at HR of 120bpm and +4.3mmHg at 40bpm, indicating that heart rate can affect an individual's blood pressure measurement (Cahan et al., 2012). Clinical conditions including arrhythmias, dysrhythmias, irregularity of timing of Korotkoff sounds due to atrial fibrillation, and atherosclerotic vascular disease can decrease the accuracy of blood pressure measurements (Williams et al., 2009).

According to Babbs (2015) there is uncertainty as to the end point of diastolic pressure, and whether it should be taken as the point where the Korotkoff sounds become muffled, or when they disappear. The difference between muffling and disappearance of sounds can be as much as 10mmHg; this can be quite contentious when it comes to diagnosis and treatment of hypertension (Babbs, 2015). Babbs (2015) determined that cuff size, deflation rate, the starting point for deflation, psychological factors, arm elevation and tension, atrial fibrillation, type of manometer and stethoscope used can affect the accuracy of blood pressure measurement.

Similar concerns of accurate diastolic blood pressure measures relating to the interpretation of Korotkoff sounds including reactions to auditory cues, auscultation method (diaphragm vs bell of stethoscope), deflation rate and cuff size were noted by Tolonen et al. (2015) and Williams et al. (2009). According to Ruiz-Rodriguez et al. (2013) there is a tendency for DBP to be overestimated during auscultatory measurement. High DBP measurements have also been known to be attributed to slow deflation rates causing venous congestion, phasic changes in arterial pressure, or faint Korotkoff sounds (Ogedegbe & Pickering, 2010). The involvement of a person being present and responsible for manual sphygmomanometer measurements can result in inaccurate measurements due to inability to follow guidelines, conversation with the patient, or rounding the reading to the nearest zero (Myers, 2014).

1.3.2 Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring over a 24 hour period has recently become the gold standard for blood pressure measurement (Pickering, Eguchi & Kario, 2007; Myers, 2014; Leung et al., 2017). The reliability and validity of ambulatory devices is imperative to ensure accurate blood

pressure measurement. Pang and Brown (2006) conducted an analysis of data from 683 patients who had 4 auscultatory and 3 ambulatory measurements taken on the same arm by highly trained nurses. There was no significant difference between SBP and DBP which saw differences of 1mmHg and 2mmHg respectively, meeting the British Hypertension Society and AAMI criteria for accuracy and reliability (Pang and Brown, 2006). Differences in ambulatory monitor devices and study methodologies make it difficult to compare reliability and validity of individual devices. Pang and Brown (2006) also found that patient characteristics including age, gender and arm circumference can affect the agreement between measurement devices, affecting determination of validity.

Current diagnosis and monitoring of hypertension relies heavily on correct blood pressure measurements; recent evidence indicates that measurements taken in the individual's home, with either a home device or by ambulatory monitoring, better represents patients' actual blood pressure (Head et al., 2012; Pang & Brown, 2006). True blood pressure is recognised as mean blood pressure measurements over a period of time in a person's natural environment, and is better recorded using ambulatory monitoring (Wang et al., 2017). Ambulatory blood pressure monitoring enables normotension and hypertension to be assessed individually using both clinical and ambulatory measurement (Pickering, Davidson, Gerin and Schwartz, 2002). Pickering et al. (2002) indicated that individuals who are normotensive by both methods are true normotensives, while those that are hypertensive with both methods are true hypertensives. Individuals who are hypertensive with clinic measurements and normotensive with ambulatory have white-coat hypertension, while those that are normotensive in the clinic and hypertensive with ambulatory measurement have masked hypertension (Pickering et al., 2002; Booth et al., 2016).

White-coat and masked hypertension, as well as the extent of nocturnal dipping are able to be observed with ambulatory monitoring to assist with patient prognosis (Head, et al., 2012; Mancia & Verdecchia, 2015). According to Mancia and Verdecchia (2015) nocturnal dipping should see a drop in SBP during sleep $\geq 10\%$ from baseline or average daytime measurements, individuals who have a decrease in night-time blood pressure $< 10\%$ of baseline or average daytime measurements are classified as nondippers. Blood pressure should lower during the night whilst individuals are asleep, nocturnal nondipping is associated with increased risk of stroke, end-organ damage and cardiovascular events as well as the possibility of sleep apnoea or diabetes (Head et al., 2012; O'Flynn et al., 2015; Mancia & Verdecchia, 2015).

Twenty four hour ambulatory blood pressure monitoring is a strong predictor of clinical outcomes such as left ventricular hypertrophy, renal and vascular surrogate markers of end-organ damage, and presence or absence of nocturnal blood pressure dipping (Myers, 2005; Head et al., 2012; Mancia & Verdecchia, 2015). Incidence of myocardial infarction, stroke and sudden death peak in the first part of the morning, due to a sharp increase in blood pressure and heart rate, as well as sympathetic action which increases catecholamine levels in blood plasma (Mancia & Verdecchia, 2015). Blood pressure follows a distinct circadian rhythm, it declines whilst sleeping, then during the period from night to early morning there is a marked increase in blood pressure, known as morning surge (White, 2010; Kario, 2010). Ambulatory monitoring may assist with assessing risk of morning surge; however, as less frequent measures are generally taken during the night, the period immediately prior to arousal may not be detected.

Currently there is no set guideline for timing of blood pressure measurements using ambulatory monitoring. In the analysis conducted by Cahan and colleagues (2012) an ambulatory monitor was mounted on the non-dominant arm of participants between 8:00am and 10:00am and removed 24 hours later. Cuff size was determined by measuring the arm circumference, and blood pressure was measured every 20 minutes between 6:00 am and midnight, and every 30 minutes between midnight and 6:00am (Cahan et al., 2012). A Y-connector was used to attach a mercury sphygmomanometer to the ambulatory monitor, to verify the measurements (within 5mmHg), when initially placed on the participant (Cahan et al., 2012). According to Head et al. (2012) a cuff is placed on the upper arm and the ambulatory blood pressure device should be worn for 24 hours, with blood pressure measured every 15-30 minutes during the day and every 30-60 minutes overnight. The data is downloaded to a computer and used to assess systolic and diastolic blood pressure during the patients' usual daytime activities and during sleep. Ciolac et al. (2008) monitored ambulatory blood pressure after participants had conducted an exercise program, the monitor was set to record daytime blood pressure every 15 mins and night-time every 20 mins, based on getting in and out of bed. The participants in the study conducted by Ciolac et al. (2008) were instructed to maintain their normal routine, avoid formal physical activity, and to relax and straighten their arm when the monitor was recording blood pressure. Inflation of the blood pressure cuff can be inhibited if the person is moving their arm around or engaging in activity during inflation, this can result in erroneous and/or missing values.

Recent research has looked at the comparison of ambulatory monitoring to clinic and home blood pressure measurements. Twenty four hour ambulatory and home monitoring are currently recommended for diagnosing and managing hypertension (Myers, 2014; Leung et al., 2017). Myers did a comparison of three studies and found that daytime ambulatory blood pressure was significantly correlated with automated office blood pressure (AOBP), but not with routine manual office blood pressure, which was higher than both daytime ambulatory and AOBP. Banegas et al. (2017) analysed data from over 100,000 hypertensive individuals who had blood pressure measured with a manual sphygmomanometer and 24 hour ambulatory monitoring, with the monitor set to record every 20 minutes. Banegas and colleagues (2017) found that daytime ambulatory blood pressure was significantly lower than mean clinic SBP and DBP for > 95% of patients, white coat frequency was 36.7%, and masked hypertension was seen in 23% of treated patients with blood pressure between 130-139mmHg. In contrast, Juhanaja et al. (2015) compared ambulatory, home and office blood pressure in 461 participants and found that daytime ambulatory systolic and diastolic blood pressure was higher than home or office blood pressure.

The consensus statement developed by the Ambulatory Blood Pressure Monitoring Working Group, National Heart Foundation of Australia, National Blood Pressure and Vascular Disease Advisory Committee and the High Blood Pressure Research Council of Australia (HBPRCA) has determined differing blood pressure measurements for clinic and ambulatory blood pressure measurements shown in Tables 10 and 11 below (Head et al., 2012). The National Heart Foundation of Australia determined blood pressure guidelines in 2016 as listed in Table 12.

Table10: Australian hypertension classification in adults

Hypertension thresholds	Clinic BP (mmHg)	ABP predicted from clinic BP(mmHg)		
		24-h	Night	Day
Grade 3 (Severe)	180/110	163/101	157/93	168/105
Grade 2 (Moderate)	160/100	148/93	139/84	152/96
Grade 1 (Mild)	140/90	133/84	121/76	136/87

ABP – ambulatory blood pressure; BP – blood pressure; h – hour
 Head et al. (2012). Ambulatory blood pressure monitoring in Australia: 2011 consensus position statement. *J Hypertens*, 30(2), 253-266.
 doi:10.1097/HJH.0b013e32834de621

Table 11: Ambulatory blood pressure thresholds for hypertension in Australia

Time period	Blood pressure (mmHg)
24-h average	130/80
Daytime average	135/85
Night-time average	120/70

Head et al. (2012). Ambulatory blood pressure monitoring in Australia: 2011 consensus position statement. *J Hypertens*, 30(2), 253-266. doi:10.1097/HJH.0b013e32834de621

The 2013 ESH/ESC guidelines for the management of arterial hypertension state that although ambulatory blood pressure monitors are effective for determining blood pressure variability, morning blood pressure surge, blood pressure load and ambulatory arterial stiffness index, their predictive value is unclear and should only be regarded as experimental (Mancia et al., 2013). Hypertension was defined by the 2013 ESH/ESC guidelines as the same measurements indicated by the National Heart Foundation of Australia in Table 12.

Table 12: National Heart Foundation of Australia guideline for hypertension diagnosis

Method of Measurement	Systolic (mmHg)		Diastolic (mmHg)
Clinic Blood Pressure	≥ 140	and/or	≥ 90
ABPM daytime (awake)	≥ 135	and/or	≥ 85
ABPM night-time (asleep)	≥ 120	and/or	≥ 70
ABPM over 24 hours	≥ 130	and/or	≥ 80
HBPM	≥ 135	and/or	≥ 85

ABPM – ambulatory blood pressure monitoring; HBPM – home blood pressure monitoring
National heart foundation of Australia. Guidelines for the diagnosis and management of hypertension in adults – 2016. (2016). Melbourne, National heart foundation of Australia. Retrieved on 24/9/2017 from https://www.heartfoundation.org.au/images/uploads/publications/PRO-167_Hypertension-guideline-2016_WEB.pdf

1.3.3 Finometer®

Finometer® is a low risk, non-invasive, photoplethysmographic, haemodynamic instrument which measures blood pressure by continuously monitoring finger arterial pressure (Bakke, Hisdal, Kroese, Jørgensen, & Strandén, 2007). Blood pressure measurement in the finger is based on the arterial volume-clamp method introduced by Penaz of ‘dynamic pulsatile unloading of the finger arterial walls’ (Bogert & van Lieshout, 2005). This method involves a cuff being wrapped around the finger which keeps the diameter of the artery clamped at a constant diameter despite the changes in arterial pressure which occur during each heart beat (Truijen, van Lieshout, Wesselink, &

Westerhof, 2012). The finger cuff contains a photoplethysmograph which has 'a light source on one side of the cuff and infrared receiver on the opposite side' (Chung, Chen, Alexander, & Cannesson, 2013), this estimates blood volume using infrared light absorbance. A feedback loop adjusts the finger cuff to maintain constant blood volume, resulting in vascular unloading: maintaining the artery at its unloaded volume reduces tension in the wall of the artery (Chung et al., 2013).

A servo-controller connects to the finger cuff and is attached to the wrist for the continuous adjustment of cuff pressure (Imholz, Wieling, van Montfrans, & Wesseling, 1998). The servo-controller increases cuff pressure when arterial volume is increased during systole, to prevent volume change. The unloaded volume is determined by physiological calibration (Physiocal) from analysing the shape and magnitude of the plethysmogram signals during short periods of steady cuff pressure levels (Truijen et al., 2012). Measurement of blood pressure is temporarily interrupted, due to the cuff pressure being kept constant at regular intervals, to adjust the correct unloaded diameter of the artery based on the signal from the plethysmograph and analysis by the Physiocal algorithm. According to Truijen et al. (2012) Physiocal calibrations with an interval of 30 or more beats is acceptable for a reliable measurement.

The clinical standard for blood pressure measurement is in the brachial artery; finger arterial pressure tends to be lower than brachial as a result of the differences in pressure gradient, and the 'narrowing of the arteries towards the periphery' (Bogert & van Lieshout, 2005). Correction for the pressure gradient using an upper arm cuff and height adjusting component in the Finometer® reconstructs brachial artery pressure from the finger artery pressure (Truijen et al., 2012). This reduces pressure differences, meeting the American Association for the Advancement of Medical Instrumentation (AAMI) criteria (Bogert & van Lieshout, 2005). The Finometer® also has a beatscope software program which enables the beat-to-beat analysis of the raw finger arterial pressure signal. As well as measuring continuous blood pressure, and heart rate, beatscope software has the ability to perform a comprehensive haemodynamic analysis including mean arterial pressure, cardiac output, stroke volume, and total peripheral resistance.

Bakke and colleagues (2007) used a Finometer® to monitor beat-to-beat mean arterial pressure during their study which looked at the blood pressure response to isometric exercise in patients with peripheral atherosclerotic disease. A Finometer® was also used by Hisdal and colleagues

(2004) to measure blood pressure and MAP during their study into regulation of arterial blood pressure during isometric muscle contraction. Schutte and colleagues (2004) conducted a study with 102 participants to validate the Finometer® which indicated there was a high level of reliability, with minimal differences of 1.83mmHg for SBP and 0.88mmHg for DBP when compared to a mercury sphygmomanometer.

The Finometer® was used in this research due to concerns raised about the safety of people with hypertension conducting IRT and there being no published information on the cardiovascular effects during isometric exercise. Although previous researchers had used a Finometer® during their protocol they did not address the effect of IRT on RPP during exercise (Bakke et al., 2007; Schutte et al., 2004). Utilising the Finometer® to monitor beat-to-beat fluctuations in participants' blood pressure and heart rate enabled the determination of peak blood pressure and heart rate. Concerns over the accuracy of the Finometer® prompted the recording of resting sphygmomanometer measurements to validate the accuracy of the Finometer® measurements. Due to 24 hour ambulatory monitoring being the recommended gold standard for blood pressure measurement, the purchase of monitors was requested. An additional study was conducted to look at the effects of IRT on 24 hour ambulatory blood pressure.

1.3.4 Summary

Automated and ambulatory blood pressure measuring devices are becoming more commonly used for monitoring blood pressure in patients with hypertension, compared to traditional use of mercury sphygmomanometers. Measurement procedures have been refined due to research; however, measurement accuracy is imperative when determining blood pressure status for cardiovascular risk. Sphygmomanometry and oscillometry measurements are still commonly used, with automated oscillometry devices often used for home monitoring. Ambulatory blood pressure monitoring over a 24 hour period is the current gold standard in blood pressure measurement. Ambulatory monitoring enables the measurement of a patients actual/true blood pressure in their environment, which can be useful for diagnosing white-coat and masked hypertension, and determining cardiovascular risk. The Finometer® is a non-invasive instrument which measures beat-to-beat blood pressure in a patients finger, which may be beneficial in some research studies.

1.4 Summary Outlining the Research Questions

The gaps in the literature which were fundamental to the research decisions included the need to conduct an isometric resistance training (IRT) study increasing the length of duration conducted by previous researchers. Concerns over the hypertensive responses during isometric resistance training had not been previously investigated, and use of the Finometer® to do so was contentious due the lack of evidence to validate the accuracy of the Finometer®. The use of 24hr ambulatory blood pressure monitoring as the gold standard in determining cardiovascular risk had not previously been conducted in isometric resistance training, so conducting the longest study with 24hr ambulatory monitoring addresses a large gap in the literature.

The aim of this thesis is to investigate the efficacy of conducting isometric resistance training for blood pressure management. The thesis comprises five chapters either already published, or under review with publishers, which address the following research questions:

1. To what extent does isometric resistance training affect systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and mean arterial pressure (MAP); and which patient demographics and exercise program characteristics exhibited the largest changes?
2. Is IRT utilising handgrip exercise effective for blood pressure management in individuals aged between 35 and 70 years with hypertension; and is a low intensity (5% MVC) group suitable for use as a working control?
3. What effect does IRT conducted over 12 weeks have on 24 hour ambulatory blood pressure in individuals aged between 30 and 70 years who are pre-hypertensive or have stage 1 hypertension? Is there a detraining effect on blood pressure after ceasing IRT?
4. What is the peak SBP, DBP, HR, MAP and subsequent rate pressure product during isometric handgrip exercise in both healthy normotensive individuals and those with pre-hypertension.
5. How accurate are SBP and DBP measurements recorded by the Finometer® compared to those from an aneroid sphygmomanometer; and how much variability is there in these compared to ambulatory blood pressure measurements?

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Chapter 2: Isometric exercise training for blood pressure management: A systematic review and meta-analysis to optimize benefit.

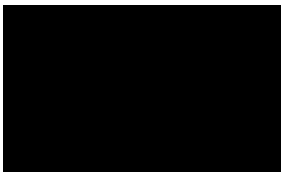
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Published in Hypertension Research

Citation: Inder, J.D., **Carlson, D.J.**, Dieberg, G. McFarlane, J.R. and Smart N.A. Isometric exercise training for blood pressure management: a systematic review and meta-analysis to optimize benefit. Hypertension Research, 2016, 39, 88-94.
Doi:10.1038/hr.2015.111



Candidate Signature



Principal Supervisor Signature

ORIGINAL ARTICLE

Isometric exercise training for blood pressure management: a systematic review and meta-analysis to optimize benefit

Jodie D Inder, Deborah J Carlson, Gudrun Dieberg, James R McFarlane, Nicole CL Hess and Neil A Smart

The objective of our study was to examine the effects of isometric resistance training (IRT) on resting blood pressure in adults. We conducted a systematic review and meta-analysis of randomized-controlled trials lasting ≥ 2 weeks, investigating the effects of isometric exercise on blood pressure in healthy adults (aged ≥ 18 years), published in a peer-reviewed journal between 1 January 1966 to 31 January 2015. We included 11 randomized trials, totaling 302 participants. The following reductions were observed after isometric exercise training; systolic blood pressure (SBP) mean difference (MD) -5.20 mm Hg (95% confidence interval (CI) -6.08 to -4.33 , $P < 0.00001$); diastolic blood pressure (DBP) MD -3.91 mm Hg (95% CI -5.68 to -2.14 , $P < 0.0001$); and mean arterial blood pressure (MAP) MD -3.33 mm Hg (95% CI -4.01 to -2.66 , $P < 0.00001$). Sub-analyses showed males tended to reduce MAP MD -4.13 mm Hg (95% CI -5.08 to -3.18) more than females. Subjects aged ≥ 45 years demonstrated larger reductions in MAP MD -5.51 mm Hg (95% CI -6.95 to -4.06) than those < 45 years. Subjects undertaking ≥ 8 weeks of IRT demonstrated a larger reduction in SBP MD -7.26 mm Hg (95% CI -8.47 to -6.04) and MAP MD -4.22 mm Hg (95% CI -5.08 to -3.37) than those undertaking < 8 weeks. Hypertensive participants in IRT demonstrated a larger reduction in MAP MD -5.91 mm Hg (95% CI -7.94 to -3.87) than normotensive participants MD -3.01 mm Hg (95% CI -3.73 to -2.29). Our study indicated that IRT lowers SBP, DBP and MAP. The magnitude of effect may be larger in hypertensive males aged ≥ 45 years, using unilateral arm IRT for > 8 weeks.

Hypertension Research (2016) 39, 88–94; doi:10.1038/hr.2015.111; published online 15 October 2015

Keywords: blood pressure; isometric exercise training; meta-analysis

INTRODUCTION

In light of the prevalence of hypertension¹ the associated economic health-care costs are significant. In addition, although anti-hypertensive medications generally have minimal side-effect, they are perhaps efficacious in 50% of those prescribed treatment.² Both European and North American treatment guidelines for primary and secondary prevention of hypertension recommend non-pharmacological lifestyle modifications as the first line of therapy, including increasing levels of physical activity.^{3,4} There is Class I, Level B evidence that 150 min weekly physical activity offers an alternative that may be used to complement anti-hypertensive medication,⁵ although optimal exercise training prescription remains unclear.

One important factor that may impact the effectiveness to lower blood pressure (BP) is the type of exercise performed. Recent analyses suggest isometric exercise may elicit BP reductions greater than those seen with dynamic aerobic and resistance exercise.^{6–8} Currently, dynamic aerobic endurance activity is the preferred exercise modality for BP management. However, adherence to aerobic exercise is often sub-optimal.⁹ Isometric exercise involves sustained contraction against an immovable load or resistance with no or minimal change in length

of the involved muscle group. Aerobic exercise performance has been shown to be inversely related to hemodynamic measurements,¹⁰ similarly isometric activity has previously been associated with exaggerated hypertensive responses. Recent work has, however, suggested isometric handgrip activity may become a new tool in the non-pharmacological treatment of high BP.^{11,12} Previous meta-analyses have examined effects of endurance training,¹³ dynamic resistance training^{14,15} and isometric resistance training (IRT) on BP.¹² The findings showed that isometric resistance exercise does lower BP; however, the sample sizes of the trials to date are generally small. Recently, several isometric exercise training trials have been published that necessitate an updated search and for the first time sub-analyses of patient and exercise program characteristics that optimize anti-hypertensive effects. Our meta-analysis is the first to examine which patient or exercise program characteristics are most likely to produce anti-hypertensive effects.

The aims of this work were: (i) to conduct a systematic review and meta-analysis quantifying the effects of IRT on the change in systolic BP (SBP), diastolic BP (DBP) and mean arterial pressure (MAP) in adults and (ii) to conduct sub-analyses to examine which patient

demographics and exercise program characteristics exhibited the largest BP changes.

METHODS

Search strategy

Potential studies were identified by conducting a systematic search using Pub Med, www.ncbi.nlm.nih.gov/pubmed (1 January 1966 to 31 January 2015), the Pub Med search strategy can be seen in the Supplementary Files (Supplementary Figure S1). CINAHL and the Cochrane controlled trials registry were also searched (1966–31 January 2015). The search strategy included the key concepts of hypertension, BP, isometric exercise, IRT, physical training and exercise training. These were combined with a sensitive search strategy to identify randomized-controlled and crossover trials. Reference lists of papers found were scrutinized for new references. All identified papers were assessed independently by two reviewers (JDI and GD), a third reviewer (NAS) was consulted to resolve disputes. Searches of published papers were also conducted up until 31 January 2015.

Inclusions

Randomized, controlled trials and cross-over studies of isometric exercise training in adults were included. There were no language restrictions.

Exclusions

Animal studies, review papers, acute exercise studies and non-randomized controlled trials were excluded. Studies that did not have any of the desired outcome measures or a sedentary control group were excluded. Several authors were contacted to provide missing data or to clarify if data were duplicated in multiple publications. Incomplete data, or data from an already included study, were excluded. Studies using interventions other than pure isometric exercise (for example, aerobic or dynamic resistance exercise) were excluded.

Studies included in the review

Our initial search identified 1288 manuscripts, examination of the latest editions of relevant journals yielded a further 2 manuscripts. Out of 1290 studies, 368 were excluded at first inspection as duplicates, 152 were removed after reading titles or abstracts, 598 studies were not trials of isometric exercise therapy adults, leaving 172 studies; 159 were not randomized-controlled trials with a duration of 2 weeks or longer and 2 others were excluded because of data duplication, leaving 11 included studies (14 intervention groups as 3 studies had more than 1 intervention group) for analysis (see Figure 1).

Data synthesis

Information on outcome measures was archived in a database. The outcome measures were SBP, DBP, MAP (which was calculated by study authors by adding diastolic plus one-third pulse pressure) and heart rate.

Statistical analysis

Meta-analyses were completed for continuous data by using the change in the mean and standard deviation of outcome measures. It is an accepted practice to only use post-intervention data for meta-analysis but this method assumes that random allocation of participants always creates intervention groups matched at baseline for age, disease severity and so on. Change in post-intervention mean was calculated by subtracting baseline from post-intervention values. Change in the standard deviation of post-intervention outcomes was calculated by using Revman 5.2 (Nordic Cochrane Centre, Copenhagen, Denmark). Data required was either (i) 95% confidence interval data for pre–post intervention change for each group, or when this was unavailable, (ii) actual *P*-values for pre–post intervention change for each group, or if only the level of statistical significance was available (iii) we tried, where possible, to obtain precise *P*-values (for example, $P=0.034$) or 95% confidence intervals from authors. We attempted where possible to obtain these precise data, but if these data were not forthcoming then we used default *P*-values, for example, $P<0.05$ becomes $P=0.049$, and P = not significant becomes $P=0.05$. We conducted analyses for

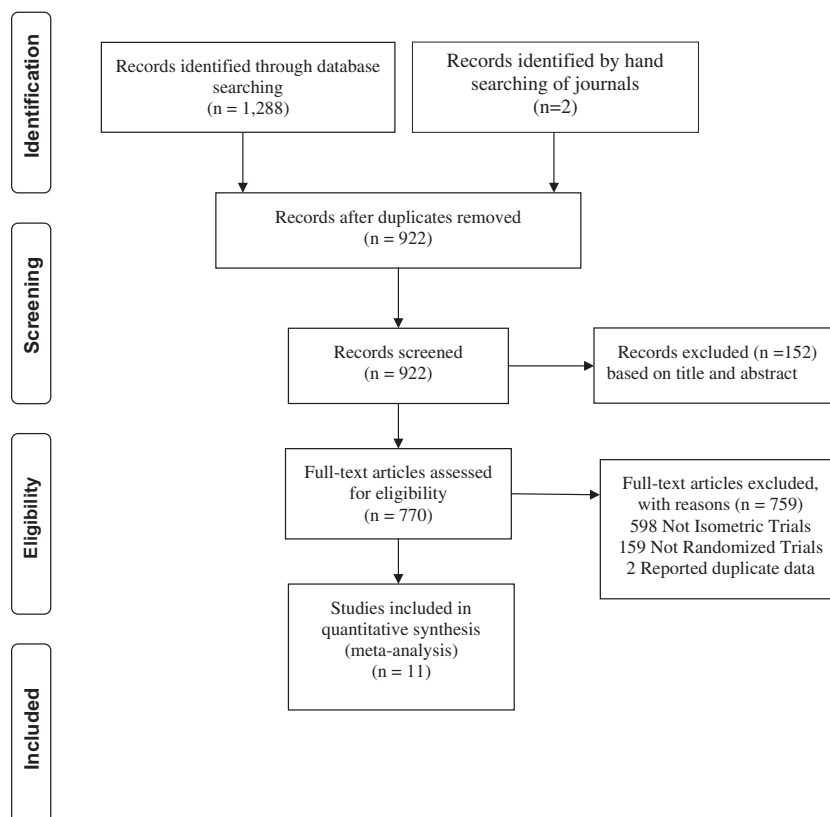


Figure 1 Consort statement.

SBP, DBP and MAP. We also conducted the following sub-analyses; male vs female, age ≥ 45 vs < 45 years, intervention > 8 weeks vs ≤ 8 weeks, unilateral vs bilateral limb IRT, arm vs leg IRT and hypertensive vs normotensive. The BP results represent the net effect or the change in the exercising group, minus the change in the control group, described as the mean difference (MD). A fixed effects model was used unless heterogeneity was $> 75\%$, in which case a random effects inverse variance was used with the effects measure of MD, which indicates which group, if any, shows a benefit, so the analysis is two-tailed. We examined whether the 95% CIs overlapped between sub-groups; if not, then this indicated a significant difference between sub-groups.

Heterogeneity was quantified using the Cochrane Q test.¹⁶ Egger plots were provided to assess the risk of publication bias. Study quality was assessed by

using the TESTEX scale (maximum score = 15).¹⁷ We used a 5% level of significance and 95% confidence intervals; all figures were produced using Revman 5.2. A PRISMA statement can be seen in the Supplementary Files.

RESULTS

Eleven studies^{18–28} were included in our analysis, totaling 302 participants (Table 1). Ten studies are RCTs and one crossover study by Devereux *et al.*²² which reported baseline BP before randomization. Six studies used handgrip and five studies used leg exercise. None of the studies reported any adverse events from isometric exercise. Six studies used automated BP measurements, two others used Doppler

Table 1 Characteristics of included studies

Study and country	Duration (weeks)	Participants	Withdrawal	Frequency	Exercise training characteristics
Badrov <i>et al.</i> ¹⁸ Canada	8	Women ($n=36$) 16–32 years	3 controls 1 5x/week	3/5 Days per week	4 × 2 min unilateral IHG contractions at 30% MVC, separated by 4 min of rest. All contractions in non-dominant hand. 3 × per week group ($n=12$), 5 × per week group ($n=11$), controls ($n=9$).
Badrov <i>et al.</i> ¹⁹ Canada	10	Men ($n=13$) Women ($n=11$) 51–74 years Hypertensive medicated	None	3 Days per week	4 × 2 min IHG bilateral contractions at 30% MVC, separated by 1-min rest periods ($n=12$) Non-exercising controls ($n=12$), no intervention. Participants recorded any changes in exercise, diet and medication.
Baross <i>et al.</i> ²¹ UK	8	Men ($n=30$) 45–60 years	None	3 Days per week	4 × 2 min double-leg extension isometric exercises at 14% MVC, separated by 2-min rest periods. 14% MVC ($n=10$); 8% MVC ($n=10$). Controls remained sedentary ($n=10$).
Baross <i>et al.</i> ²⁰ UK	8	Men ($n=20$) 45–60 years	None	3 Days per week	4 × 2 min double-leg extension isometric exercises at 85% HR _{peak} , separated by 2-min rest periods ($n=10$). Controls remained sedentary ($n=10$).
Devereux <i>et al.</i> ²² UK	4	Men ($n=13$) 21.0 ± 2.4 years	Unknown	3 Days per week	Four × 2 min bilateral leg isometric exercise at 95% HR _{peak} , separated by 3-min rest periods. No control group.
Gill <i>et al.</i> ²³ USA	3	Men ($n=11$) Women ($n=29$) 22.3 ± 3.4 years	5	3 Days per week	4 × 2 min bilateral leg isometric exercise, separated by 3-min rest periods. 20% EMG _{peak} –23% MVC ($n=8$); 30% EMG _{peak} –34% MVC ($n=9$). Controls ($n=18$), no intervention.
Millar <i>et al.</i> ²⁴ Canada	8	Men ($n=21$) Women ($n=28$) 66.4 ± 0.9 years	None	3 Days per week	4 × 2 min alternating bilateral IHG contractions at 30–40% MVC, separated by 1-min rest periods ($n=25$). Controls ($n=24$) engaged in a brief (10 min) weekly one-on-one session relating to hypertension.
Stiller-Moldovan <i>et al.</i> ²⁵ Canada	8	Men ($n=10$) Women ($n=10$) 60.0 ± 8.5 years Control 62.7 ± 6.1 years Hypertensive medicated	$n=25$ 2 Training 3 Controls	3 Days per week	4 × 2 min alternating IHG contractions at 30% MVC, separated by 1-min rest periods ($n=11$). Controls ($n=9$). *Numbers of participants does not include dropouts
Taylor <i>et al.</i> ²⁶ Canada	10	Men ($n=10$) Women ($n=7$) 60–80 years ($\bar{x} = 67.5$) Hypertensive medicated	Unknown	3 Days per week	4 × 2 min IHG contractions at 30% MVC using alternate hands, separated by 1-min rest periods ($n=9$). Controls ($n=8$).
Wiles <i>et al.</i> ²⁷ UK	8	Men ($n=33$) 18–34 years	None	3 Days per week	4 × 2 min double-leg extension isometric exercise, separated by 2-min rest periods. HI—95% HR _{peak} –21% MVC ($n=11$); LO—75% HR _{peak} –10% MVC ($n=11$). Controls ($n=11$).
Wiley <i>et al.</i> ²⁸ USA	8	$n=20$ 20–35 years	2 Training 3 Controls	3 Days per week	4 × 2 min unilateral IHG contractions at 30% of MVC, separated by 3-min rest periods. Contractions completed in dominant arm ($n=8$). Controls ($n=7$ after 3 dropped out).

Abbreviations: EMG, electromyography; HI, high; HR, heart rate; IHG, isometric handgrip; LO, low; MVC, maximum voluntary contraction.

analyses and three used auscultation, but methods were not otherwise standardized. The study by Stiller-Moldovan *et al.*²⁵ is the only work to report both single and ambulatory BP measurements.

Primary analyses

SBP was significantly reduced with a MD of -5.20 mm Hg (95% CI -6.08 to -4.33, $P < 0.00001$, $I^2 = 71%$; see Figure 2).

DBP was significantly reduced with a MD of -3.91 mm Hg (95% CI -5.68 to -2.14, $P < 0.0001$, $I^2 = 86%$; see Figure 3).

MAP was reduced with a MD of -3.33 mm Hg (95% CI -4.01 to -2.66, $P < 0.00001$, $I^2 = 61%$; see Figure 4).

Heart rate (beats min^{-1}) was significantly reduced by a MD of -1.42 beats min^{-1} (95% CI -2.64, -0.20, $P = 0.02$, $I^2 = 77%$; see Figure 5).

Sub-analyses

Sub-analyses are shown in Table 2. Please note results in bold identify significant differences between sub-groups.

Gender. Males tended to reduce MAP more than females with MD -4.13 mm Hg (95% CI -5.08 to -3.18, $I^2 = 0%$) vs females MD

-2.29 mm Hg (95% CI -3.87 to -0.71, $I^2 = 0%$), noting 95% CIs overlap slightly. No significant differences for change in SBP, DBP or heart rate were observed in males vs females.

Age. Those subjects aged 45 years or over demonstrated larger reductions in MAP than those under 45 years, noting 95% CIs do not overlap, ≥ 45 years MD -5.51 mm Hg (95% CI -6.95 to -4.06, $I^2 = 0%$) vs those < 45 years MD -2.72 mm Hg (95% CI -3.49 to -1.96, $I^2 = 58%$). No significant differences for change in SBP, DBP or heart rate were observed between age categories.

Duration. Those subjects undertaking 8 weeks or more of IRT demonstrated a larger reduction in SBP MD -7.26 mm Hg (95% CI -8.47 to -6.04, $I^2 = 52%$) than those undertaking less than 8 weeks IRT MD -2.99 mm Hg (95% CI -4.25 to -1.73, $I^2 = 0%$), noting 95% CIs do not overlap. Those subjects undertaking 8 weeks or more of IRT demonstrated a larger reduction in MAP MD -4.22 mm Hg (95% CI -5.08 to -3.37, $I^2 = 34%$) than those undertaking < 8 weeks IRT MD -1.85 mm Hg (95% CI -2.95 to -0.74, $I^2 = 54%$), noting 95% CIs do not overlap. No significant difference for change in DBP or heart rate was observed between IRT duration categories.

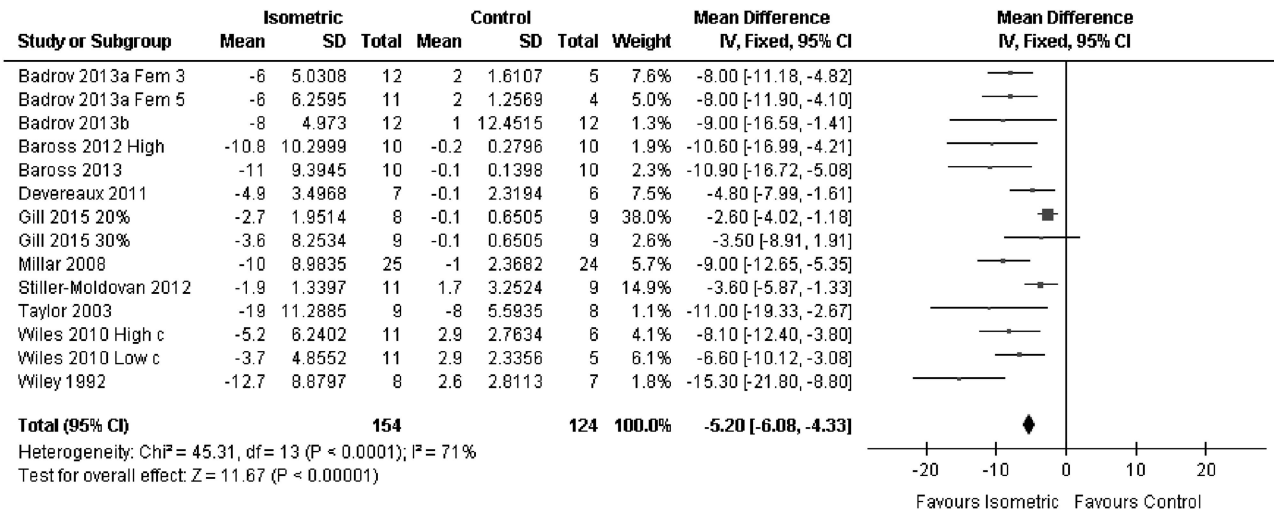


Figure 2 Analysis of change in systolic blood pressure.

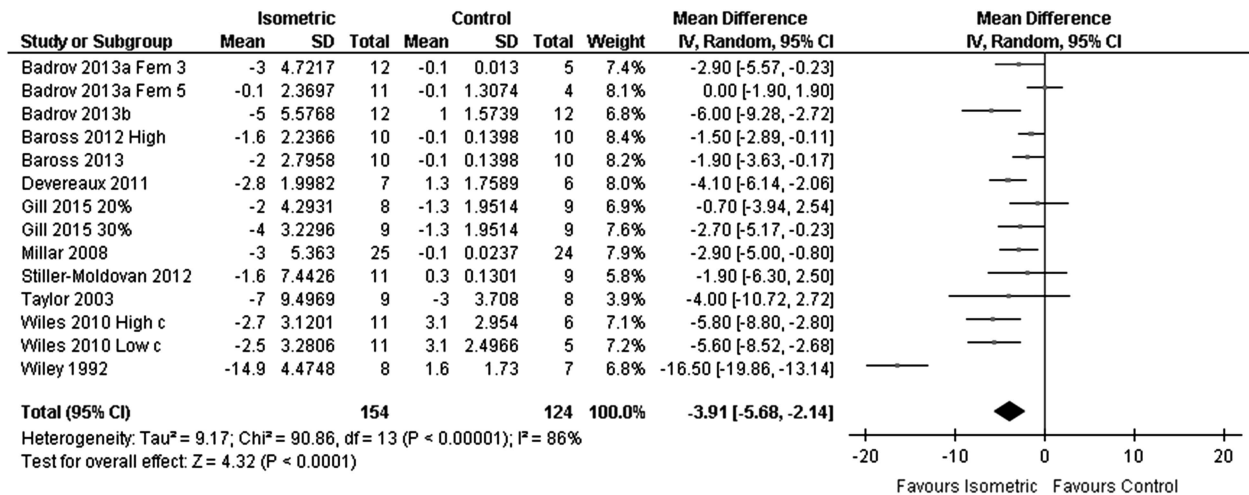


Figure 3 Analysis of change in diastolic blood pressure.

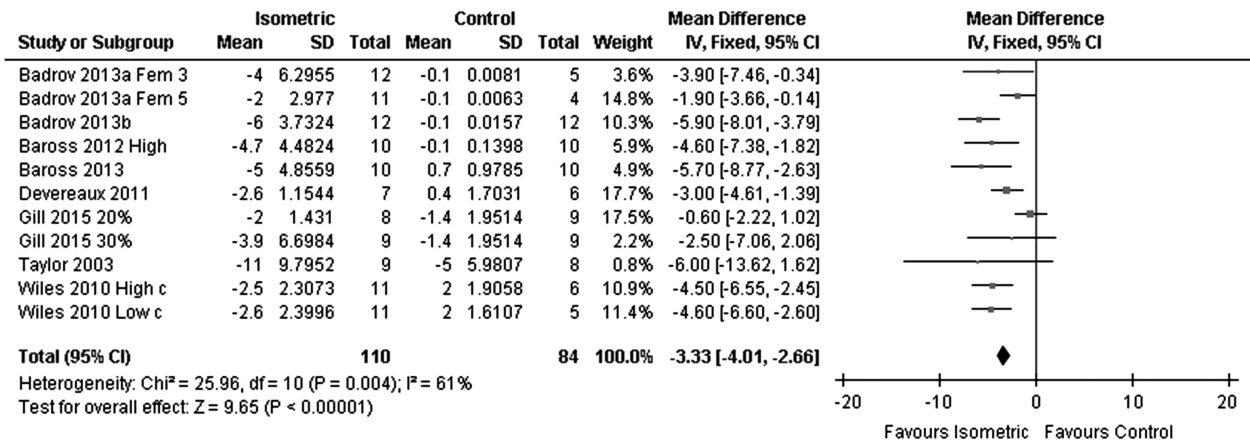


Figure 4 Analysis of change in mean arterial blood pressure.

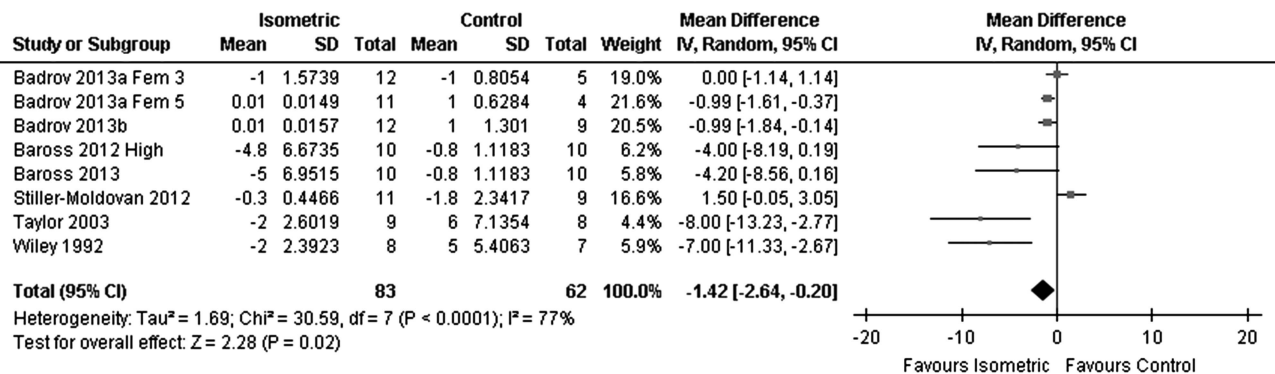


Figure 5 Analysis of change in resting heart rate.

Unilateral. Those subjects undertaking unilateral IRT demonstrated a larger reduction in SBP MD -8.92 mm Hg (95% CI -11.22 to -6.61 , $I^2 = 53\%$) than those undertaking bilateral IRT MD -4.58 mm Hg (95% CI -5.52 to -3.63 , $I^2 = 66\%$), noting 95% CIs do not overlap. No significant differences for change in DBP, MAP or heart rate were observed between unilateral and bilateral categories.

Arm. Those subjects undertaking arm IRT demonstrated a larger reduction in SBP MD -6.88 mm Hg (95% CI -8.31 to -5.46 , $I^2 = 66\%$) than those undertaking lower limb IRT MD -4.20 mm Hg (95% CI -5.30 to -3.09 , $I^2 = 68\%$), noting 95% CIs do not overlap. No significant differences for change in DBP, MAP or heart rate were observed between limb categories.

Hypertension status. Hypertensive participants in IRT demonstrated a larger reduction in MAP MD -5.91 mm Hg (95% CI -7.94 to -3.87 , $I^2 = 0\%$) than normotensive participants MD -3.01 mm Hg (95% CI -3.73 to -2.29 , $I^2 = 58\%$), noting 95% CIs do not overlap. No significant differences for change in SBP, DBP or heart rate were observed between hypertension categories.

Ambulatory BP monitoring. We removed the study that reported ambulatory BP measurements from our primary analyses; however, removal of these data from our primary analyses does not alter the SBP and DBP findings.

Study quality assessment

Study quality and reporting was assessed using the TESTEX scale, median score was 10 out of a scale of 15 (higher score indicates better quality). Four studies scored 9 and seven scored 10 (see Supplementary Files, Supplementary Table S1).

Heterogeneity

Heterogeneity was not high in any of the analyses or sub-analyses where between group 95% CIs did not overlap. Heterogeneity was higher in the analyses of diastolic BP and heart rate.

Publication bias

Egger Plots showed minimal evidence of publication bias (see Supplementary Files, Supplementary Figures S2–S4).

DISCUSSION

Our updated systematic review and subsequent meta-analysis confirms previous findings that IRT reduces arterial BP. The BP reductions were observed in SBP, DBP and MAP and were consistent across included trials. BP reductions appear to be larger in hypertensive males and those over 45 years of age. Certain IRT training regimes also produced larger BP reductions, for example, unilateral arm IRT for >8 weeks duration.

Our results showed that SBP was lowered almost 6 mm Hg in response to isometric training, which is a similar effect size to the SBP fall in our previous meta-analyses.⁸ Although the inclusion of the

Table 2 Isometric resistance training: sub-analyses

	Systolic blood pressure		Diastolic blood pressure		Mean arterial pressure		Resting heart rate	
	N	Effect size (95% CI)	N	Effect size (95% CI)	N	Effect size (95% CI)	N	Effect size (95% CI)
<i>Gender</i>								
Male	86 (4)	-7.05 (-8.91, -5.18)	86 (4)	-2.80 (-3.67, -1.93)	86 (4)	-4.13 (-5.08, -3.18)	40 (2)	-4.10 (-7.12, -1.07)
Female	32 (1)	-8.00 (-10.46, -5.54)	32 (1)	-0.97 (-2.52, 0.57)	32 (1)	-2.29 (-3.87, -0.71)	32 (1)	-0.77 (-1.31, -0.22)
<i>Age</i>								
< 45 years	126 (5)	-4.76 (-5.78, -3.73)	126 (5)	-3.78 (-4.68, -2.88)	113 (4)	-2.72 (-3.49, -1.96)	47 (2)	-0.86 (-1.40, -0.32)
≥ 45 years	150 (6)	-6.39 (-8.07, -4.72)	150 (6)	-2.26 (-3.16, -1.36)	81 (4)	-5.51 (-6.95, -4.06)	98 (5)	-0.77 (-1.48, -0.05)
<i>Duration of the intervention</i>								
< 8 weeks	48 (2)	-2.99 (-4.25, -1.73)	48 (2)	-2.99 (-4.40, -1.57)	48 (2)	-1.85 (-2.95, -0.74)	NA	Not estimable
≥ 8 weeks	230 (9)	-7.26 (-8.47, -6.04)	230 (9)	-3.02 (-3.73, -2.31)	146 (6)	-4.22 (-5.08, -3.37)	145 (7)	-0.83 (-1.26, -0.40)
<i>Unilateral or bilateral</i>								
Unilateral	47 (2)	-8.92 (-11.22, -6.61)	47 (2)	-3.70 (-5.10, -2.29)	32 (1)	-2.29 (-3.87, -0.71)	47 (2)	-0.86 (-1.40, -0.32)
Bilateral	231 (9)	-4.58 (-5.52, -3.63)	231 (9)	-2.84 (-3.55, -2.13)	162 (7)	-3.57 (-4.31, -2.82)	98 (5)	-0.77 (-1.48, -0.05)
<i>Limbs</i>								
Arm	157 (6)	-6.88 (-8.31, -5.46)	157 (6)	-3.64 (-4.69, -2.58)	73 (3)	-3.65 (-4.90, -2.40)	105 (5)	-0.76 (-1.19, -0.32)
Leg	121 (5)	-4.20 (-5.30, -3.09)	121 (5)	-2.66 (-3.46, -1.87)	121 (5)	-3.20 (-4.00, -2.39)	40 (2)	-4.10 (-7.12, -1.07)
<i>Hypertensive or normotensive</i>								
Hypertensive	61 (3)	-4.49 (-6.59, -2.38)	61 (3)	-4.46 (-6.91, -2.02)	41 (2)	-5.91 (-7.94, -3.87)	58 (3)	-0.57 (-1.30, 0.17)
Normotensive	217 (8)	-5.35 (-6.31, -4.39)	217 (8)	-2.91 (-3.57, -2.25)	153 (6)	-3.01 (-3.73, -2.29)	87 (4)	-0.96 (-1.49, -0.43)

Abbreviations: CI, confidence interval; NA, not available.

N is the number of participants whereas the number in parentheses represents the number of studies—results in bold indicate significant differences are present (95% confidence intervals do not overlap).

recently published trials increases statistical power of this analysis, there is a small decrease in the absolute effect size, compared with our earlier work.⁸ Nevertheless the effect size remains highly significant with a relatively small confidence interval and substantiates the recent inclusion by the American Heart Association of isometric exercise as a potential non-pharmacologic therapy to lower BP.²⁹ Furthermore, the effect size lends weight to the notion that isometric exercise training is comparable or superior to dynamic-exercise training (aerobic or resistance) or combined dynamic exercise for reducing systolic BP. Although the reductions in DBP and MAP are smaller than those seen in SBP, the effect sizes are at least comparable with changes observed from other exercise modalities.⁷

Our secondary analyses appear to demonstrate that there is greater potential for BP lowering in people with greater risk of hypertension. In our sub-analyses males, those aged 45 or over and people with hypertension showed larger reductions in some BP measurements. These findings are similar to previous work⁷ and we believe this is probably because older, hypertensive people are more likely to be deconditioned and therefore have greater potential for improvement. It also notable that BP reductions were observed independent of weight loss. Previous work has shown weight loss to have anti-hypertensive effects in older adults.³⁰ Certain aspects of the delivery of IRT appear to optimize the potential anti-hypertensive benefit, for example IRT lasting 8 weeks or longer appears to be optimal. It may be that 8 weeks or more is desirable to elicit optimal anti-hypertensive changes. It is possible that longer training periods are required to initiate regional alterations in ventricular function, as described

previously.³¹ Arm IRT appears to be superior to leg IRT, this may be explained by the fact that the active muscle mass is smaller in the arm so the threshold at which the arteries become occluded may also be lower. This is relevant as we believe that repeated exposure to arterial occlusion, leading to repeated bouts of hypoxia in the forearm are the stimulus for changes in arterial stiffness.³² We are, however, unclear about which metabolites, formed during hypoxic episodes, are precisely responsible for BP reductions. Regardless of the mechanistic explanation, health practitioners and those with hypertension can perhaps exploit benefit from the simplicity and relatively low cost of administering isometric resistance exercise.

Low-to-moderate intensity isometric activity can be performed anywhere, requires relatively inexpensive equipment and does not elicit the same level of cardiovascular stress (for example, rate-pressure product) as aerobic activity. Relative to aerobic activity, isometric exercise has the potential for superior adherence owing to simplicity, lower cost and perhaps less exercise time.

We recommend isometric handgrip exercise may produce greatest reduction in BP in hypertensive males aged ≥ 45 years, using unilateral arm IRT, 4 × 2 min, three times weekly at 30% MVC, for > 8 weeks. We strongly recommend that future studies should report ambulatory BP monitoring values.

Limitations

Our analyses exhibit moderate-to-high evidence of between-study heterogeneity. Although most comparisons of exercise training studies show variations in study duration and exercise modality, the

commonality of protocols renders differences negligible in this analysis. Although the investigators performing assessment measures were aware of group assignment; this was not necessarily a limitation as we utilized the TESTEX scale¹⁷ to assess study quality as all studies would have found it difficult to blind participants and investigators to the allocation of isometric exercise training or sedentary control. Median TESTEX score was 10 suggesting a good-to-moderate study design and reporting. Future studies should seek to employ sham isometric training (such as at a sub-optimal intensity) to permit studies to use a stronger double-blind design. The Egger plots showed minimal evidence of publication bias, which is understandable as studies show consistent improvements and authors are apt to emphasize the anti-hypertensive benefits. It is therefore unlikely unpublished negative or neutral data sets exist for the majority of our outcome measures and the level of significance suggest unpublished data would not change the findings presented here.

The major limitation of this field of study is that several desired measures such as continuous BP monitoring, neuro-hormonal and blood vessel compliance and flow are unavailable, making it difficult to unravel the mechanistic interpretation of these anti-hypertensive findings.

CONCLUSIONS

IRT lowers SBP, DBP and MAP. The magnitude of effect may be larger in hypertensive males aged ≥ 45 years, using unilateral arm IRT for > 8 weeks. Our data suggest that this form of training has the potential to produce significant and clinically meaningful BP reductions and could serve as an adjunct exercise modality.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (<http://www.nature.com/hr>)

Chapter 2: Isometric exercise training for blood pressure management:
A systematic review and meta-analysis to optimize benefit.

Higher Degree Research Thesis by Publication
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STATEMENT OF AUTHORS' CONTRIBUTION

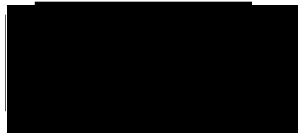
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	Author's Name (please print clearly)	% of contribution
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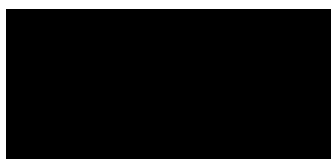
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Chapter 2: Isometric exercise training for blood pressure management:
A systematic review and meta-analysis to optimize benefit.

**Higher Degree Research Thesis by
Publication University of New England**

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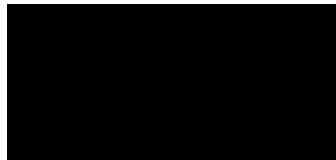
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**Chapter 3: The efficacy of isometric resistance training
utilizing handgrip exercise for blood pressure management.
A randomized trial.**

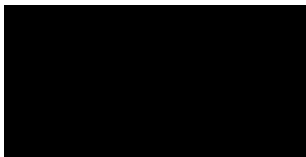
D.J. Carlson, J. Inder, S.K.A Palanisamy, J.R. McFarlane, G. Dieberg and N.A. Smart

Published online in Medicine

Citation: Carlson, D.J., Inder, J., Palanisamy, S.K.A., McFarlane, J.R., Dieberg, D. and Smart, N.A. The efficacy of isometric resistance training utilizing handgrip exercise for blood pressure management. A randomized trial. *Medicine*, 2016, 95:52(e5791), 1-7. <http://dx.doi.org/10.1097/MD.0000000000005791>.



Candidate Signature



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The efficacy of isometric resistance training utilizing handgrip exercise for blood pressure management

A randomized trial

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Abstract

Introduction: Hypertension is a major risk factor contributing to cardiovascular disease, which is the number one cause of deaths worldwide. Although antihypertensive medications are effective at controlling blood pressure, current first-line treatment for hypertension is nonpharmacological lifestyle modifications. Recent studies indicate that isometric resistance training (IRT) may also be effective for assisting with blood pressure management. The aim of this study was to determine the efficacy of IRT for blood pressure management and the suitability of a low-intensity working control group.

Methods: Forty hypertensive individuals, aged between 36 and 65 years, conducted IRT for 8 weeks. Participants were randomized into 2 groups, working at an intensity of either 5% or 30% of their maximum voluntary contraction. Participants performed 4 × 2 minute isometric handgrip exercises with their nondominant hand, each separated by a 3-minute rest period, 3 days a week.

Results: Blood pressure measurements were conducted at baseline and at the end of the protocol using a Finometer. Eight weeks of isometric resistance training resulted in a 7-mmHg reduction of resting systolic blood pressure (SBP) (136 ± 12 to 129 ± 15 ; $P = 0.04$) in the 30% group. Reductions of 4 mmHg were also seen in mean arterial pressure (MAP) (100 ± 8 to 96 ± 11 ; $P = 0.04$) in the 30% group. There were no statistically significant reductions in diastolic blood pressure for the 30% group, or any of the data for the 5% group.

Conclusion: Isometric resistance training conducted using handgrip exercise at 30% of maximum voluntary contraction significantly reduced SBP and MAP. A lack of reduction in blood pressure in the 5% group indicates that a low-intensity group may be suitable as a working control for future studies.

Abbreviations: ANCOVA = analysis of covariance, ANOVA = analysis of variance, CVD = cardiovascular disease, DBP = diastolic blood pressure, HR = heart rate, IRT = isometric resistance training, MANOVA = multivariate analysis of variance, MAP = mean arterial pressure, MVC = maximum voluntary contraction, SBP = systolic blood pressure, sec = second.

Keywords: handgrip exercise, hypertension, isometric resistance training

Editor: Massimo Sacchetti.

This research project is registered with ClinicalTrials.gov, the identifier for the study is Isometric handgrip exercise for blood pressure management, number NCT02458456.

Source of Funding: Australian Postgraduate Award (postgraduate student scholarship). University of New England, postgraduate research funds for equipment purchases. University of New England, Seed Grant to assist with paying research assistants.

The authors report no financial disclosures or conflicts of interest.

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Medicine (2016) 95:52(e5791)

Received: 22 July 2016 / Received in final form: 29 October 2016 / Accepted: 6 December 2016

<http://dx.doi.org/10.1097/MD.0000000000005791>

1. Introduction

Approximately 40% of adults aged 25 years and older worldwide have been diagnosed with hypertension.^[1] Hypertension is a major risk factor that contributes to cardiovascular disease, including coronary artery disease, stroke, and heart failure.^[2,3] Cardiovascular diseases (CVDs) are the number one cause of death globally; according to World Health Organisation (2015), in 2012, 31% of global deaths (approximately 17.5 million people) were due to CVD.^[4] Hypertension is responsible for 45% of cardiovascular deaths owing to heart disease and 51% owing to stroke worldwide.^[1] Antihypertensive medications are effective at controlling blood pressure and have minimal side effects; however, only half the people with hypertension reach treatment goals.^[5] Current first-line treatment for hypertension is non-pharmacological lifestyle modification including eating a healthy diet, cessation of smoking, and increasing physical activity.^[2,3,6]

Currently, the recommended exercise programme for blood pressure management in adults is dynamic endurance aerobic exercise of at least 150-minute moderate intensity, 75-minute vigorous intensity, or an equivalent combination of both each

week, as well as at least 2 days of muscle strengthening.^[7] In 2011/12, only 44% of adults in the United States adhered to recommended exercise criteria.^[7] Recent analyses suggest that isometric resistance training (IRT) may elicit blood pressure reductions greater than those seen with dynamic aerobic and resistance exercise.^[2,8,9]

A recent systematic review and subsequent meta-analysis confirms previous findings that IRT reduces systolic blood pressure (SBP) by almost 7 mmHg, whereas diastolic blood pressure (DBP) and mean arterial pressure (MAP) were both lowered by almost 4 mmHg.^[2] Low- to moderate-intensity isometric handgrip exercise can be performed anywhere, requires relatively inexpensive equipment, and does not elicit the same level of cardiovascular stress as aerobic exercise.^[2] Recent work suggests that IRT may become a new tool in the nonpharmacological treatment of high blood pressure.^[10–12] The 2015 systematic review by Inder et al.^[13] suggests certain demographic groups, males and individuals aged ≥ 45 years, may acquire greater blood pressure reductions from IRT.

Randomized controlled studies of IRT, for ≥ 4 weeks in duration, have predominately used a 30% maximum voluntary contraction (MVC) and a sedentary control.^[9] Ray and Carrasco^[14] utilized a sham group, which held a handgrip dynamometer, but did not generate any force. Previous studies have utilized a low intensity during isometric leg training.^[15,16] We have found no reported studies, which have utilized an intensity $< 10\%$ MVC handgrip exercise with prehypertensive and/or hypertensive participants. In addition, previous studies of 4 to 10 weeks duration have focused on people aged between 20 and 35 years or 60 and 80 years with a sedentary control. Peters et al.^[17] conducted an isometric handgrip study with 10 participants aged 52 ± 5 over 6 weeks. A larger, longer trial was needed to look at handgrip exercise in prehypertensive and hypertensive individuals aged between 35 and 70 years.

The primary aim of this study was to establish the size of reduction in blood pressure using handgrip exercise at 30% vs. 5% MVC in individuals aged 35 to 70 years. A 5% MVC was chosen to determine whether the low intensity would elicit reductions in BP, and therefore test suitability for control group allocation in future studies.

2. Methods

2.1. Participants

This study consisted of 40 white participants with mild or prehypertension, men ($n=15$) and women ($n=25$), aged between 36 and 65 years recruited from Armidale, NSW, Australia. Participants had a resting SBP ≥ 120 mmHg and/or a resting DBP ≥ 80 mmHg, or were receiving pharmacotherapy to treat their BP (65%). Participants were given a standardized health questionnaire and were excluded if they had known cardiovascular disease or multiple comorbidities, were unable to participate under their doctor's recommendation, smokers, and/or those with arthritis or carpal tunnel, which may have been aggravated with handgrip exercise. Participant baseline characteristics are displayed in Table 1.

The University of New England Human Ethics Committee approved the investigation, all participants provided written informed consent before participation, and all procedures were in accordance with the University's guidelines. This research project is registered with ClinicalTrials.gov, the identifier for the study is NCT02458456.

Table 1

Participant baseline characteristics.

Characteristics	30% MVC (Training)	5% MVC (Control)
n (Male)	20 (7)	20 (8)
Age, y	52 \pm 8	54 \pm 8
Height, cm	170 \pm 9	171 \pm 8
Weight, kg	88 \pm 16	87 \pm 19
BMI, kg/m ²	30 \pm 6	30 \pm 8
Systolic blood pressure, mmHg	136 \pm 12	128 \pm 15
Diastolic blood pressure, mmHg	77 \pm 7	74 \pm 9
Mean arterial pressure, mmHg	100 \pm 8	95 \pm 10
Heart rate, bpm	67 \pm 9	70 \pm 11
Antihypertensive medication classification (n)		
ACE inhibitor	3	3
ARB	3	5
Calcium channel blocker	1	
ACE inhibitor and calcium channel blocker	1	
ARB and calcium channel blocker	1	1
ACE inhibitor and diuretic	1	
ARB and diuretic	2	
ACE inhibitor, calcium channel blocker, and Diuretic	1	2
ARB, calcium channel blocker, and Diuretic		1
Alpha-adrenoreceptor antagonist, calcium channel blocker, and diuretic		1
Unmedicated	7	7

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, BMI = body mass index, MVC = maximum voluntary contraction.

2.2. Study design

The blood pressure-lowering effects of IRT have been previously established; however, previous studies have used a nonexercising control group, and one study used a sham group.^[9] The objectives of this study were to determine BP reductions utilizing handgrip exercise at 30% MVC as well as to test whether a 5% MVC training group would elicit blood pressure-lowering effects, or could be utilized as a working control. Eligible participants were familiarized to all testing equipments and randomized into either a 30% MVC ($n=20$) or a 5% MVC ($n=20$) training group. Participant enrolment and randomization were conducted by D. Carlson. Randomization was conducted before baseline blood pressure measurements using a computer-generated random number assignment, resulting in differences in SBP at baseline.

Participants were blinded as to which group they were randomized into; only the research team members who conducted the protocol were aware of group assignment. A numbered code system was used to identify participants, which allowed the researchers supervising the exercise protocol to ensure that participants worked at the correct intensity, while blinding participants to group assignment. A specifically designed light box was set up as a feedback mechanism for participants during IRT to prevent them knowing what intensity they were working at. All participants were exposed to the same conditions and equal attention to counteract concerns of disparities between groups owing to the Hawthorne effect.^[18,19]

2.3. IRT training protocol

Participants trained 3 days per week for 8 weeks using a DHD-3 Digital Hand Dynamometer (Saehan Corporation, South Korea) with their nondominant hand. At the start of each training session, the participants conducted 3 contractions using maxi-

mum force, each separated by 30 seconds; these were then averaged to calculate the resistance at which they would perform either 30% MVC or 5% MVC on the day. Participants then completed 4 sets of 2-minute isometric handgrip contractions separated by 3-minute rest periods. Each training session was conducted in the Exercise Physiology Lab at the University of New England, Armidale, under direct supervision of a member of the research team.

2.4. Blood pressure measurements

Baseline and postintervention blood pressure was established using a beat-to-beat Finometer Midi Model-2 (Finapres Medical Systems B.V., Amsterdam, The Netherlands). Two minutes of continuous blood pressure measurement were recorded to assess resting SBP, DBP, heart rate (HR), and MAP. The Finometer utilizes an infrared photo-plethysmograph built into a finger cuff based on the Penaz volume-clamp method to enable continuous noninvasive BP measurements.^[20,21] To address concerns of the accuracy of the Finometer, raised after commencement of the study, and to gauge consistency with brachial cuff BP, we compared the Finometer measurements with those of a sphygmomanometer in some participants. All baseline and post comparison data were performed with BP measurements, which were conducted using the Finometer. Upper arm cuff measurements were conducted on the last 16 participants at baseline, and 24 participants postintervention. The purpose of this was to assess the coefficient of variation between the Finometer and manual sphygmomanometer measurements.

All testing was conducted in a quiet, temperature-controlled room, following a 4-hour fast from food and caffeine, and a 12-hour abstinence from alcohol and vigorous exercise. All post-tests were conducted 24 hours after the final day of week 8 IRT and within 2 hours of the initial pretesting time of day, time of medication ingestion was standardized. Blood pressure was measured in the participants' dominant arm (right $n = 38$, left $n = 2$) using the Finometer Midi and sphygmomanometer. Baseline and 24-hour post-IRT blood pressure measurements were conducted with the participant lying supine on a massage table, with their arm relaxed by their side.

An aneroid Heine Gamma G7 sphygmomanometer, which was calibrated by a technician before use, was utilized for brachial BP measurements. The auscultatory method was conducted by placing the cuff around the dominant arm of the individual and listening for Korotkoff sounds with a Littmann Classic IIE stethoscope, using the recommended blood pressure measurement guidelines.^[22,23] Three blood pressure measurements were taken, each separated by a 5-minute rest period. After another 5 minutes of rest, the Finometer was used to record 2 minutes of continuous blood pressure measurements.

The Finometer was calibrated by a technician before commencement of the study, and extensive training and practice were provided to the observers to ensure accuracy of recordings. The finger cuff was placed on the middle finger of the dominant hand and the height correction unit used to correct hydrostatic blood pressure changes for the hand being away from heart level. Use of the height-adjusting component converts finger cuff pressure to brachial pressure, meeting the American Association for the Advancement of Medical Instrumentation (AAMI) criteria.^[21]

2.5. Data analysis

BeatScope Easy software which records waveforms and beat-to-beat data were used to unpack the Finometer data into an excel

spreadsheet. Microsoft Excel (Microsoft Corporation, Redmond, WA) was then used to calculate the mean and standard deviation for the last 15, 30, 60, and the entire 120 seconds of baseline and post-IRT recording. Shapiro-Wilk test of normality, repeated measures 2-way analysis of variance (ANOVA) (measure \times time) with Tukey contrasts, and pair-wise comparisons were conducted to determine the best statistical model to use. Based on this, the entire 120 seconds of baseline and post-IRT data were used for all pre-post calculations. Paired t tests and repeated measures 2-way ANOVA (group \times time) were conducted to evaluate the P value for differences in pre-post data. Multivariate analysis of variance (MANOVA) and independent t tests were conducted to compare the 5% and 30% MVC groups. All MANOVA and paired t tests were analyzed using SPSS (version 22); $P \leq 0.05$ was considered statistically significant. Results are mean \pm standard deviation, unless otherwise specified.

Shapiro-Wilk test of normality was conducted on all groups before analysis to confirm that ANOVA was suitable to analyze the data. There was one possible outlier in the 30% MVC group, which appeared consistently in the SBP, DBP, and MAP pre and post data. Cook's distance indicated that with ranges between 23% and 32%, although it may be influential, it is unlikely that it would be a major influence, so the data were retained during analysis.

In line with intention to treat, blood pressure was recorded on the last day of IRT and used as last outcome carried forward post measurements for participants unable to complete the entire eight week protocol.

3. Results

Of the 40 participants, 2 in the 30% MVC group were unable to complete the entire program due to work circumstances. The adherence to IRT was 100% in the 38 participants who completed the eight week study. Randomized groups were matched at baseline for age, gender, height, weight, and medication status as displayed in Table 1. There were no reported changes in exercise, diet, or medication throughout the study by any of the participants, and no difference between baseline and post weight for either group. Recruitment was conducted during 3 months, the trial ended when participants' time of recruitment meant that completion of the 8-week protocol would be mid-December, and no follow-up was conducted. There was no harm or unintended effects reported in either group.

To establish the size of reduction in blood pressure in both groups, a 120-second resting baseline blood pressure recording was taken before and 24 hours post-IRT (Table 2). Table 3 exhibits comparisons between 15, 30, and 60-second sampling, against the 120-second blood pressure recording. Upper arm cuff measurements were taken in 16 participants at baseline and 24 participants post intervention to validate the measurements taken with the Finometer.

3.1. ANOVA analysis of blood pressure, MAP, and HR

Eight weeks of isometric handgrip training resulted in a significant 7-mmHg reduction in baseline versus postintervention SBP in the 30% MVC group, with a nonsignificant 2-mmHg reduction in the 5% MVC group (Table 2). Individual variance in SBP was greater in participants in the 5% MVC group than that seen in the 30% group, as illustrated in Figure 1. Multivariate

Table 2**Comparison of 120-second blood pressure measurements.**

	Systolic		Diastolic	
	5% MVC	30% MVC	5% MVC	30% MVC
Pre	128±15	136±12	74±9	77±7
Post	126±16	129±15	71±9	75±9
Δ mmHg	-2	-7	-3	-2
P	0.43	0.04*	0.17	0.21

* Statistical significance ≤0.05.

ANOVA with a Wilk Lambda of 0.86 ($P=0.24$), indicate no statistically significant differences between the groups across the 4 sampling duration measurements at baseline. There were no significant differences for post-intervention SBP in both groups with 30% MVC at 129 ± 15 and 5% MVC at 126 ± 16 (95% confidence interval [CI] -13.14, 6.66; $P=0.51$). The majority of participants with reductions in SBP had corresponding reductions in DBP as illustrated in Figure 2; however, there were no significant reductions in DBP in either the 30% or 5% MVC group. There was no difference between the 30% MVC and 5%

MVC groups with baseline DBP 77 ± 7 and 74 ± 9 (95% CI -8.20, 1.64; $P=0.19$) and also post-intervention 75 ± 9 and 71 ± 9 (95% CI -9.32, 2.21; $P=0.22$), respectively. Significant reductions were observed in MAP from baseline to post-intervention of -4 mmHg (95% CI 0.14, 7.98; $P=0.04$) in the 30% MVC group, but not in the 5% MVC group with -3 mmHg (95% CI -2.21, 7.56; $P=0.27$) (Table 3). Analysis indicated an unchanged HR in the 30% MVC group (95% CI -6.13, 2.41; $P=0.37$), and in the 5% MVC group (95% CI -2.04, 4.33; $P=0.46$).

Table 3**Comparison of effect of sampling duration.**

	15seconds	30seconds	60seconds	120seconds	ANOVA (F)	P
Systolic						
Pre 5%	126±13	127±14	128±15	128±15	4.030	0.03*
Post 5%	124±16	124±16	125±16	126±16	3.142	0.68
Δ mmHg	-2	-3	-3	-2		
P	0.53	0.51	0.47	0.43		
Pre 30%	135±13	135±13	135±13	136±12	0.482	0.58
Post 30%	129±16	128±16	129±16	129±15	0.414	0.67
Δ mmHg	-6	-7	-6	-7		
P	0.07	0.06	0.06	0.04*		
Diastolic						
Pre 5%	73±8	73±8	73±9	74±9	2.590	0.10
Post 5%	71±11	71±10	71±10	71±9	2.590	0.10
Δ mmHg	-2	-2	-2	-3		
P	0.31	0.32	0.22	0.17		
Pre 30%	76±7	76±7	77±7	77±7	2.204	0.13
Post 30%	75±9	74±9	74±9	75±9	0.120	0.86
Δ mmHg	-1	-2	-3	-2		
P	0.43	0.32	0.27	0.21		
MAP						
Pre 5%	93±9	93±10	94±10	95±10	3.315	0.06
Post 5%	91±12	91±11	92±11	92±11	3.315	0.06
Δ mmHg	-2	-2	-2	-3		
P	0.40	0.39	0.33	0.27		
Pre 30%	99±9	99±9	99±9	100±8	1.466	0.25
Post 30%	95±11	95±11	95±11	96±11	0.143	0.87
Δ mmHg	-4	-4	-4	-4		
P	0.12	0.07	0.05*	0.04*		
HR						
Pre 5%	70±11	70±11	70±11	70±11	0.165	0.81
Post 5%	70±11	69±11	69±11	69±11	0.165	0.81
Δ mmHg	0	-1	-1	-1		
P	0.62	0.49	0.46	0.46		
Pre 30%	67±9	67±9	67±9	67±9	0.247	0.71
Post 30%	69±12	69±11	69±11	69±11	0.814	0.42
Δ mmHg	2	2	2	2		
P	0.33	0.34	0.43	0.37		

ANOVA=analysis of variance, HR=heart rate, MAP=mean arterial pressure.

* Statistical significance ≤0.05.

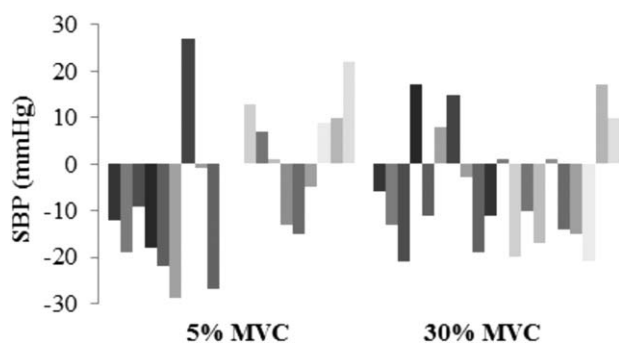


Figure 1. Individual participant changes in systolic blood pressure from baseline to post-intervention.

3.2. Analysis of covariance analysis of blood pressure, MAP, and HR

Univariate analysis of covariance (ANCOVA) with baseline SBP as a covariate was conducted to verify possible outcome variances between the 5% and 30% groups. ANCOVA indicated significant reductions in SBP in both groups with 30% MVC ($P=0.03$ and 5% MVC $P=0.02$). There were no statistically significant differences in post-intervention SBP between the groups, when the analysis was conducted with baseline SBP as a covariate, with 30% MVC at 127 ± 3 (SEM) and 5% MVC at 128 ± 3 (SEM) (95% CI $-8.19, 10.02$, $P=0.84$). Analysis of change in DBP with baseline DBP as a covariate indicated significant reductions in both groups of 30% MVC ($P=0.02$) and 5% MVC ($P<0.01$), with reductions of 2 and 3 mmHg, respectively. Analysis using baseline MAP as a covariate indicates significant reductions at 30% MVC ($P<0.01$) and 5% MVC ($P=0.02$). Analysis using baseline HR as a covariate shows significant differences between baseline and post-IRT in both groups ($P<0.01$), despite HR reducing by 1 bpm in the 5% MVC group, and increasing by 2 bpm in the 30% MVC group. Post-intervention comparisons of HR indicated that both groups were identical at 69 ± 11 with no statistically significant differences (95% CI $-6.46, 7.59$; $P=0.87$).

3.3. Effect of sampling duration

Repeated measures ANOVA for 15, 30, 60, and 120 seconds of pre- and post-resting SBP, DBP, MAP, and HR showed that the only data with statistically significant variation across the 4

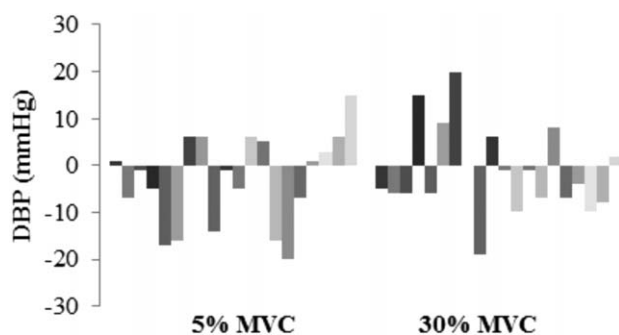


Figure 2. Individual participant changes in diastolic blood pressure from baseline to post-intervention.

measurements was the SBP in the 5% MVC group, as seen in Table 3. Population mean for SBP in the 5% group ranged from 126 mmHg at 15 seconds to 128 mmHg at both 60 and 120 seconds, ($P=0.03$). Based on this analysis, it was determined that the 120-second data were more robust, so the consensus was for it to be used for our pre-post analyses.

3.4. Comparison of groups

Multivariate analysis of variance was conducted to compare SBP, DBP, MAP, and HR pre- and post-data for the 5% and 30% groups; all comparisons have a Wilk Lambda close to 1, all with a P value >0.05 . No statistically significant group differences were indicated by the correlation between the dependent variables (measurement and time). Levene Test of Equality of error variances were not statistically significant for the 15, 30, 60, or 120 seconds of pre or post-data in any of the measures with all having a P value >0.05 . As the assumption of homogeneity of variance has not been violated and Wilk Lambda shows correlation of the 5% and 30% groups, it is reasonable to say that both groups were the same, despite the 30% group having a larger baseline SBP than the 5% group.

3.5. Comparison of sphygmomanometer and Finometer averages

Owing to possible concerns regarding the accuracy of the Finometer, arm cuff measures using a sphygmomanometer were also taken at baseline and 24 hours post-intervention in some of the participants (baseline $n=16$, post $n=24$). As the following data are a comparison of measurement tools, all participants, regardless of which group they were in, were used for the analyses. Baseline SBPs using sphygmomanometer and Finometer was 132 ± 9 and 136 ± 17 (95% CI $-11.69, 3.69$; $P=0.29$), whereas post measurements were 130 ± 9 and 131 ± 15 (95% CI $-6.14, 4.39$; $P=0.73$), respectively. No significant difference was indicated between measurement tools for baseline and post-intervention SBP. There was a statistically significant difference in sphygmomanometer and Finometer DBP measurements with baseline 84 ± 7 and 77 ± 9 (95% CI $3.50, 11.00$; $P<0.01$), respectively. Post-DBP sphygmomanometer measurements of 81 ± 9 and Finometer 74 ± 10 (95% CI $2.54, 11.12$; $P<0.01$) were also significantly different.

There was a significant positive linear relationship between the sphygmomanometer versus Finometer measurements in both SBP and DBP at baseline and 24 hours post-intervention. Pearson correlation coefficients indicated positive correlation with baseline SBP 0.55 ($P=0.03$) and DBP 0.64 ($P<0.01$); 24-hour post-SBP 0.59 ($P<0.01$) and DBP 0.44 ($P=0.05$).

4. Discussion

The main finding of this study was that significant reductions were seen (with the primary analysis) in SBP and MAP in individuals conducting IRT for 8 weeks at 30% MVC. The reduction in SBP was clinically significant (>3 mmHg). It appears unlikely that 5% MVC elicits significant blood pressure reductions. Instead of a sedentary control, we might therefore consider utilizing a control group for future IRT studies at an intensity of 5% MVC.

4.1. Blood pressure, MAP, and HR

Our primary analysis showed that SBP reductions were seen in the 30% MVC group, but not the 5% MVC group. The 7-mmHg

reduction in SBP is considered clinically meaningful (>3 mmHg).^[24,25] The results seen in this study reflect those seen in previous IRT studies, which also demonstrated significant reductions in SBP over an 8-week period at 30% MVC.^[2,6,8,13] When baseline blood pressure was added as a covariate, secondary analysis showed that SBP, DBP, MAP, and HR were all significantly reduced in both the 30% and the 5% MVC groups. Although it is unclear whether the size of these reductions is clinically meaningful, it has been previously found that the magnitude of blood pressure reductions following IRT is directly related to pre-training blood pressure levels,^[26] which could perhaps be explained by regression to the mean.

Mean DBPs at baseline in both the 5% and 30% MVC groups in our study were within the normal range with both groups having population baseline mean <85 mmHg. Taking into account the limited potential for further reductions in DBP, we did not expect to see much of a reduction in DBP after IRT intervention in either group. We saw no significant reduction in DBP for both the 5% and 30% groups. Previous studies conducting isometric handgrip training at 30% MVC produced conflicting results. Some small studies have failed to show DBP reductions; Howden et al^[27] who had 8 participants conducting 5 weeks of IRT and Taylor et al^[28] with 9 participants after 10 weeks of IRT, saw no statistical reductions in DBP with baseline <85 mmHg. In contrast, both single studies^[29] and pooled analyses from several studies^[2,8,10] have shown significant reductions in DBP after IRT. Although baseline DBP may predict significant responses to IRT, again it is unclear whether the size of these reductions is clinically meaningful.

The significant reduction in MAP in the 30% group saw MAP lowered from 100 to 96 mmHg, which is clinically meaningful. Reductions in MAP at 30% MVC were also seen by Carlson et al^[2] and Millar et al.^[6] There were no statistically significant changes in HR for either the 5% or 30% MVC groups. The absence of change in resting HR indicates that IRT has a minimal effect on the parasympathetic nervous system. Other analyses have failed to show a reduction in HR with IRT when conducting an isometric handgrip protocol.^[29–31]

4.2. Clinical significance

The risk of adverse health outcomes can be reduced if individuals with grade 1 hypertension can lower their blood pressure, there exists a dose-response.^[32] Despite a 2-mmHg reduction in SBP in the 5% MVC group, this was only statistically significant when baseline blood pressure was used as a covariate. Reductions of 2 mmHg would be borderline for clinical significance.^[33,34] One individual in the 5% group and 6 in the 30% group with SBP >120 mmHg at baseline were reduced to <120 mmHg post-intervention. The recent SPRINT trial demonstrated that lowering SBP to <120 mmHg resulted in significantly lower rates of cardiovascular events in adults with hypertension.^[35] Although there is individual variation among participants, DBP population reductions of 3 mmHg in the 5% group and 2 mmHg in the 30% indicate IRT can have an impact on preventing adverse events.^[9,36] According to the Framingham Heart Study, small reductions in DBP as low as 2 mmHg were shown to be associated with decreased risk of coronary heart disease and stroke.^[9,34,36]

4.3. Limitations

The number of medicated ($n=26$) versus nonmedicated participants ($n=14$) prevented sub-analyses comparing the 2

groups. Although the 5% and 30% MVC groups were matched for equal numbers of participants, there were only 7 non-medicated participants in each group. Parameters were matched at baseline for both groups; however, the 5% and 30% groups were not matched at baseline for SBP, resulting in the 30% SBP baseline being $>5\%$. Two of the participants (30% MVC group) had to withdraw from the study because of work commitments, one after completing 4 weeks and the other at 5 weeks. As both had informed the researchers with enough notice, their blood pressure was measured on their last day of attending and their 2-minute rest period post-IRT was used as last outcome carried forward for analysis.

Controversy over the accuracy of the Finometer was mitigated to some extent by a comparative analysis with sphygmomanometer measures, which showed significant correlation. Previous studies looking at variation in the Finapres in relation to intra-arterial pressure indicated variability and bias in SBP and DBP measurements resulting in incorrect measurements.^[37–39] We used a more recent Finometer, which supersedes the Finapres; although there was a significant variation in DBP, there was no significant variation in our SBP, and this was also seen by Schutte et al.^[40]

4.4. Recommendations for future research

A larger cohort would enable subanalyses to look at individual variation in response to IRT, such as comparison of males and females and medicated versus nonmedicated participants. Future research would benefit from utilizing the current criterion standard for blood pressure measurement of 24-hour ambulatory monitoring; only 1 study to date has used ambulatory blood pressure. To date there has only been 2 randomized controlled studies of IRT for 10 weeks, the longest study duration.^[9] Future studies should look at the effect of IRT over a period of ≥ 10 weeks, with a follow-up equivalent to the duration of IRT intervention. Investigation into the physiological mechanisms responsible for reductions in blood pressure will enable more understanding of the antihypertensive effects of IRT and aid in development of future research.

4.5. Novelty and significance

Previous isometric handgrip studies of ≥ 8 weeks have had small participant numbers; this is currently the largest cohort of participants in this field. This is the only study to utilize a low-intensity group for use as a control group; previous studies have either had a sedentary or sham control group.

5. Conclusion

A reduction in SBP was seen after 8 weeks of IRT, indicating that IRT may be an alternative exercise for people who are unable to reach the current recommendations of 2.5 hours of weekly aerobic exercise, to aid in their blood pressure management.

Acknowledgements

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Chapter 3: The efficacy of isometric resistance training utilizing handgrip exercise for blood pressure management. A randomized trial.

**Higher Degree Research Thesis by Publication
University of New England**

STATEMENT OF AUTHORS' CONTRIBUTION

(To appear at the end of each thesis chapter submitted as an article/paper)

We, the Research Master/PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

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Chapter 3: The efficacy of isometric resistance training utilizing handgrip exercise for blood pressure management. A randomized trial.

**Higher Degree Research Thesis by
Publication University of New England**

STATEMENT OF ORIGINALITY

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Type of work	Page number/s
All text, tables and figures	Chapter 3, pp 70-77

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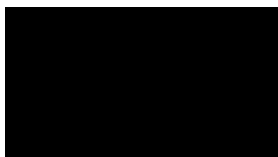
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Chapter 4: A randomized controlled trial on the effects of isometric handgrip exercise, followed by detraining, on 24-h ambulatory blood pressure.

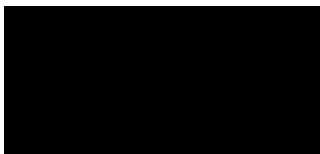
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Submitted to Medicine on 20 September 2017

Currently in the review process

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A randomized controlled trial on the effects of isometric handgrip exercise, followed by detraining, on 24-h ambulatory blood pressure.

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There is no funding for this work, and there are no conflicts of interest

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Word count: 4824

Number of Tables: 4

Number of Figures: 3

No supplementary digital content files

List of Abbreviations

ABPM: Ambulatory blood pressure monitoring; ANOVA: Analysis of variance; ANCOVA: Analysis of covariance; DBP: Diastolic blood pressure; HR: Heart rate; IRT: Isometric resistance training; LOCF: Last outcome carried forward; MAP: Mean arterial pressure; MVC: Maximum voluntary contraction; NHANES: National health and nutrition examination survey; SBP: Systolic blood pressure.

Keywords

Hypertension; ambulatory blood pressure; isometric handgrip exercise; detraining.

Abstract

Introduction

Hypertension is a worldwide health issue; globally there are over 1 billion adults with hypertension. Exercise is an important lifestyle intervention for individuals with hypertension; however, there is approximately only a 50% adherence rate to the current recommended guidelines. Isometric handgrip exercise provides a simple, affordable and effective exercise to aid in blood pressure management for individuals with hypertension. The main aim of this study was to look at the effect of 12wks of isometric handgrip exercise on 24-h ambulatory blood pressure and to determine the detraining effect 12wks after completion of the protocol.

Methods

Twenty pre hypertensive to stage 1 hypertensive participants, men (n=12), aged 55±10 years were recruited to conduct isometric handgrip exercise 3 times/week for 12wks. Participants were randomized into two groups which exercised at either 5% or 30% of their maximum voluntary contraction. 24-h ambulatory blood pressure measurements were conducted prior to commencement of exercise, at 12wks and after a 12wk detraining period.

Results

The 30% group saw significant reductions in systolic ambulatory blood pressure after 12wks of exercise of -7mmHg from 154±4.5 to 147±2.5, (95% CI 0.096, 0.967; p=0.023). Diastolic reduced by -5mmHg from 89±2.8 to 84±1.5, (95% CI 0.232, 0.989; p=0.007). There was no change in either the systolic or diastolic ambulatory blood pressure of the 5% group with -2mmHg from 148±3.9 to 146±1.7 (95% CI -0.021, 0.620; p=0.064), and -2mmHg from 86±1.8 to 84±1.5 (95% CI -0.253, 0.989; p=0.209), respectively. Systolic and diastolic ambulatory blood pressure in the 30% group was statistically significantly lower than baseline after detraining, both p<0.01, with no change in the 5% group.

Conclusions

Isometric resistance training at 30% maximum voluntary contraction over 12wks significantly reduces systolic and diastolic 24-h ambulatory blood pressure. After cessation of the protocol, blood pressure increased during detraining but still remained significantly lower than at baseline, indicating trends of continued benefit. Lack of change in the 5% group solidifies the use of a low intensity sham group as a working control.

Introduction

Approximately 1.39 billion adults over 20 years of age worldwide have hypertension; with the majority aged between 40-59 years, living in low and middle income countries.¹ According to the National Health and Nutrition Examination Survey (NHANES), 2011-14, there has been no significant change in the percentage of US adults with hypertension from 1999 to 2014; despite increased awareness, treatment and control of hypertension.² Although controlled hypertension (blood pressure < 140/90mmHg) has increased from 31.5% in 1999 to 54% in 2014 in the US, the prevalence of hypertension has remained the same.²

The American Heart Association's, Health Campaign for Life's Simple 7, emphasises that individuals should avoid smoking, engage in daily physical activity, eat a healthy diet, maintain a healthy weight, and healthy cholesterol, blood pressure, and glucose levels.³ Current guidelines indicate that adults should conduct a minimum of 150 mins of moderate or 75 mins of vigorous exercise (or a combination of both) each week, as well as a minimum of 2 days of muscle strengthening, for ideal cardiovascular health.³ According to NHANES 2014, only 50% of adults over 18 years of age with hypertension meet the recommended aerobic activity guidelines, with 21.4% meeting the guidelines for both aerobic activity and muscle strengthening.⁴

Isometric resistance training (IRT) offers an effective alternative to aerobic exercise for blood pressure management, particularly for individuals with limited mobility. Recent studies have indicated blood pressure reductions from IRT which are similar to those seen with aerobic exercise.⁵⁻⁸ The majority of IRT studies have a duration of 4 or 8 weeks, the longest published IRT studies are 10 weeks duration, with one newly published 12 week study.⁹⁻¹²

This is the second ambulatory study in relation to IRT over 12 weeks, and the first detraining study. Currently there are only four published studies who have utilised ambulatory blood pressure monitoring (ABPM) in relation to IRT.¹²⁻¹⁵ Ambulatory blood pressure provides a more accurate indication of true blood pressure than clinic measurements.^{16,17} Utilizing ABPM can prevent confounding blood pressure data due to white coat or masked hypertension, which can often occur in a clinical setting.^{17,18} To date the only published study which has looked at the detraining effect after completing an IRT protocol was conducted by Wiley and colleagues (1992), that involved five weeks of IRT and five weeks detraining.¹⁹

Previous IRT studies have employed a sedentary control, or a sham group which involved participants holding a dynamometer without applying any resistance.^{7, 20,21} Research indicates that low intensity isometric handgrip exercise invokes clinically meaningful reductions in blood pressure; however, it is suitable for use as a working control.^{6,22} Due to the possibility of participants knowing whether or not they are in a control group, we employed a low intensity working control to minimise disparities across the groups from the Hawthorne effect. The Hawthorne effect has numerous interpretations including the response of participants to an interest in their welfare leading to a change in behaviour upon awareness of being studied, which could influence experiments.²³⁻²⁵ Utilizing a working control, with participants blinded to their group assignment, and all participants receiving equal attention should alleviate disparities among participants, minimising the Hawthorne effect.²⁶

The primary aim of this study was to determine the effect of conducting isometric handgrip exercise for 12 weeks on ambulatory blood pressure in individuals aged between 30 and 70 years who were either pre-hypertensive or had stage 1 hypertension. The secondary aim was to establish whether or not the participant's 24-h ambulatory blood pressure would change after a subsequent detraining period, of the same length as the training period.

Methods

Participants

Twenty pre-hypertensive to stage 1 hypertensive participants, men ($n=12$) and women ($n=8$), aged between 30 and 70 years were recruited from Armidale, NSW, Australia and the surrounding area. Participants had 24-h ambulatory baseline systolic blood pressure (SBP) ≥ 120 mmHg and/or diastolic blood pressure (DBP) ≥ 80 mmHg, or were taking medication for blood pressure management (40%). Participants were given a standardised health questionnaire and were excluded if they had known cardiovascular disease or multiple comorbidities, were unable to participate under their doctor's recommendation, and/or those with arthritis or carpal tunnel which may have been aggravated with handgrip exercise. Participant baseline characteristics are displayed in Table 1.

Table 1: Participant Baseline Characteristics

	5% MVC (Control)	30% MVC (Training)
n (male)	10 (6)	10 (6)
Age (years)	56 ± 9	55 ± 10
Height (cm)	172 ± 10	170 ± 9
Weight (kg)	87 ± 21	88 ± 18
Body Mass Index (kg/m ²)	30 ± 8	30 ± 5
Systolic Blood Pressure (mmHg)	148 ± 13	154 ± 14
Diastolic Blood Pressure (mmHg)	86 ± 6	89 ± 9
Mean Arterial Pressure (mmHg)	106 ± 7	110 ± 10
Heart Rate (bpm)	73 ± 5	77 ± 7
Medication Classification		
Beta-blocker	1	
ACE Inhibitor		1
ACE Inhibitor and Calcium channel blocker	2	
Calcium channel blocker and Diuretic	1	1
Angiotensin receptor blocker		2
Unmedicated	6	6

In accordance with the Declaration of Helsinki all participants provided written informed consent prior to participation. The University of New England Human Ethics Committee approved the investigation, and all procedures were in accordance with the University's guidelines. This research project is registered with ClinicalTrials.gov, the identifier for the study is NCT02458443.

Study Design

Isometric resistance training (IRT) has been shown to reduce blood pressure over periods of eight and ten weeks.^{6,7} The main objective of this study was to determine whether conducting IRT for 12 weeks would elicit similar or greater blood pressure responses than those previously reported. Previous research has indicated that low intensity IRT does not elicit statistically significant blood pressure reductions.^{6,22} Utilizing a low intensity IRT group enables all participants to conduct IRT, reinforcing the blinding of participants into control and working groups.

Participants were recruited during February to June 2016, sample size was restricted by the number of eligible participants who volunteered. Eligible participants were randomized into either a 5% maximum voluntary contraction (MVC) ($n=10$), or a 30% MVC ($n=10$) training group, as demonstrated in Figure 1. Randomization was conducted by a member of the research team prior

to baseline blood pressure measurements using a computer generated random number assignment, resulting in differences in systolic blood pressure at baseline. Participants were blinded to their group assignment; a numerical sequence was used to enable the supervising researcher to ensure that participants exercised at the correct intensity.

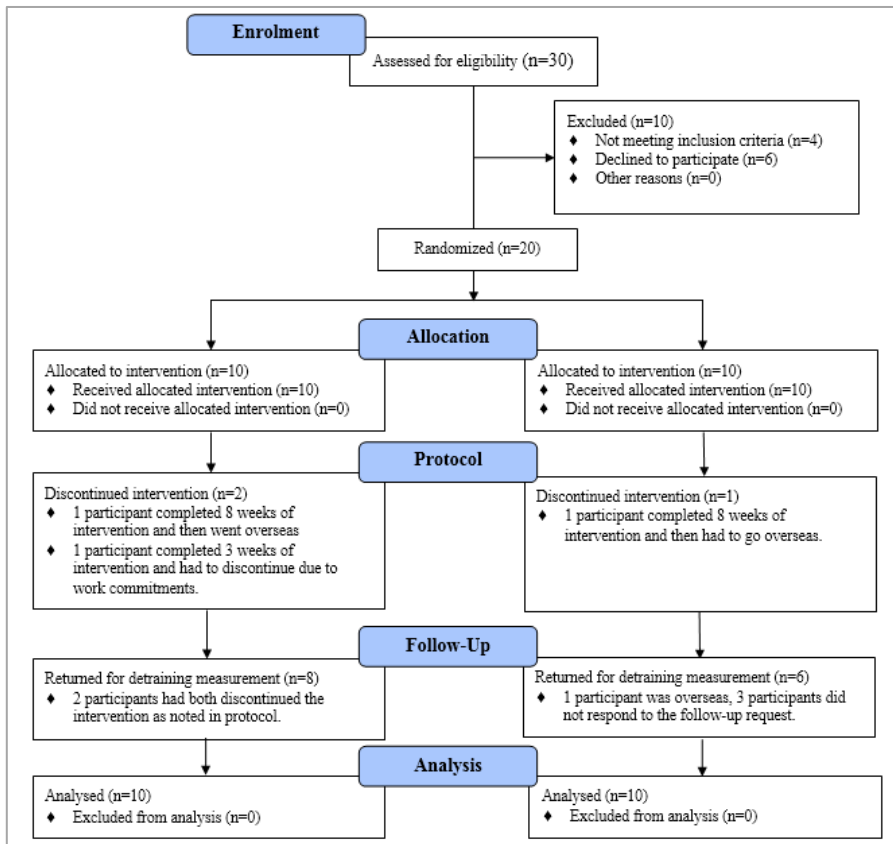


Figure 1: Participant enrolment, allocation and analysis

Procedures

Isometric Resistance Training

Participants attended the Exercise Physiology laboratory at the University of New England, 3 times a week for 12 weeks. At each session individual participant MVC was determined by averaging three contractions of maximal force. The MVC was then used to calculate the resistance level for performing IRT that day. Due to participants being blinded to group assignment the hand dynamometers used during IRT had the intensity reading facing away from the participant. A specifically designed lightbox was set up by a member of the research team at the level the

participants were required to exercise at, to provide feedback to the participants during IRT. Four sets of 2 minute isometric handgrip exercises with 3 minute rest periods in between were conducted at each session, using the participant's non-dominant arm. Participants were supervised by a member of the research team during each training session to ensure that they conducted IRT correctly and at the desired intensity, whilst monitoring the timing of IRT.

Blood Pressure Measurements

Blood pressure measurements were taken using an ambulatory blood pressure monitor (ABPM) (TM-2430) from A & D Australasia Pty Ltd, South Australia. Participants wore the cuff from the monitor on their non-dominant arm, to enable them to conduct their normal routine unhindered. All participants were trained in the general operating of the ABPM and correct cuff positioning in case they had to remove it for any reason. The monitor was programmed to take blood pressure measurements every 15 minutes during the day, and every 30 minutes during sleep. Participants were instructed to set the monitor to sleep mode when they went to bed, and to turn sleep mode off upon waking. Participants wore the monitor for 24 hours; at baseline prior to commencing the study, and at the completion of the 12 week IRT exercise protocol. On the last day of training, each participant was connected to the ABPM immediately following their last isometric handgrip exercise. Participants were instructed to maintain their regular routine in relation to exercise, medication and diet during detraining. Participants were contacted 12 weeks after their post measurements, and returned to conduct 24-h ABPM to assess the detraining effect on blood pressure after ceasing isometric training.

Data analysis

Data from the ABPM was downloaded into Doctor Pro3 blood pressure data analysis software (A & D, TM-9501), then exported into Excel (Microsoft Corporation). Individual mean systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) from Doctor Pro3 was then transferred to SPSS for analysis. Preliminary analyses were conducted to assess data normality and possible outliers. Independent samples T test was conducted to compare baseline measures between both groups to test for equality of means. Repeated measures ANOVA and Paired samples T test was conducted to compare the pre, post and detraining data for both groups. Due to disparity in the baseline SBP, Univariate ANCOVA was

conducted to verify results whilst allowing for baseline as a covariate. All T tests and ANOVA analyses were conducted using SPSS (version 22), $p \leq 0.05$ was considered statistically significant.

In line with intention to treat, blood pressure was recorded on the last day of IRT and used as last outcome carried forward (LOCF) post measurements for participants unable to complete the entire twelve week protocol. LOCF was used for all participants with no detraining data.

Results

Initial recruitment comprised 20 participants who commenced IRT. Adherence to IRT was 100% in the 17 participants who completed the entire 12 week IRT protocol and the 2 participants who completed 8 weeks of IRT; 1 participant withdrew after 3 weeks due to work commitments. Fourteen of the original participants who completed the initial IRT training protocol participated in the detraining; 8 from the 5% group, and 6 from the 30% group, as outlined in Figure 1.

Randomized groups were matched at baseline for age, gender, height, weight and medication status as displayed in Table 1. All participants were asked to let a member of the research team know if their regular exercise routine, diet or medication changed during the study, including detraining. There were no reported changes in exercise, diet and medication throughout the study by any of the participants, and there was no change in baseline-post participant weight.

Baseline comparison between groups

Tests of normality suggested that the assumption of normality had not been violated with $p > .05$ for all measures except for MAP in the 5% MVC group with $p = .01$. The only outlier identified was in the heart rate of the 30% MVC group, due to the mean being 75.6bpm with a 5% trimmed mean of 75.4bpm it appeared to have no effect and was retained for analysis.

Due to the difference in baseline SBP between the 5% MVC and 30% MVC groups an independent samples T-test was conducted, which indicated that there was no significant differences between the groups (95% CI -18.86, 6.26; $p = .31$). Independent samples T-tests also indicated that baseline DBP (95% CI -9.89, 4.09; $p = .39$), MAP (95% CI -12.14, 4.34; $p = .33$) and HR (95% CI -9.11, 2.31; $p = .23$) were not statistically different between the groups.

Post isometric resistance training

Twelve weeks of IRT resulted in a significant -7mmHg reduction in baseline versus post intervention 24-h ambulatory SBP in the 30% MVC group, with a nonsignificant reduction of -2mmHg in the 5% MVC group, as shown in Table 2. Initial repeated measures ANOVA analysis of SBP in the 30% group was borderline significant (95% CI -14.26, 0.06; $p = .05$). Due to disparities in baseline SBP between the 5% and 30% MVC groups, univariate ANCOVA was conducted with baseline SBP as a covariate. The 5% MVC group SBP was still not statistically significant with ANCOVA (95% CI -0.02, 0.62; $p = .06$); however, the significance in the 30% MVC group was strengthened (95% CI 0.09, 0.97; $p = .02$).

ANCOVA with baseline as a covariate was also used for DBP and MAP due to differences between the groups at baseline. A significant -5mmHg reduction in DBP was observed in the 30% MVC group (95% CI 0.23, 0.99; $p = .01$), while the 5% MVC group had a minimal reduction of -2mmHg (95% CI -0.25, 0.99; $p = .21$). Similar results were seen in MAP for the 30% and 5% MVC groups with -6mmHg (95% CI 0.17, 0.97; $p = .01$) and -2mmHg (95% CI -0.21, 0.77; $p = .23$), respectively.

There was no change in HR with both groups seeing a reduction of only -1bpm. Initial ANOVA analysis of HR indicated no significance from either the 30% (95% CI -2.63, 4.83; $p = .52$) or 5% group (95% CI -0.82, 3.82; $p = .18$). Vigorous analysis using ANCOVA with baseline as a covariate indicated both the 30% and 5% MVC groups were highly significant with (95% CI 0.60, 1.76; $p = .002$) and (95% CI 0.64, 1.71; $p = .001$), respectively. As there was no change in HR from baseline to post, ANCOVA appears to skew this data.

There were no significant reductions in 24-h ABPM of SBP, DBP and MAP in the 5% MVC group, all with $p > .05$ from both ANOVA and ANCOVA. The 30% MVC group saw statistically significant reductions in SBP, DBP and MAP from both ANOVA and ANCOVA, all with $p < .05$.

Table 2: Baseline and Post intervention measurements

	SBP	DBP	MAP	HR
5%				
Baseline	148 ± 3.9	86 ± 1.8	106 ± 2.3	73 ± 1.5
Post	146 ± 1.7	84 ± 1.5	104 ± 1.5	72 ± 1.0
Δ change	-2	-2	-2	-1
SEM change	3.2	1.8	2.2	1.0
p-value	0.06	0.21	0.23	0.001
30%				
Baseline	154 ± 4.5	89 ± 2.8	110 ± 3.2	77 ± 2.3
Post	147 ± 2.5	84 ± 1.5	104 ± 1.7	76 ± 1.7
Δ change	-7	-5	-6	-1
SEM change	3.2	1.7	2.1	1.7
p-value	0.02	0.01	0.01	0.002

Mean ± Standard Error of the Mean. SEM change-standard error of the mean for Δ change, SBP-systolic blood pressure, DBP-diastolic blood pressure, MAP-mean arterial pressure, HR-heart rate.

Detraining

Twelve weeks of detraining after ceasing isometric resistance training saw varying differences in 24-h ABPM compared to baseline and post IRT blood pressure, as shown in Tables 3 and 4. Comparison of baseline and detraining data in Table 3 indicates that SBP, DBP and MAP all remained lower after detraining in both the 30% and 5% MVC groups. Heart rate was also lower in the 30% MVC group, with no change in the 5% group.

As detailed in Table 3, analysis with ANCOVA indicates statistically significant reductions in SBP, DBP, MAP and HR in the 30% MVC group from baseline to detraining, all with $p < .01$. No significant differences were seen in the 5% MVC group with SBP, DBP and MAP all with $p > .05$. Heart rate in the 5% MVC group saw no change; however, was statistically significant with $p = .03$, indicating that use of ANCOVA appears to skew this data.

Table 3: Baseline – Detraining comparison measurements

	Baseline	Detraining	Δ change	p-value	95% CI
5%	n=10	n=10			
SBP	148 ± 4.0	144 ± 1.7	-4	0.38	-0.197, 0.462
DBP	86 ± 1.8	83 ± 1.6	-3	0.12	-0.143, 1.033
MAP	106 ± 2.3	103 ± 1.6	-3	0.29	-0.266, 0.779
HR	73 ± 1.5	73 ± 1.7	0	0.03	0.572, 1.577
30%	n=10	n=10			
SBP	154 ± 4.5	151 ± 5.6	-3	0.002	0.532, 1.600
DBP	89 ± 2.8	86 ± 2.7	-3	0.005	0.310, 1.274
MAP	110 ± 3.2	108 ± 3.5	-2	0.005	0.360, 1.421
HR	77 ± 2.3	75 ± 2.8	-2	0.001	0.572, 1.577

Mean ± standard error of the mean. SBP – systolic blood pressure, DBP – diastolic blood pressure, MAP – mean arterial pressure, HR – heart rate.

Table 4 shows the variation from post IRT to 12 weeks of detraining. The 30% MVC group saw statistically significant increases in SBP, DBP and MAP, all with $p > .01$; while HR indicates - 1bpm, $p = .00$. There was no significant change in SBP in the 5% MVC group; however, minimal changes of -1mmHg for DBP and MAP and 1bpm for HR were indicated as significant, with $p < .05$.

Table 4: Post Intervention – Detraining comparison measurements

	Post	Detraining	Δ change	p-value	95% CI
5%	n=10	n=10			
SBP	146 ± 2.0	144 ± 1.7	-2	0.15	-0.183, 1.037
DBP	84 ± 1.6	83 ± 1.6	-1	0.01	0.241, 1.291
MAP	104 ± 1.6	103 ± 1.6	-1	0.03	0.098, 1.327
HR	72 ± 2.0	73 ± 1.7	+1	0.01	0.222, 1.090
30%	n=10	n=10			
SBP	147 ± 3.4	151 ± 5.6	+4	0.04	0.099, 2.115
DBP	84 ± 2.3	86 ± 2.7	+2	0.004	0.418, 1.554
MAP	104 ± 2.4	108 ± 3.5	+4	0.02	0.224, 1.884
HR	76 ± 3.1	75 ± 2.8	-1	0.00	0.572, 1.102

Mean ± standard error of the mean. SBP – systolic blood pressure, DBP – diastolic blood pressure, MAP – mean arterial pressure, HR – heart rate.

Figures 2 and 3 show the individual effects of detraining on SBP and DBP for the 5% MVC and 30% MVC groups, respectively. LOCF was used for the 2 participants in the 5% group and 4 participants in the 30% group who did not conduct detraining ABPM.

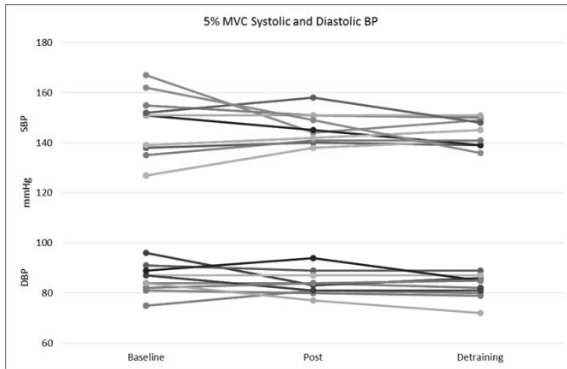


Figure 2: 5% MVC Individual participant Baseline, Post and Detraining SBP and DBP

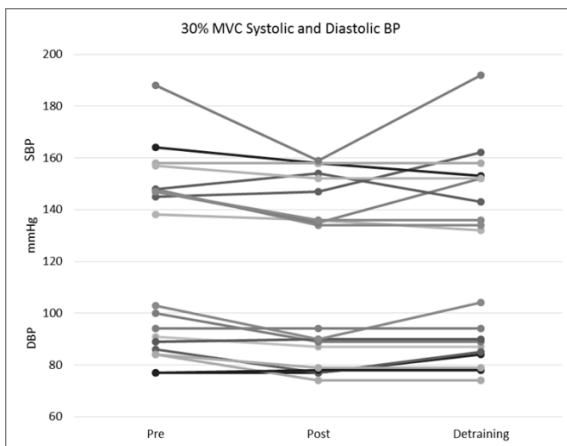


Figure 3: 30% MVC Individual participants Baseline, Post and Detraining SBP and DBP

Discussion

Ambulatory Blood Pressure

We conducted a randomized controlled trial to examine the effects of IRT over 12 weeks on 24-h ambulatory blood pressure. Based on evidence from our previous research, which indicates that there are no significant changes in blood pressure from low intensity IRT, a sham group was utilized as a working control.^{6,22} As hypothesized, our primary outcome showed no change in 24-h

ambulatory SBP, DBP, MAP or HR in the 5% MVC sham control group. Individual participant data for the 5% MVC group in Figure 2 indicates that five of the participants had an increase in SBP, three of whom also had an increase in DBP, after 12 weeks of IRT. Similar results indicating no mean overall change in SBP or DBP were seen in our previous research conducted over 8 weeks, or by Pagonas et al. (2017) over 12 weeks.^{6,12}

Mean population reductions of -7mmHg in SBP, -5mmHg in DBP and -6mmHg in MAP, with no change in HR were seen in the 30% MVC group over 24-h ABPM. Similar results were seen in our previous 8 week study and meta-analysis, as well as being evidenced by Millar et al. (2014) in their review.⁵⁻⁷ Somani et al. (2017)¹³ looked at the effect of 10 weeks of IRT on 24-h ABPM on normotensive participants and also noted reductions in SBP, with no change in DBP and HR.

In contrast Ash et al. (2017)¹⁴ saw no reduction in 24-h ambulatory SBP and DBP after 8 weeks; however, there were only 5 participants in the IRT group, larger participant numbers may have shown different results. Pagonas et al. (2017)¹² saw no change in 24-h ambulatory SBP and DBP after 12 weeks of IRT resistance training; however, the study design was a 2x2 and previous research has indicated that a 4x2 protocol is more effective²⁷. An earlier study conducted by Stiller-Moldovan, Kenno and McGowan (2012)¹⁵ which looked at 24-h ABPM on medicated hypertensives also showed no change in SBP, DBP or HR after 8 weeks of IRT. Individual participant data of our research in Figure 3 indicates that 2 participants, who were both medicated, saw increases in SBP after 12 weeks. As the other 2 medicated participants in the 30% MVC group had reductions in SBP, more detailed research needs to be conducted to ascertain individual reactions to IRT.

Detraining

This study is the first prospective one to examine the effects of detraining on blood pressure after completing a 12 week isometric handgrip IRT protocol. Numerous studies have been published on the antihypertensive effects of IRT, but to date there has only been one published article discussing any detraining effects, which was after 5 weeks of IRT.

Figure 2 shows the individual effects of detraining within the 5% MVC group. There was one participant who had an increase in both SBP and DBP at the end of the 12 week detraining period; however, they were both still below the original baseline. Two participants, who had increases in

SBP at the end of the IRT protocol, had further increases at the end of detraining. All other participants had either minimal or no change in SBP or DBP at the end of detraining compared to post IRT.

Among the six participants in the 30% MVC group who completed detraining, three had increases in both SBP and DBP compared to post IRT, as shown in Figure 3. The increases in SBP at detraining were all higher than baseline; however, DBP had increased in one and returned to baseline in the other two participants. The other three participants in the 30% MVC group saw SBP at detraining lower than both baseline and post IRT. However, their DBP at detraining was lower than baseline, and remained the same as it was post IRT for two of the participants, and showed no change at all for the third participant.

Similar results were seen by Oliveira et al. 2017²⁸ who looked at three months of detraining after nine months of aerobic and resistance exercise. In their study SBP and DBP both reduced from baseline to post-training, and then increased during detraining, still remaining lower than they were at baseline. A study by Bonsu and Terblanche in 2016²⁹ looked at the effect of two weeks of detraining following high intensity interval training and indicated that blood pressure returned to near baseline values after detraining.

Despite the emphasis on exercise to aid in reducing hypertension, studies indicate that not all individuals will respond to exercise the same, and that 20%-25% will not lower blood pressure after exercise.³⁰⁻³¹ Moker et al. 2014³¹ found that only 34.5% of their participants who reduced SBP during exercise training, had continued decreases in SBP during detraining. Overall, Moker et al. 2014³¹ ascertained that the majority of their participants with lowered blood pressure after training, increased blood pressure after detraining, and those with increased blood pressure after training decreased during detraining.

Other Information

Conclusions

There is a continual growing body of evidence on the efficacy of IRT protocols to aid in blood pressure management for individuals with hypertension. Utilization of a low intensity working control group has again proven to be effective with this research. The evidence so far shows no

indication that increasing the study length to 12 weeks increases the reduction in blood pressure, from those seen previously after 8 and 10 weeks. This research indicates that there is a trend for the blood pressure lowering effects of IRT to remain lower than those seen at baseline for a short time after completion of IRT. However, indications are that continued IRT is required to sustain blood pressure reductions long term.

Strengths and Limitations

The main strengths of this research are utilization of 24-h ABPM with an increase of study length to 12 weeks, and determination of the detraining effect on blood pressure after ceasing IRT. The main limitation of this research is the number of participants, and inability of some participants to return to establish the detraining effect on their blood pressure. One participant in the 5% MVC group withdrew from the study after 3 weeks due to work commitments and was unable to perform post ABPM, so the baseline was used as last outcome carried forward. No detraining data was available for the two participants in the 5% MVC group who did not complete the entire 12 week protocol. One participant in the 30% MVC group was unable to perform detraining ABPM, and there was no response from three other participants, so there was no detraining data for four participants in the 30% MVC group.

Conflicts of Interest

There are no conflicts of interest.

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**Higher Degree Research Thesis by Publication
University of New England**

STATEMENT OF AUTHORS' CONTRIBUTION

(To appear at the end of each thesis chapter submitted as an article/paper)

We, the Research Master/PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

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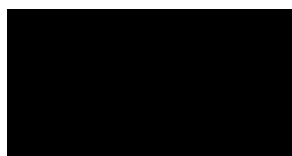
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Chapter 4: A randomized controlled trial on the effects of isometric handgrip exercise, followed by detraining, on 24-h ambulatory blood pressure

**Higher Degree Research Thesis by
Publication University of New England**

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Type of work	Page number/s
All text, tables and figures	Chapter 4, pp 80-98

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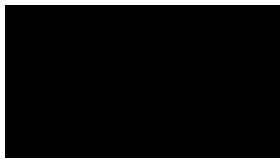
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Chapter 5: Rate pressure product responses during an acute session of isometric resistance training: A randomized trial.

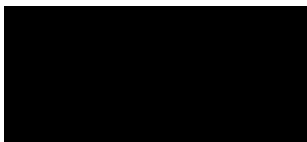
D.J. Carlson, J.R. McFarlane, G. Dieberg and N.A. Smart

Published online in the Journal of Hypertension and Cardiology

Citation: Carlson, D.J., McFarlane, J.R., Dieberg, G. and Smart, N.A. Rate pressure product responses during an acute session of isometric resistance training: A randomized trial. Journal of Hypertension and Cardiology. 2017, 2(3), 1-11. Doi:10.14302/issn.2329-9487.jhc-17-1428.



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Rate Pressure Product Responses during an Acute Session of Isometric Resistance Training: A Randomized Trial

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Abstract

Hypertension is a major modifiable risk factor for cardiovascular disease, responsible for approximately 31% of global mortality. The aim of this study was to examine the hypertensive responses and determine the peak rate pressure product, calculated by multiplying systolic blood pressure and heart rate, during isometric handgrip exercise.

Rate pressure product is a surrogate measure of myocardial oxygen consumption. Hypertensive responses utilising rate pressure product during isometric handgrip exercise have not previously been reported.

A randomized trial was conducted with 60 normotensive and 60 pre-hypertensive participants who attended once for an acute session of isometric handgrip exercise. Participants were randomized into groups exercising at 5%, 10% or 30% of their maximum voluntary contraction. Training was conducted using 4x2min isometric handgrip exercises each separated by a 3min rest period.

There were no significant differences between peak systolic and diastolic blood pressure, mean arterial pressure, heart rate and rate pressure product across the four bouts of isometric handgrip exercise in all groups, all $p > .05$. Peak increases in rate pressure product were significantly higher than baseline at all intensities assessed; all normotensive groups $p < .02$, all pre-hypertensive groups $p \leq .001$. Increases were relative to baseline blood pressure status and intensity of isometric handgrip exercise, with no significant differences between normotensive and pre-hypertensive groups.

Rate pressure product responses to isometric handgrip exercise indicate that it may be a safe alternative for people unable to perform recommended levels of aerobic exercise for blood pressure management.

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Running title: Rate pressure product during isometric exercise

Keywords: Isometric exercise, blood pressure, rate pressure product, hypertension

Received Jan 10, 2017; **Accepted** Jan 31, 2017; **Published** Feb 09, 2017;

Introduction

Cardiovascular disease remains the leading cause of death, representing approximately 31% of global mortality.¹ The most common modifiable risk factor for cardiovascular disease is hypertension, which contributes to approximately 50% of adverse outcomes in the US, including myocardial infarction and heart failure.² Current exercise recommendations from the American Heart Association to aid in controlling hypertension are a minimum 30 minutes per day, at least 5 days per week, of physical activity.³

A series of recent analyses have shown that isometric resistance training (IRT) can be effective in producing significant blood pressure lowering effects.⁴⁻⁷ Concerns over hypertensive responses during IRT mean some health professionals remain reluctant to recommend IRT. Consequently, moderate and vigorous aerobic exercise combined with resistance training remains the preferred exercise prescription to manage hypertension.⁸ Cardiovascular responses during resistance training are relative to intensity, number of repetitions, rest intervals and the duration of muscle recruitment.⁹ Aerobic exercise increases systolic blood pressure (SBP) and heart rate (HR), and consequently myocardial oxygen consumption, relative to the intensity and duration of the exercise.¹⁰

Rate pressure product (RPP), calculated by multiplying SBP and HR, is a valid non-invasive surrogate measure of myocardial oxygen consumption.^{11, 12} Coronary blood flow, cardiac workload and left ventricular hypertrophy have also been found to be relative to RPP.^{13, 14} Rate pressure product during stress tests is also a determinant of cardiovascular mortality.¹⁵

Despite concerns that RPP is raised during IRT, evidence suggests that during maximal isometric resistance exercise, RPP is lower than that seen during maximal aerobic exercise.^{9, 10} Previous studies into the

effect of isometric exercise on blood pressure have not looked at peak SBP, HR and RPP during exercise. The primary aim of this study was to determine the peak SBP, HR and RPP during an acute isometric handgrip exercise session at 5%, 10% and 30% maximum voluntary contraction, in both healthy normotensive individuals and those with pre-hypertension.

Methods

Study Design

A randomized trial was conducted with the objective of determining peak rate pressure product (RPP) during isometric handgrip exercise. After establishing the eligibility of participants they were randomized into either a 5%, 10% or 30% maximum voluntary contraction (MVC) intensity subgroup based on their normotensive/pre-hypertensive status. A computer generated random number assignment was used by D Carlson for randomization of participants. Each subgroup contained 20 participants who were blinded to intensity allocation and matched at baseline for blood pressure, age, height and weight. Adherence by randomized individuals was 100%, none of the participants reported any adverse effects from the isometric handgrip exercise protocol. The University of New England Ethics Committee approved the investigation, all participants provided written informed consent prior to participation, and all procedures were in accordance with the University's guidelines. The research project is registered with ClinicalTrials.gov (NCT0245845).

Participants

This study recruited 120 participants; 60 normotensives (men; n=34) and 60 pre-hypertensives (men; n=25), aged between 30 and 66 years, from the New England Region NSW Australia. Healthy normotensive participants, for the purpose of this study, were those with a resting systolic blood pressure (SBP) < 125mmHg and/or diastolic blood pressure (DBP) <

85mmHg not currently taking anti-hypertensive medication. Participants with a resting SBP \geq 125mmHg and/or DBP \geq 85mmHg, and those receiving pharmacological intervention for blood pressure management were classified as pre-hypertensive. Participants were excluded if they had known cardiovascular disease or multiple comorbidities, were unable to participate under their doctor's recommendation, smokers, and/or those with arthritis or carpal tunnel which may have been aggravated with handgrip exercise. Participant baseline characteristics are displayed in Table 1.

correct intensity.

Prior to commencing the protocol participants conducted three contractions using maximum force, each separated by 30 seconds. These were then averaged to calculate the resistance at which they would conduct their handgrip exercise, either 5%, 10% or 30% of MVC dependent upon which subgroup they were randomized into. Participants then completed four bouts of two-minute IHG contractions at the allocated intensity separated by three-minute rest periods. This training protocol has been used in previous studies which have

Table 1: Participant Baseline Characteristics

	Normotensive 5% MVC	10% MVC	30% MVC	Pre-Hypertensive 5% MVC	10% MVC	30% MVC
Characteristics						
n (male)	20 (12)	20 (12)	20 (10)	20 (8)	20 (10)	20 (7)
Age (years)	39 \pm 9	39 \pm 11	39 \pm 12	54 \pm 7	55 \pm 8	52 \pm 8
Height (cm)	174 \pm 8	174 \pm 11	171 \pm 9	171 \pm 9	171 \pm 10	170 \pm 9
Weight (kg)	81 \pm 17	81 \pm 20	74 \pm 13	88 \pm 20	92 \pm 18	88 \pm 16
SBP (mmHg)	115 \pm 11	119 \pm 13	115 \pm 9	131 \pm 13	133 \pm 13	136 \pm 12
DBP (mmHg)	67 \pm 7	70 \pm 7	69 \pm 8	75 \pm 8	75 \pm 8	77 \pm 7
MAP (mmHg)	85 \pm 8	88 \pm 9	87 \pm 8	97 \pm 9	97 \pm 10	100 \pm 9
HR (bpm)	68 \pm 10	70 \pm 11	68 \pm 9	69 \pm 10	70 \pm 7	67 \pm 9
RPP	7865 \pm 1355	8251 \pm 1103	7764 \pm 1254	9001 \pm 1186	9325 \pm 1157	9074 \pm 1353

Values are mean \pm SD. DBP-diastolic blood pressure, HR-heart rate, MAP-mean arterial pressure, MVC-maximum voluntary contraction, RPP-rate pressure product, SBP-systolic blood pressure.

Training Protocol

Participants attended the Exercise Physiology laboratory at the University of New England for one isometric handgrip exercise session, supervised by a member of the research team. During this session participants conducted isometric handgrip (IHG) exercise using a DHD-3 Digital Hand Dynamometer (Saehan Corporation, South Korea) with their non-dominant hand. Participants received feedback via a specifically designed light box calibrated to each participant's % of MVC, to screen them from knowing their group allocation whilst ensuring they performed IHG at the

utilized 30% MVC to investigate the blood pressure lowering effects of IHG.⁴ Exercise intensities up to 50% MVC have been utilized in IHG studies where participants conducted the exercise for durations of 45seconds; however, this intensity is not sustainable for 2 minutes of IHG.

Blood Pressure Measurements

Baseline blood pressure was established using a Finometer® Midi Model-2 (Finapres Medical Systems B.V., Amsterdam, The Netherlands) to monitor beat-to-beat blood pressure, heart rate (HR) and mean arterial pressure (MAP). Two minutes of continuous resting

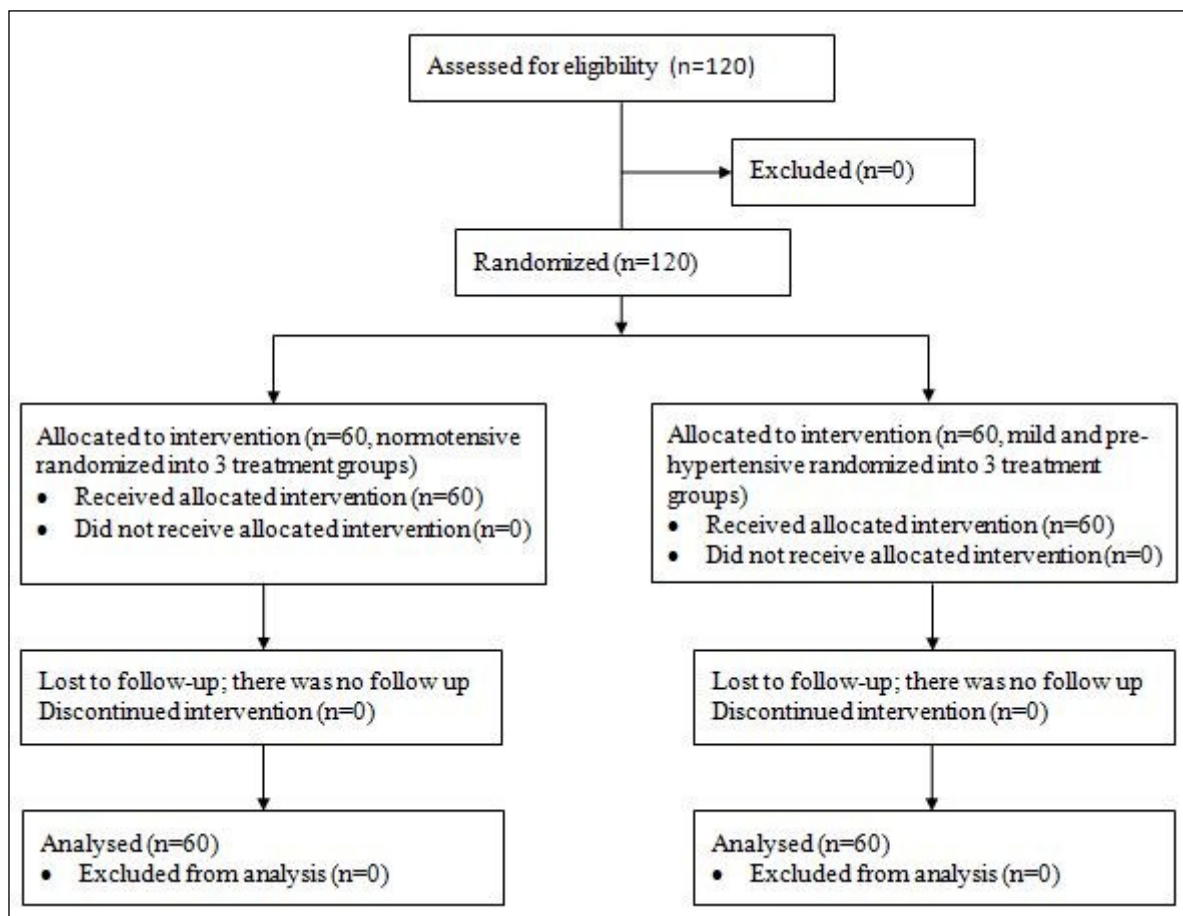


Figure 1: Flow chart demonstrating participant recruitment, randomization and retention.

baseline blood pressure was recorded using the Finometer® prior to commencement of the training protocol. Whilst conducting the training protocol participants remained connected to the Finometer® to monitor cardiovascular measurements, for determining peak RPP during each bout of IHG exercise.

Data from a previous trial conducted by the research team showed that there was no significant difference between sphygmomanometer and Finometer® measurements. We conducted a reliability study containing 40 participants that indicated SBP measurements by sphygmomanometer 131 ± 8.9 and Finometer® 133 ± 16.2 (95% CI -6.35, 2.08 $p=.47$). This non-significant difference between sphygmomanometer and Finometer® SBP measurements was accompanied by a strong positive correlation; $r=0.58$.

Statistical Analysis

BeatScope® Easy software which records waveforms and beat-to-beat data was used to unpack the Finometer® data into Excel (Microsoft Corporation, Redmond, USA). The entire two minutes of baseline data was averaged to determine individual baseline SBP, DBP, HR, MAP and RPP. Two minute baseline data was used to (i) categorise participants according to blood pressure and (ii) calculate differences between baseline and peak measures during IHG exercise. Individual participant data for each bout of IHG exercise was scrutinized to determine peak SBP and HR for peak RPP calculation. Mean baseline and peak exercise SBP, DBP, HR, MAP and RPP were used in our analysis.

Data analysis was conducted using SPSS version 22 (Chicago, Illinois, USA), $p \leq .05$ was considered statistically significant. Results are presented as mean \pm standard deviation and 95% confidence interval (95%

Table 2: Peak Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Pressure and Heart Rate during Isometric Handgrip Exercise

MVC	Normotensive			Pre-hypertensive		
	5%	10%	30%	5%	10%	30%
Systolic Blood Pressure						
Baseline	115 ± 11	119 ± 13	115 ± 9	131 ± 13	133 ± 13	136 ± 12
Bout 1	130 ± 11	140 ± 25	142 ± 17	147 ± 14	151 ± 17	154 ± 15
Δ change	15	21	27	16	18	18
Δ %	13	17.6	23.5	12.2	13.5	13.2
Bout 2	132 ± 20	136 ± 14	146 ± 18	147 ± 19	154 ± 18	169 ± 36
Δ change	17	17	31	16	21	33
Δ %	14.8	14.3	27	12.2	15.8	24.3
Bout 3	133 ± 16	136 ± 15	154 ± 23	143 ± 15	156 ± 19	174 ± 36
Δ change	18	17	39	12	23	38
Δ %	15.7	14.3	33.9	9.16	17.3	27.9
Bout 4	137 ± 29	138 ± 18	150 ± 17	144 ± 17	156 ± 17	172 ± 33
Δ change	22	19	35	13	23	36
Δ %	19	16	30.4	9.9	17.3	26.5
ANOVA F(3,76)	0.48	0.22	1.49	0.36	0.28	1.66
p-value	0.7	0.88	0.22	0.78	0.84	0.18
Diastolic Blood Pressure						
Baseline	67 ± 7	70 ± 7	69 ± 8	75 ± 8	75 ± 8	77 ± 7
Bout 1	76 ± 8	79 ± 8	82 ± 11	81 ± 10	84 ± 13	87 ± 9
Δ change	9	9	13	6	9	10
Δ %	13.4	12.9	18.8	8	12	13
Bout 2	74 ± 7	80 ± 10	90 ± 22	82 ± 9	85 ± 11	92 ± 15
Δ change	7	10	21	7	10	15
Δ %	10.4	14.3	30.4	9.3	13.3	19.5
Bout 3	77 ± 10	79 ± 8	91 ± 17	82 ± 9	85 ± 13	98 ± 22
Δ change	10	9	22	7	10	21
Δ %	14.9	12.9	31.88	9.3	13.3	27.3
Bout 4	76 ± 7	79 ± 11	92 ± 14	81 ± 11	86 ± 12	96 ± 22
Δ change	9	9	23	6	11	19
Δ %	13.4	12.9	33.3	8	14.7	24.7
ANOVA F(3,76)	0.56	0.07	1.51	0.04	0.07	1.34
p-value	0.65	0.98	0.22	0.99	0.97	0.27

	Normotensive			Pre-hypertensive		
Mean Arterial Pressure						
Baseline	85 ± 8	88 ± 9	87 ± 8	97 ± 9	97 ± 10	100 ± 9
Bout 1	95 ± 9	101 ± 11	106 ± 12	104 ± 11	109 ± 12	112 ± 11
Δ change	10	13	19	7	12	2
Δ %	11.8	14.8	21.8	7.2	12.4	2
Bout 2	97 ± 11	101 ± 10	112 ± 20	107 ± 13	111 ± 13	121 ± 21
Δ change	12	13	25	10	14	21
Δ %	14.1	14.8	28.7	10.3	14.4	21
Bout 3	98 ± 10	100 ± 11	118 ± 21	105 ± 11	110 ± 12	128 ± 28
Δ change	13	12	31	8	13	28
Δ %	15.3	13.6	35.6	8.2	13.4	28
Bout 4	100 ± 16	100 ± 14	114 ± 13	105 ± 12	112 ± 13	125 ± 29
Δ change	15	12	27	8	15	25
Δ %	17.6	13.6	31	8.2	15.5	25
ANOVA F(3,76)	0.51	0.02	1.61	0.22	0.18	1.66
p-value	0.68	0.99	0.19	0.88	0.91	0.18
Heart Rate						
Baseline	68 ± 10	70 ± 11	68 ± 9	69 ± 10	70 ± 7	67 ± 9
Bout 1	67 ± 12	68 ± 15	71 ± 11	71 ± 10	71 ± 11	73 ± 10
Δ change	1	2	3	2	1	6
Δ %	1.5	2.9	4.4	2.9	1.4	9
Bout 2	66 ± 10	66 ± 11	74 ± 11	72 ± 9	70 ± 8	73 ± 12
Δ change	2	4	6	3	0	6
Δ %	2.9	5.7	8.8	4.3	0	9
Bout 3	65 ± 10	67 ± 12	74 ± 13	72 ± 9	69 ± 7	79 ± 16
Δ change	3	3	6	3	-1	12
Δ %	4.4	4.3	8.8	4.3	-1.4	17.9
Bout 4	70 ± 11	66 ± 12	75 ± 12	72 ± 10	71 ± 11	75 ± 13
Δ change	2	4	7	3	1	8
Δ %	2.9	5.7	10.3	4.3	1.4	11.9
ANOVA F(3,76)	0.72	0.13	0.77	0.03	0.27	1.03
p-value	0.54	0.94	0.52	0.99	0.85	0.38

Mean ± Standard deviation. MVC – Maximum voluntary contraction.

CI), unless otherwise specified. One-way ANOVA was conducted to compare mean peak SBP, DBP, HR, MAP and RPP across four bouts of isometric handgrip exercise for each intensity within the normotensive and pre-hypertensive groups. Comparison of the various

all statistically significant, $p < .01$. Peak exercise SBP, DBP and MAP was higher than baseline for all groups.

Peak exercise HR was higher than baseline at 30% intensity with statistically significant differences

Table 3: Comparison of Peak Rate Pressure Product across Isometric Handgrip Exercise Bouts

	Normotensive			Pre-hypertensive		
	5% MVC	10% MVC	30% MVC	5% MVC	10% MVC	30% MVC
Baseline	7865 ± 1355	8251 ± 1103	7764 ± 1254	9001 ± 1186	9325 ± 1157	9074 ± 1353
Bout 1	8754 ± 1762	9409 ± 2334	10085 ± 2392	10473 ± 1885	10724 ± 2028	11274 ± 2120
Δ change	889	1158	2321	1472	1399	2200
Δ %	11.3	14	29.9	16.4	15	24.2
Bout 2	8785 ± 2244	8931 ± 1624	10546 ± 2713	10479 ± 1716	10756 ± 1798	12301 ± 3235
Δ change	920	680	2782	1478	1431	3227
Δ %	11.7	8.2	35.8	16.4	15.3	35.6
Bout 3	8609 ± 1697	9073 ± 1535	11586 ± 3297	10244 ± 1353	10677 ± 1482	14136 ± 5879
Δ change	744	822	3822	1243	1352	5062
Δ %	9.5	10	49.2	13.8	14.5	55.8
Bout 4	9617 ± 3115	9137 ± 1931	11320 ± 2352	10260 ± 1776	11041 ± 1984	13077 ± 4878
Δ change	1752	886	3556	1259	1716	4003
Δ %	22.3	10.7	45.8	14	18.4	44.1
ANOVA F(3,76)	0.81	0.23	1.3	0.12	0.16	1.6
p-value	0.49	0.88	0.28	0.95	0.92	0.2

Mean ± Standard deviation. MVC – Maximum voluntary contraction.

intensities within the normotensive and pre-hypertensive groups was conducted using MANOVA. Comparison of normotensive versus hypertensive peak RPP for each bout was conducted using one-way ANOVA, with independent t-test used to compare peak bouts for each intensity.

Results

Peak Blood Pressure and Heart Rate during handgrip exercise

Comparison of mean peak SBP, DBP, MAP and HR across the four bouts of IHG exercise for each intensity; in both the normotensive and pre-hypertensive groups, showed no significant differences between the four bouts, as shown in Table 2. Comparison of mean baseline SBP, DBP and MAP with the peak of four bouts for the normotensive and pre-hypertensive groups were

seen in the normotensive and pre-hypertensive groups, $p < .05$. Peak HR during IHG exercise was higher in the pre-hypertensive group than the normotensive group. Normotensive 5% and pre-hypertensive 5% and 10% MVC intensities saw minimal increases in HR from baseline to peak exercise with no statistical significance; while peak exercise HR in the normotensive 10% MVC group was lower than baseline.

Peak Rate Pressure Product during handgrip exercise

There were no significant differences in peak RPP across the four bouts of 2 minute IHG exercise for each of the intensities, in either the normotensive or pre-hypertensive groups, as shown in Table 3. The high probability and low f-statistic for all of the normotensive and hypertensive groups indicate that there is very little

Table 4: Comparison of Baseline Rate Pressure Product and Peak Rate Pressure Product during Isometric Handgrip Exercise

	Baseline RPP Mean \pm SD	Peak RPP Mean \pm SD	95% CI	p-value	Δ change	$\Delta\%$
Normotensive						
5% MVC	7865 \pm 1355	9617 \pm 3115	-3378, -127	P=.003	1752	22.3
10% MVC	8251 \pm 1103	9409 \pm 2334	-1260, -100	P=.015	1158	14
30% MVC	7764 \pm 1254	11586 \pm 3297	-5894, -1751	P<.001	3822	49.2
Pre-hypertensive						
5% MVC	9001 \pm 1186	10479 \pm 1716	-2449, -507	P<.001	1478	16.4
10% MVC	9325 \pm 1157	11041 \pm 1984	-2906, -526	P<.001	1716	18.4
30% MVC	9074 \pm 1353	14136 \pm 5879	-8923, -1201	P=.001	5062	55.8

MVC-maximum voluntary contraction, RPP-rate pressure product

difference in peak RPP between bouts with IHG.

Significant differences were seen between baseline RPP and the peak RPP during IHG exercise in both the normotensive and pre-hypertensive groups, as displayed in Table 4. The peak bout varied amongst groups with the highest being bout 4, bout 1 and bout 3 for the 5%, 10% and 30% MVC normotensive groups respectively. Variation was seen in the pre-hypertensive peak bouts with 5%, 10% and 30% MVC groups peaking at bout 2, bout 4 and bout 3 respectively. Although rate pressure product increases from baseline to peak were statistically significant for all groups, the actual increase in RPP was relatively minimal in the 5% and 10% groups compared to those seen in the 30% group, Table 4.

Comparison of normotensive versus hypertensive

As expected peak RPP was higher for all of the pre-hypertensive intensities than those seen in the corresponding normotensive groups. There were no significant differences between the normotensive and pre-hypertensive peak bouts in either the 5% intensity (95% CI -748, 2472, p=0.29) or the 30% intensity (95%

CI -501, 5601, p=0.99) groups. Statistically significant differences were seen between the peak bouts in the normotensive and pre-hypertensive groups in the 10% intensity (95% CI 246, 3019, p=0.02).

Discussion

The primary aim of this study was to determine the effect of isometric handgrip exercise on blood pressure, heart rate and consequently rate pressure product. The study demonstrates that IHG exercise increases blood pressure, and consequently RPP in both healthy normotensive and pre-hypertensive individuals during IHG exercise, but to a lesser extent than aerobic exercise. Blood pressure increases were greater with increased intensity, as indicated by Maior et al. (2014).⁹

Blood Pressure and Heart Rate

As anticipated we saw significant increases in SBP, DBP, MAP and HR from baseline to peak exercise during IRT. The pre-hypertensives had an initial higher baseline than the normotensives; interestingly, increases in SBP, DBP, MAP and HR across all intensities for both the normotensive and pre-hypertensive groups were similar. Within the 30% intensity the normotensives increased SBP by 39mmHg, while the pre-hypertensives

increased by 38mmHg. When we compare our IRT responses to previously published aerobic exercise response data, we find that hypertensive responses of SBP during exercise stress tests have reached greater increases and peaks than those seen in this IRT study. Kurl et al.¹⁶ saw mean maximal SBP during an exercise stress test of 210mmHg, while Gupta et al.¹⁷ saw increases greater than 44mmHg with a peak of 195mmHg. A meta-analysis conducted by Schultz et al.¹⁸ indicated SBP hypertensive responses to moderate and maximal exercise reaching 230mmHg during aerobic exercise.

Increases from baseline to peak in DBP for the 30% normotensives were 23mmHg while pre-hypertensives increased 21mmHg. More moderate increases from baseline to peak in DBP were seen by

Gupta et al.¹⁷ with only an 8mmHg increase to 88mmHg during a stress test. The increases from baseline to peak in MAP were 31mmHg for the 30% normotensives and 28mmHg for the pre-hypertensives. The highest peak MAP observed in this study was 128mmHg which is comparable with those seen by Simonson and Wyatt¹⁹ with MAP of 142mmHg cycling and 124mmHg using treadmill.

Heart rate increases seen in this study were minimal even in the 30% intensity groups with only a 7bpm increase and peak of 75bpm in the normotensives, and a 12bpm increase with a peak of 79bpm in the pre-hypertensives. The Finnish cardiovascular study saw HR more than double with peaks during exercise of 152bpm and 131bpm during an exercise stress test.¹⁵ Similar increases in HR were seen by Simonson and Wyatt¹⁹ who saw HR peaks of 175bpm during supine cycle ergometry and 187bpm on a treadmill in maximum stress tests. The recovery seen after IRT occurs within 20 seconds, indicating that it is less dangerous than aerobic exercise due to low increases in heart rate and fast recovery.

Rate Pressure Product

Baseline to peak RPP for the 30% intensity normotensive group increased by 3822 to a peak of 11586, with the pre-hypertensive group increasing by 5062 to a peak of 14136.

The RPP increases which we saw are similar to those seen by Maior et al. (2014)⁹, who looked at blood pressure measurements taken immediately following isometric bench presses conducted by healthy individuals, and calculated RPP at approximately 12500 at 25% intensity. Atkinson et al. (2009)¹³ assessed RPP from 24hour ambulatory monitoring in patients attending a hypertension clinic and saw mean RPP of 9824 with a peak of 11284, from people conducting their normal routine.

Overall maximal RPP during stress tests conducted by Pinkstaff et al. (2010)²⁰ reached 27729 with one group averaging 28302. Maximum stress tests conducted by Simonson and Wyatt (2003)¹⁹ saw RPP during supine cycle ergometry of 34475 and treadmill of 31930, when taking oxygen consumption into account they equated to 27190 and 22600, respectively. The comparatively low, peak RPP which we observed, is attributed to the minimal effect of isometric exercise on heart rate.

Conclusion

The increases in rate pressure product observed during isometric handgrip exercise were not as substantial as those seen during moderate and vigorous aerobic exercise in previous studies. Positive correlation among the four bouts of isometric handgrip exercise and baseline data in this study indicates that there is a positive linear relationship between blood pressure and intensity of isometric handgrip exercise. Statistical analyses show that increases in blood pressure, and consequently rate pressure product, are relative to baseline blood pressure. Greater increases in blood pressure and rate pressure product were observed with

increased intensity; however, these were correlated with similar increases in both normotensives and pre-hypertensives. Previous studies reporting SBP, HR and RPP during exercise stress testing indicate that increases in these are a lot greater than those seen during IRT; indicating that cardiovascular responses during IRT are within safe limits.

Limitations and Future Research

The main limitation of this study is a lack of direct comparison data with aerobic exercise. Recommendation for future research would be to conduct IRT and aerobic exercise with participants to get a direct comparison of SBP, DBP, HR and RPP in the two exercise modalities within the same cohort.

Acknowledgements

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Chapter 5: Rate pressure product responses during an acute session
of isometric resistance training: A randomized trial

Higher Degree Research Thesis by Publication
University of New England

STATEMENT OF AUTHORS' CONTRIBUTION

(To appear at the end of each thesis chapter submitted as an article/paper)

We, the Research Master/PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

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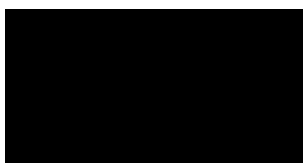
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Chapter 5: Rate pressure product responses during an acute session
of isometric resistance training: A randomized trial

**Higher Degree Research Thesis by
Publication University of New England**

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Type of work	Page number/s
All text, tables and figures	Chapter 5, pp 101-112

Name of Candidate: Debra Carlson

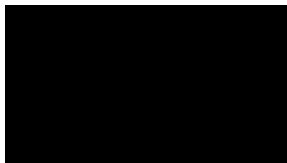
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Chapter 6: Blood pressure measurements in research – suitability of sphygmomanometer, beat-to-beat and ambulatory blood pressure measurements

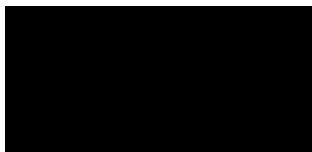
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Submitted to Blood Pressure Monitoring on 17 October 2017

Currently in the review process



Candidate Signature



Principal Supervisor Signature

Blood pressure measurements in research – suitability of sphygmomanometer, beat-to-beat and ambulatory blood pressure measurements.

Short title: Blood pressure measurement in research

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Word count: 4458

Number of Tables: 3

Number of Figures: 0

No supplementary digital content files

Conflict of interest and source of funding: none declared

Key Words: blood pressure, ambulatory, sphygmomanometer, beat-to-beat

Abstract Objective

The objective of this study was to validate the accuracy of beat-to-beat measurements with those taken with an aneroid sphygmomanometer by auscultatory method. A secondary aim was to explore differences between sphygmomanometer and beat-to-beat blood pressure with daytime ambulatory blood pressure measurements.

Methods

Forty six participants, males ($n=21$), aged 47 ± 13 years, height 171 ± 8.5 cm and weight 82 ± 16.8 kg attended the Exercise Physiology Laboratory at the University of New England, Armidale, NSW Australia. During the visit participants had their blood pressure – systolic (SBP) and diastolic (DBP) measured using the sphygmomanometer and Finometer. An ambulatory blood pressure monitor was fitted during the same visit and worn for a minimum of 12h.

Results

Sphygmomanometer measurements were slightly higher than beat-to-beat for both SBP and DBP. There was no difference between sphygmomanometer and beat-to-beat SBP with a mean difference of 0.23 mmHg, $p=0.87$. There were disparities between sphygmomanometer and beat-to-beat DBP with a mean difference of 4.82 mmHg, $p<0.01$. Daytime ambulatory blood pressure was higher than both sphygmomanometer and beat-to-beat measurements for both SBP and DBP with $p<0.001$ for all measures.

Conclusions

There was a high level of reliability in the beat-to-beat SBP with that seen by sphygmomanometer; however, there were disparities in DBP measurements using the same devices which raise concerns over the accuracy of beat-to-beat DBP. Ambulatory systolic and diastolic measures were higher than beat-to-beat and sphygmomanometer; however, they may be more suitable for monitoring diurnal changes in blood pressure, depending upon the research model.

Introduction

Blood pressure measurement is generally taken at the brachial artery; however, monitors are available that take measurements at the wrist and finger. Due to the hydrostatic effect of differences in systolic and diastolic pressures, wrist and finger devices may be inaccurate if they are not held at heart height during measurement [1]. The most common blood pressure measurement has been brachial auscultation using a mercury sphygmomanometer and stethoscope listening for Korotkoff sounds. Mercury sphygmomanometer use is being diminished and replaced by aneroid and oscillometric blood pressure devices [2].

The Finometer® is a low risk, non-invasive, photoplethysmographic, hemodynamic instrument which measures beat-to-beat blood pressure by continuously monitoring finger arterial pressure [3]. High frequency pressure vibration is used for blood pressure measurement in the finger, based on the arterial volume-clamp method introduced by Penaz [4 5]. A cuff is wrapped around the finger which keeps the diameter of the artery clamped at a constant diameter to maintain maximum arterial compliance, so that cuff pressure and intra-arterial pressure are at equal levels [4 6]. A photoplethysmograph containing a light source on one side, and an infrared receiver on the opposite side of the cuff estimates blood volume [7]. Due to the resistance in small arteries affecting finger arterial pressure, a height adjusting component in the Finometer reconstructs brachial artery pressure from the finger artery [6]. This reduces pressure differences, and has been shown to meet the American Association for the Advancement of Medical Instrumentation (AAMI) criteria [5]. Numerous conditions can affect the accuracy of the Finometer including temperature and arterial stiffness. Concerns over the accuracy of measurements from the Finometer during hypotensive events, alternating vascular tone and hemodynamic instability have been noted by Njoum and Kyriacou (2016) [8].

Ambulatory blood pressure measurements taken over a 24 hour period are currently considered the gold standard in some countries for blood pressure measurement for hypertension diagnosis as it

better reflects clinical outcomes [9-11]. A cuff is placed on the upper arm and the ambulatory blood pressure device worn for 24 hours, with blood pressure measured every 15-30 minutes during the day and 30-60 minutes during the night [9]. Twenty four hour ambulatory blood pressure can be relevant for hypertension diagnosis in individuals at cardiovascular risk, assessment of treatment effects, and end-organ damage associated with hypertension [9 11 12]. Ambulatory blood pressure is a strong predictor of clinical outcomes such as left ventricular hypertrophy, renal and vascular surrogate markers of end-organ damage, and presence or absence of nocturnal blood pressure dipping [9].

The Joint National Committee (JNC) in the US and the World Health Organization-International Society of Hypertension (WHO-ISH), as well as the European Society of Hypertension/European Society of Cardiology (ESH/ESC) endorse the use of 24-h ambulatory blood pressure monitoring for diagnosing hypertension [10 13]. Ambulatory blood pressure monitoring gives an estimate of the true blood pressure, describes the diurnal rhythm, and estimates short-term variability [13].

Ambulatory blood pressure monitors are accurate when the person wearing it is resting, but may not be as accurate during physical activity [9 14]. Higher daytime ambulatory blood pressure is indicative of increased cardiovascular risk; however daytime blood pressure is expected to be higher than nocturnal blood pressure [15]. In a study by Ciolec et al. (2008) daytime ambulatory blood pressure was higher in participants in all cohorts than that seen over 24 hours [16].

Researchers have utilized the various forms of blood pressure measurement in their research. There have been numerous studies comparing clinic/office blood pressure and ambulatory blood pressure, and a study comparing sphygmomanometer and Finometer measurements [17-19]. Currently there is no direct comparison of aneroid sphygmomanometer, Finometer beat-to-beat, and ambulatory blood pressure measurements. Due to concerns over the accuracy of Finometer blood pressure measurements our primary aim was to compare beat-to-beat resting blood pressure measurements with those from an aneroid sphygmomanometer. Our secondary aim was to examine the difference

between resting (sphygmomanometer and beat-to-beat) and ambulatory blood pressure measurements and compare this with previous studies.

Methods

Study participants

Forty six participants, males ($n=21$), aged 47 ± 13 years, height 171 ± 8.5 cm and weight 82 ± 16.8 kg were recruited from Armidale, NSW, Australia and the surrounding area. Participants attended the Exercise Physiology Laboratory at the University of New England on one occasion to have their blood pressure measured by auscultatory method using a sphygmomanometer, a Finometer for beat-to-beat measurements and an ambulatory blood pressure monitor in the same visit. Participants had an ambulatory blood pressure monitor attached to them after the sphygmomanometer and Finometer measurements were taken, they then left and went about their normal routine and returned the monitor the following day.

Participant characteristics and mean blood pressure overall, as well as normotensive and hypertensive breakdown are shown in Table 1. Participants classified as hypertensive were all pre-hypertensive, had mild hypertension, or were receiving pharmacotherapy to treat their BP and had a resting SBP ≥ 120 mmHg and/or a resting DBP ≥ 80 mmHg. Participants were excluded if they had known cardiovascular disease or multiple comorbidities.

In accordance with the Declaration of Helsinki all participants provided written informed consent prior to participation. This research was approved by the University of New England Human Ethics Committee, and all procedures were conducted in accordance with the University's guidelines. The research project is registered with ClinicalTrials.gov, the identifiers are NCT02458443 and NCT02458456.

Table 1: Participant Characteristics

	All Participants	Normotensive	Hypertensive
Participants	(n=46) Males (n=21)	(n=18) Males (n=6)	(n=28) Males (n=15)
	Mean ± SD	Mean ± SD	Mean ± SD
Age	47 ± 13.4	36 ± 12.0	54 ± 8.9
Height	171 ± 8.5	172 ± 7.4	170 ± 9.2
Weight	82 ± 16.8	76 ± 15.8	85 ± 16.8
Systolic Blood Pressure			
Sphygmomanometer	129 ± 11.0	121 ± 7.0	134 ± 10.3
Finometer	128 ± 12.7	121 ± 8.3	133 ± 13.0
Ambulatory	146 ± 14.2	137 ± 12.8	152 ± 12.2
Diastolic Blood Pressure			
Sphygmomanometer	76 ± 11.4	71 ± 9.7	80 ± 11.1
Finometer	71 ± 8.3	70 ± 4.5	72 ± 10.0
Ambulatory	86 ± 8.9	81 ± 7.8	90 ± 7.8

Blood Pressure Measurements

All resting measurements were conducted in a quiet temperature controlled room, 21-24°C, between 8am and 10am. Participants rested for 10 mins by lying supine on a massage table in the laboratory prior to any measurements being conducted. Sphygmomanometer and Finometer measurements were conducted whilst the participant was lying supine on the massage table. Blood pressure was measured in each participant's non-dominant arm to ensure resting and ambulatory blood pressure measurements were all conducted on the same arm.

Sphygmomanometer measurements were conducted using an aneroid Heine Gamma G7 sphygmomanometer calibrated by a technician prior to study commencement. Brachial blood pressure measurements were conducted according to recommended guidelines, using a Littmann Classic IISE stethoscope to listen for the Korotkoff sounds [1 20]. Three blood pressure measurements were recorded, each separated by a 5min rest period, followed by another 5min rest period prior to Finometer measurements.

Beat-to-beat continuous blood pressure measurements were then recorded for 2mins using a Finometer Midi Model-2 (Finapres Medical Systems B.V., Amsterdam, The Netherlands). The Finometer was calibrated against the Heine sphygmomanometer by a technician, in accordance with recommended guidelines prior to study commencement, to ensure the accuracy of recordings. The finger cuff was placed on the middle finger of the non-dominant hand and the height correction unit used to correct hydrostatic blood pressure changes for the hand being away from heart level.

At completion of resting blood pressure measurements, participants then wore an ambulatory blood pressure monitor (A & D Australasia Pty Ltd, South Australia) for a minimum of 12 hours. Calibration of the ambulatory blood pressure monitor was performed by a technician to ensure that it was equivalent to the Heine sphygmomanometer. The monitor's cuff was placed on the non-dominant arm of participants to enable them to conduct their regular daily activities unhindered. Participants were instructed to relax their arm by their side and not to use it when the cuff started to inflate, to prevent over-inflation and ensure measurement accuracy. The monitor was programmed to record blood pressure measurements every 15 mins, and participants were instructed on the earliest time that the monitor could be removed to ensure 12 hours of data was collected.

Data Analysis

BeatScope Easy software which records waveforms and beat-to-beat data was used to unpack the Finometer data into a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA). Excel was then used to calculate the mean and standard deviation of each participant's 2min SBP and DBP measurements. Doctor Pro3 software was used to download each participant's data from the ambulatory blood pressure monitor. The data was exported to Excel and compared to a summary provided by the Doctor Pro3 software for accuracy, the first 12 hours of data from each participant was then used for analysis.

Multivariate ANOVA and Paired samples T Tests were conducted to determine differences between the various groups. Correlations between sphygmomanometer, Finometer and ambulatory blood

pressure were conducted using Pearson correlation coefficient, then linear regression conducted to explore the relationships further. Data analysis was conducted using IBM SPSS Statistics 22 (SPSS Inc., Chicago, Illinois, USA), $p \leq 0.05$ was considered statistically significant.

Results

Adherence to sphygmomanometer, Finometer and ambulatory blood pressure measurements was 100% in all participants. Kolmogorov-Smirnov normality tests were $p > 0.05$ for each of the groups analysed, indicating the data was normally distributed. One participant appeared to be an outlier for SBP in cuff and ambulatory blood pressure measurements, as there was no effect on the 5% trimmed mean for both, the data was retained for analysis.

Ambulatory SBP and DBP were higher than both sphygmomanometer and Finometer blood pressure measurements, with Finometer being lowest across all groups, as shown in Table 1. A one-way between groups multivariate ANOVA was performed to investigate the blood pressure differences with the measuring device groups. Multivariate ANOVA of sphygmomanometer, Finometer and ambulatory SBP indicates that there was a significant difference among groups; with a Wilk's Lambda of 0.006, $p < 0.01$. Similar results were seen with sphygmomanometer, Finometer and ambulatory DBP; with a Wilk's Lambda of 0.008, $p < 0.01$.

Resting blood pressure

Although sphygmomanometer measures were slightly higher than Finometer, paired samples T test indicates that there is no overall difference between sphygmomanometer SBP of 128.5mmHg and Finometer SBP of 128.3mmHg, $p = 0.87$, as shown in Tables 1 and 2. Similar results were seen when the data was separated into normotensive and hypertensive groups. In the normotensive group the sphygmomanometer SBP was 120.7mmHg and Finometer SBP 121.0mmHg, $p = 0.89$. While the hypertensive group had a sphygmomanometer of SBP 133.5 mmHg and Finometer SBP of 133.0mmHg, $p = 0.79$.

Table 2: Mean Difference between Measurement Devices

	Mean Difference (mmHg)	SD of Mean Difference	95% CI of the Difference		P-value
			Lower	Upper	
All Participants					
Systolic Blood Pressure					
Sphygmomanometer vs Finometer	0.23	9.81	-2.68	3.15	0.87
Sphygmomanometer vs Ambulatory	-17.48	11.04	-20.76	-14.20	< 0.001
Finometer vs Ambulatory	-17.71	13.35	-21.68	-13.75	< 0.001
Diastolic Blood Pressure					
Sphygmomanometer vs Finometer	4.82	10.67	1.65	7.99	< 0.01
Sphygmomanometer vs Ambulatory	-9.88	9.61	-12.74	-7.03	< 0.001
Finometer vs Ambulatory	-14.70	9.05	-17.39	-12.02	< 0.001
Normotensive Participants					
Systolic Blood Pressure					
Sphygmomanometer vs Finometer	-0.26	8.17	-4.32	3.80	0.89
Sphygmomanometer vs Ambulatory	-16.36	12.42	-22.53	-10.18	< 0.001
Finometer vs Ambulatory	-16.10	11.53	-21.83	-10.36	< 0.001
Diastolic Blood Pressure					
Sphygmomanometer vs Finometer	0.20	10.40	-4.97	5.38	0.94
Sphygmomanometer vs Ambulatory	-10.15	8.99	-14.62	-5.68	< 0.001
Finometer vs Ambulatory	-10.35	7.51	-14.09	-6.62	< 0.001
Hypertensive Participants					
Systolic Blood Pressure					
Sphygmomanometer vs Finometer	0.55	10.87	-3.67	4.76	0.79
Sphygmomanometer vs Ambulatory	-18.20	10.23	-22.17	-14.23	< 0.001
Finometer vs Ambulatory	-18.75	14.51	-24.38	-13.12	< 0.001
Diastolic Blood Pressure					
Sphygmomanometer vs Finometer	7.79	9.91	3.94	11.63	< 0.001
Sphygmomanometer vs Ambulatory	-9.71	10.14	-13.65	-5.78	< 0.001
Finometer vs Ambulatory	-17.50	8.95	-20.97	-14.03	< 0.001

Differences were seen in overall resting DBP measures which indicated that sphygmomanometer DBP of 76.3mmHg was significantly higher than Finometer DBP of 71.5mmHg, $p<0.01$. In the normotensive group sphygmomanometer DBP of 70.6mmHg was only slightly higher than Finometer of 70.4mmHg, $p=0.94$. The hypertensive group saw a much higher sphygmomanometer DBP of 80.0mmHg than the Finometer 72.2mmHg, $p<0.001$.

There was a positive linear association between sphygmomanometer and Finometer for both SBP and DBP among each group. Pearson correlation coefficient and linear regression r^2 results are detailed in Table 3. Significant strong correlations were seen for SBP with overall data for all participants ($r=0.67$, $p<0.001$) while the hypertensive group was ($r=0.59$, $p=0.01$). There was a strong correlation for SBP among the normotensive group which was not significant ($r=0.44$, $p=0.07$). Similar results were seen for DBP with strong significant correlation for the overall data ($r=0.45$, $p<0.01$) and the hypertensive group ($r=0.56$, $p<0.01$). The normotensive group had a negligible correlation which was not significant for DBP ($r=0.07$, $p=0.79$).

Resting vs ambulatory blood pressure

Ambulatory SBP and DBP measurements were significantly higher than both resting sphygmomanometer and Finometer measurements for all measures overall, as well as when separated into normotensive and hypertensive groups. Overall, the average ambulatory SBP of 146.0mmHg was higher than the sphygmomanometer of 128.5mmHg and Finometer SBP of 128.3mmHg, both $p<0.001$. The normotensive group ambulatory SBP of 137.1mmHg was significantly higher than both sphygmomanometer SBP of 120.7mmHg and Finometer of 121.0mmHg, with $p<0.001$ for both. The hypertensive group also had significantly higher ambulatory SBP of 151.7mmHg, while sphygmomanometer was 133.5mmHg and Finometer 133.0mmHg, both $p<0.001$.

There was also a significant difference between ambulatory, sphygmomanometer and Finometer DBP compared to ambulatory DBP for all participants overall, as well as separated into normotensive

and hypertensive groups. Overall ambulatory DBP of 86.2mmHg was significantly higher than sphygmomanometer of 76.3mmHg and Finometer of 71.5mmHg, $p<0.001$ for both. Ambulatory DBP in the normotensive group at 80.7mmHg was significantly higher than sphygmomanometer at 70.6mmHg and Finometer at 70.4mmHg, both $p<0.001$. The hypertensive group saw similar results with significantly higher ambulatory DBP of 89.7mmHg compared to sphygmomanometer DBP of 80.0mmHg and Finometer DBP 72.2mmHg, both $p<0.001$.

There was a strong significant association between sphygmomanometer and ambulatory SBP ($r=0.64$, $p<0.001$) and Finometer and ambulatory SBP ($r=0.51$, $p<0.001$) with overall data from all participants combined. Conflicting results were seen when the data was separated into hypertensive and normotensive groups as shown in Table 3. The hypertensive group saw a strong significant association between ambulatory and sphygmomanometer SBP ($r=0.60$, $p<0.001$), and a moderate association with Finometer which was not significant ($r=0.34$, $p=0.08$). Among the normotensive group there was a moderate association which was not significant for ambulatory vs sphygmomanometer SBP ($r=0.32$, $p=0.19$), while Finometer had a strong association which was borderline significant ($r=0.47$, $p=0.05$).

Similar results were seen for DBP with a strong significant association for sphygmomanometer vs ambulatory ($r=0.58$, $p<0.001$) and Finometer vs ambulatory ($r=0.45$, $p<0.01$) among all participants overall. The hypertensive group had strong significant associations of DBP for both ambulatory vs sphygmomanometer ($r=0.47$, $p=0.01$) and Finometer ($r=0.52$, $p<0.01$). There was a strong significant association between ambulatory and sphygmomanometer DBP with the normotensive group ($r=0.49$, $p=0.04$), and a moderate association with the Finometer which was not significant ($r=0.36$, $p=0.15$).

Table 3: Correlations between measurement devices

	Correlation	r ²	P-value
All Participants			
Systolic Blood Pressure			
Sphygmomanometer vs Finometer	0.67	0.45	< 0.001
Sphygmomanometer vs Ambulatory	0.64	0.42	< 0.001
Finometer vs Ambulatory	0.51	0.27	< 0.001
Diastolic Blood Pressure			
Sphygmomanometer vs Finometer	0.45	0.20	< 0.01
Sphygmomanometer vs Ambulatory	0.58	0.34	< 0.001
Finometer vs Ambulatory	0.45	0.20	< 0.01
Normotensive			
Systolic Blood Pressure			
Sphygmomanometer vs Finometer	0.44	0.19	0.07
Sphygmomanometer vs Ambulatory	0.32	0.10	0.19
Finometer vs Ambulatory	0.47	0.22	0.05
Diastolic Blood Pressure			
Sphygmomanometer vs Finometer	0.07	0.005	0.79
Sphygmomanometer vs Ambulatory	0.49	0.24	0.04
Finometer vs Ambulatory	0.36	0.13	0.15
Hypertensive			
Systolic Blood Pressure			
Sphygmomanometer vs Finometer	0.59	0.34	0.01
Sphygmomanometer vs Ambulatory	0.60	0.36	< 0.001
Finometer vs Ambulatory	0.34	0.11	0.08
Diastolic Blood Pressure			
Sphygmomanometer vs Finometer	0.56	0.32	< 0.01
Sphygmomanometer vs Ambulatory	0.47	0.22	0.01
Finometer vs Ambulatory	0.52	0.27	< 0.01

Discussion

Auscultatory blood pressure measurement using a sphygmomanometer is adequate for monitoring an individual's blood pressure for medical use; however, there are other devices available for use in a research setting. Due to auscultatory measurements providing an instantaneous measure, short-term changes in blood pressure are unable to be detected, resulting in a possible inaccurate representation of the individual's blood pressure over time [8]. Utilizing beat-to-beat continuous blood pressure measurements provides data at every heartbeat, but due to their size and cost they

may not always be the most effective tool for use during research. Ambulatory blood pressure monitors are the current gold standard for measurement; however, physical exertion may interfere with the monitor and provide inaccurate recordings [9].

The data in our study showed that SBP was the same for both auscultatory and beat-to-beat measures indicating a high accuracy of SBP measurement. In a study conducted by Schutte et al. (2004) with 102 participants, there were no differences for either SBP or DBP between sphygmomanometer and Finometer measurements [19]. There was an overall decline of 0.23mmHg from sphygmomanometer to Finometer SBP in our study which was not significant, while Schutte et al. (2004) saw a difference of -1.8mmHg, with Finometer SBP higher than sphygmomanometer [19]. Sphygmomanometer DBP was higher than Finometer in both our study and that by Schutte et al. (2004)[19]. Although there was a significant overall difference in DBP in our study of 4.8mmHg, Schutte et al. (2004) saw a greater accuracy of 0.9mmHg [19].

Discrepancies between the auscultatory and Finometer DBP may be due to either the Finometer recording DBP incorrectly, or human error hearing the Korotkoff sounds fade at diastole.

Interpretation of Korotkoff sounds, reactions to auditory cues, auscultation method (diaphragm vs bell of stethoscope), deflation rate and cuff size can all affect the accuracy of auscultatory blood pressure measurement [21 22]. According to Ruiz-Rodriguez et al. (2013) there is a tendency for DBP to be overestimated during auscultatory measurement, which may explain the discrepancy seen in our study [23]. High DBP measurements have also been known to be attributed to slow deflation rates causing venous congestion, phasic changes in arterial pressure, or faint Korotkoff sounds from the patient [14].

The data in our study indicated that systolic and diastolic ambulatory blood pressure were both significantly higher than sphygmomanometer and Finometer resting SBP and DBP in both the normotensive and hypertensive groups. Juhanoja et al. (2016) also saw higher SBP and DBP measurements with daytime ambulatory blood pressure compared to home and office blood

pressure measurements [24]. We saw a 17.5mmHg increase in SBP with ambulatory blood pressure compared to the sphygmomanometer, while Juhanoja et al. (2016) saw an increase of 5.6mmHg in office SBP and 8.4mmHg in home SBP [24]. Although we saw an increase in DBP of 9.9mmHg from sphygmomanometer to ambulatory DBP, there were no differences between daytime ambulatory blood pressure, home and office DBP seen by Juhanoja et al. (2016)[24].

A meta-analysis conducted by Banegas et al. (2017) indicates that daytime ambulatory blood pressure is generally lower in individuals with hypertension than that seen in a clinic, and saw a 17.4mmHg decrease in SBP with ambulatory blood pressure [17]. Similar differences were seen in DBP with an increase of 9.9mmHg in our research, and a decrease of 8.4mmHg seen by Banegas et al. (2017) [17]. According to Ishikawa et al. (2011) lower ambulatory blood pressure than clinic measurements indicate white coat hypertension, while higher ambulatory blood pressure than clinic measurements indicate masked hypertension [18]. Ishikawa et al. (2011) also noted that home blood pressure measurements were either lower than or similar to daytime ambulatory blood pressure [18]. Ambulatory blood pressure measures may be more meaningful than clinic/office blood pressure when diagnosing hypertension, and a better predictor of cardiovascular risk and outcomes including coronary morbid or fatal events and stroke [10].

Conclusions

Despite concerns over beat-to-beat accuracy, the data indicates that SBP measurements correlate with an aneroid sphygmomanometer, although there is still some doubt of the accuracy of DBP measurements. The Finometer is suitable for monitoring continual beat-to-beat blood pressure but it is cumbersome and may not be suitable for a lot of studies due to its size. As such, the Finometer is more suited to studies where researchers want to monitor continual change of blood pressure in a dedicated setting. Ambulatory blood pressure monitors provide a portable method of measuring blood pressure enabling researchers to see changes over a period of numerous hours.

Study Limitations

Although the same person performed all auscultatory measures in this study, there is still the propensity for human error; use of an oscillometric automated blood pressure sphygmomanometer may clarify the accuracy of Finometer DBP. Differences between resting and ambulatory blood pressure may not be so large had we looked at 24 hour ambulatory blood pressure, or if the participants wore the monitor on a day when they were not as active.

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**Higher Degree Research Thesis by Publication
University of New England**

STATEMENT OF AUTHORS' CONTRIBUTION

(To appear at the end of each thesis chapter submitted as an article/paper)

We, the Research Master/PhD candidate and the candidate's Principal Supervisor, certify that all co-authors have consented to their work being included in the thesis and they have accepted the candidate's contribution as indicated in the *Statement of Originality*.

BP measurement study

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**Higher Degree Research Thesis by
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Type of work	Page number/s
All text, tables and figures	Chapter 6, pp 115-132

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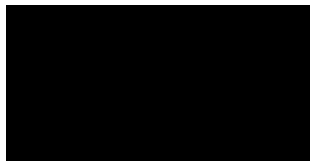
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Chapter 7 – Conclusions

7.1 The problem and the research questions

Worldwide approximately 40% of adults ≥ 25 years old have hypertension, which is a modifiable risk factor for cardiovascular disease (Chobanian et al., 2003; WHO, 2013). Cardiovascular disease is the number one cause of death globally, almost 50% of individuals who die from cardiovascular disease in the U.S. have hypertension (WHO, 2017; Whelton et al., 2017). Non-pharmacological lifestyle modifications are the first line treatment for hypertension followed by pharmacological treatment; however, only half of the individuals prescribed antihypertensive medication reach treatment goals (Chobanian et al., 2003; Nuchols et al., 2011; Whelton et al., 2017). Conducting a minimum of 150 mins of moderate or 75 mins of vigorous exercise (or a combination of both) each week, as well as a minimum of 2 days of muscle strengthening, is the recommended exercise prescription for people with hypertension (Mozaffarian et al., 2016). The use of isometric resistance training (IRT) to aid in blood pressure measurement has been added to the recent Hypertension Canada's 2017 Guidelines for Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults, and the 2017 High Blood Pressure Clinical Practice Guideline (Leung et al., 2017; Whelton, 2017). The meta-analyses conducted in Chapter 2 and the appendix are both cited in the current 2017 High Blood Pressure Clinical Practice Guideline, and based upon Class I Level A evidence, IRT is now recommended to aid in blood pressure management (Whelton, 2017).

Due to the low compliance to the recommended exercise guidelines and the growing body of evidence into isometric resistance training IRT, the efficacy of conducting IRT to aid in blood pressure management was investigated (Cornelissen & Smart, 2013; Carlson et al., 2014; Millar et al., 2014; Clarke, Norris & Schiller, 2017). Exploring the effect on hypertensive responses during IRT was essential to address safety concerns which generally prevents health professionals from recommending IRT. Hypertensive responses during exercise are determined by measuring rate pressure product; systolic blood pressure multiplied by heart rate. This is a valid non-invasive surrogate measure of myocardial oxygen consumption, and often measured during stress tests (Gobel et al., 1978; Hui, Jackson & Wier, 2000). Beat-to-beat blood pressure measurement allows rate pressure product to be calculated during exercise to determine cardiovascular responses during exercise. However, there have been concerns over the accuracy of these blood pressure measurement devices (Njoun & Kyriacou, 2016). Validation of blood pressure measuring

devices was conducive to determining which was more appropriate to use during research. The current guidelines state that measurement accuracy is paramount and that medical personnel need to be taught how to perform it properly (Whelton et al., 2017). Currently, ambulatory blood pressure monitoring is seen as the gold standard (Mancia et al., 2013; Boggia et al., 2014).

This thesis investigated these issues by addressing the following questions:

1. To what extent does isometric resistance training affect systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and mean arterial pressure (MAP); and which patient demographics and exercise program characteristics exhibited the largest changes?
2. Is IRT utilising handgrip exercise effective for blood pressure management in individuals aged between 35 and 70 years with hypertension; and is a low intensity (5% MVC) group suitable for use as a working control?
3. What effect does IRT conducted over 12 weeks have on 24 hour ambulatory blood pressure in individuals aged between 30 and 70 years who are pre-hypertensive or have stage 1 hypertension? Is there a detraining effect on blood pressure after ceasing IRT?
4. What is the peak SBP, DBP, HR, MAP and subsequent rate pressure product during isometric handgrip exercise in both healthy normotensive individuals and those with pre-hypertension.
5. How accurate are SBP and DBP measurements recorded by the Finometer® compared to those from an aneroid sphygmomanometer; and how much variability is there in these compared to ambulatory blood pressure measurements?

7.2 How the research was conducted

7.2.1 Systematic review and meta-analysis

A systematic review and meta-analysis (Chapter 2) focused on randomized controlled trials including treatment and sedentary control groups conducting IRT for four weeks or longer. The search was conducted using PubMed, CINAHL and Cochrane controlled trials from 1 January 1966 to 31 January 2015. The systematic review and meta-analysis confirmed significant reductions in systolic and diastolic blood pressure with IRT.

7.2.2 8 Week randomised IRT study

Chapter 3 detailed a randomised trial conducted to investigate the efficacy of IRT for blood pressure management. Based on prior research, a low intensity sham control group was used to investigate whether this intensity would show changes in blood pressure and be suitable as a working control in future research. Previous research has predominantly used sedentary control groups. This research presumed that this may affect the results due to participants knowing whether or not they were conducting IRT and sought to develop a sham protocol to blind participants.

Forty participants were randomly allocated into groups conducting IRT at either 5% or 30% of their maximum voluntary contraction (MVC). Participants attended the Exercise Physiology laboratory 3 times a week for 8 weeks to conduct IRT. During each visit they performed four 2 minute isometric handgrip exercises, each separated by a 3 minute rest period. Baseline measurements were conducted prior to commencement, and post measurements were conducted 24 hours after completion of the 8 week protocol. Cardiovascular measurements were recorded using a Finometer® which records beat-to-beat measurements, at each heartbeat.

Eight weeks of IRT saw a significant reduction of SBP in the 30% MVC group; however, there was no significant reduction in DBP in the same group. There were no significant reductions in SBP or DBP in the 5% MVC group, indicating the suitability of it being a working control.

7.2.3 12 Week randomised IRT study

Chapter 4 discussed a randomised trial to investigate the effect of IRT on 24-h ambulatory blood pressure. The longest IRT study published prior to this research was for 10 weeks, and 24-h ambulatory monitoring had become the gold standard for determining cardiovascular risk (Pickering, Eguchi & Kario, 2007; Myers, 2014). Therefore, it was a natural progression to look at the effects of IRT on 24-h ambulatory blood pressure after 12 weeks of IRT. Since there has been no previous research into the detraining effect on blood pressure after ceasing IRT, the assessment of the detraining effect was the secondary aim of this research.

Twenty participants were randomly allocated into groups conducting IRT at either 5% or 30% of their maximum voluntary contraction (MVC). The isometric handgrip protocol in the

12 week study was the same as that used for the participants in the 8 week study. Baseline and post-intervention blood pressure measurements were conducted using 24 hour ambulatory monitoring. Participants were asked to return 12 weeks after ceasing IRT to conduct 24-h monitoring to determine the detraining effect on blood pressure.

Twelve weeks of IRT at 30% MVC saw significant reductions of systolic and diastolic 24-h ambulatory blood pressure. There was no change in systolic or diastolic 24-h ambulatory blood pressure at 5% MVC, reinforcing the efficacy of its use as a working control. After ceasing the protocol, blood pressure increased during detraining but still remained significantly lower than at baseline, indicating trends of continued benefit.

7.2.4 Rate Pressure Product during IRT

Chapter 5 presented the results of a randomised trial with both normotensive and hypertensive participants to determine the cardiovascular responses during IRT. Concerns over the hypertensive responses during IRT have made it difficult for researchers to have their research translated into practice.

One hundred and twenty participants were randomized into a 5%, 10% or 30% MVC group based on their blood pressure status. A 5% and 10% group were both investigated to establish the use of a sham control group, and they had been used in another project of the research team (see appendix A). The 30% intensity group was used as it is the level indicated by previous research which elicits blood pressure reductions. The participants attended the training laboratory for one session of isometric handgrip exercise which consisted of four sets of two minute contractions in their non-dominant arm, each followed by three minute rest periods between contractions. During IRT participants were connected to Finometer® which records beat-to-beat systolic and diastolic blood pressure, heart rate, and mean arterial pressure to measure cardiovascular responses during IRT.

Peak increases in rate pressure product were significantly higher than those at baseline, at all intensities assessed. Increases were relative to baseline blood pressure status and intensity of IRT, with no significant differences between the normotensive and hypertensive groups. The rate pressure responses indicate that IRT is a safe alternative for people unable to perform recommended levels of aerobic exercise for blood pressure management.

7.2.5 Blood Pressure measurement device comparison

Chapter 6 looked at the various blood pressure measurement devices to address concerns over which is the most suitable for use in research. Forty six participants attended the lab on one occasion to have their blood pressure measured by auscultatory method using an aneroid sphygmomanometer, a Finometer® for beat-to-beat measurements and an ambulatory blood pressure monitor in the same visit. Sphygmomanometer measurements were slightly higher than beat-to-beat for both SBP and DBP. There were no significant differences between sphygmomanometer and beat-to-beat SBP; however, there were disparities in DBP. Daytime ambulatory blood pressure was higher than both sphygmomanometer and beat-to-beat measurements for both SBP and DBP for all measures. Sphygmomanometer and beat-to-beat measurements were taken while the participants were resting, while ambulatory measurements were taken throughout the day while participants were conducting their regular routine. Ambulatory measurements can indicate the possibility of resistant, masked or white coat hypertension as well as spikes in blood pressure, and the ongoing physiological effects up to 24 hours after conducting exercise.

7.3 Research Findings

The results of the systematic review and meta-analysis showed IRT is effective at lowering SBP, DBP and MAP. The magnitude of this effect appears to be greater in hypertensive males aged 45 years and over, using unilateral handgrip exercises for a minimum of four weeks. In the 8 week study, SBP and MAP showed significant reductions at high intensity (30% MVC) in SBP and MAP; however, no significant change in DBP was shown after 8 weeks. Upon increasing the duration of IRT to 12 weeks the reductions in SBP were the same as those seen at 8 weeks; as well, there were significant reductions in DBP. During both the 8 week and 12 week studies a low intensity (5% MVC) group was used as a working control. There were no significant changes in SBP, DBP, MAP or HR for the low intensity group in either study, indicating it's suitability as a working control (sham group) for future studies. This research demonstrated a detraining trend which indicates that the blood pressure lowering effects remain lower than at baseline after completing IRT. Indications are that continued IRT is required to sustain blood pressure reductions long term.

Hypertensive responses during isometric exercise were investigated to determine the safety of conducting IRT. There is a positive linear relationship between blood pressure and IRT intensity, with increases in blood pressure and rate pressure product during handgrip exercise relative to baseline blood pressure. Increases in SBP, DBP, MAP and HR during IRT are much less than those reported in previous studies (Siminson & Wyatt, 2003; Pinkstaff et al., 2010). This indicates that cardiovascular responses during IRT are well within safe limits.

When comparing the commonly used blood pressure measuring devices, the present data indicated a strong correlation between beat-to-beat and sphygmomanometer SBP; however, there were doubts about the accuracy of DBP measurements. Daytime ambulatory SBP and DBP measurements were significantly higher than those seen with both beat-to-beat and the sphygmomanometer measurements. Beat-to-beat monitoring can be cumbersome but can be suitable for monitoring continual cardiovascular changes during research. Ambulatory monitoring enables researchers to see changes over time after a participant has conducted exercise whilst allowing the individual to maintain their usual routine.

7.4 How the research addressed the gaps in the literature

At the time of initiating the research, previous studies into IRT predominantly had small participant numbers, and only one study had a duration > 8 weeks. At the commencement of the 12 week study, there were no published studies of 12 weeks duration, making it the longest IRT study investigating the effect on 24-h ambulatory blood pressure at that time. The only prior study which has looked at the detraining effect of IRT was conducted by Wiley and colleagues in 1992; with a duration of five weeks, after five weeks of IRT. This research addressed a gap in the literature by looking at the 12 week detraining effect, after 12 weeks of IRT. This research was the first handgrip IRT study to implement a low intensity working control of 5%. Previous studies had used beat-to-beat measurements with IRT; however, this was the first published research exploring the cardiovascular response of rate pressure product during IRT.

7.5 Limitations of the studies

7.5.1 8 Week randomised IRT study

The 5% and 30% MVC groups were matched for participant numbers, gender, age, height and weight; however, there were disparities in the baseline blood pressure measurements. Due to the cohort obtainable there was an unequal amount of participants who were medicated and unmedicated making any sub-analyses infeasible. Participant withdrawal is always a concern with research, and two participants, out of 40, had to withdraw early for personal reasons. Blood pressure measurements were conducted using beat-to-beat measurements, controversy over the accuracy of the device used, led to the study presented in chapter 6.

7.5.2 12 Week randomised IRT study

Participant numbers and retention were the main limitations of this study. Although the participant numbers were larger than many previously published studies, greater numbers are needed to strengthen the data. Three participants, out of 20, had to withdraw early due to personal commitments during the IRT protocol. Due to the 12 week detraining period, only 14 of the original 20 participants returned to conduct detraining blood pressure measurements.

7.5.3 Rate Pressure Product during IRT

The randomized controlled study investigating the cardiovascular responses (SBP, DBP, rate pressure product) during IRT was the first study of this kind. There is very little published data on rate pressure product. The main limitation of this study was the inability to directly compare the cardiovascular responses and rate pressure product between IRT and aerobic exercise.

7.5.4 Blood Pressure measurement device comparison

There are many variables which can affect the accuracy of auscultatory sphygmomanometer measurements, including the propensity for human error. Use of an automated oscillometric device may show different comparison data against the beat-to-beat than that seen in this research. A large number of the participants did not wear the ambulatory monitor for 24 hours so this study was limited to 12 hours of daytime measurements for

comparisons. Differences in resting and ambulatory measurements may not have been as large had the participants all worn the monitor for 24 hours.

7.6 Future research potential

Despite the increased interest in the blood pressure lowering effects of IRT, there is still the potential for future research. There are no published studies confirming the mechanism behind how IRT aids in blood pressure management. Although there has been research into endothelial dysfunction and IRT, more research into this area still needs to be conducted. Specific medications may influence the size of blood pressure change, so a large study looking at individual participant's reactions to IRT may help determine if all medicated hypertensive individuals would benefit from IRT. Future studies will require larger participant numbers; potentially increasing the collaboration among researchers to conduct simultaneous studies for pooled analyses. Long term studies of 12 weeks or longer will be required, with periodical (monthly) blood pressure measurements to monitor change over time. More research into any detraining effect should also be conducted to determine the ongoing effect of cardiovascular changes from IRT. A better understanding of the rate of detraining may mean that once blood pressure reductions are achieved the frequency or dose of IRT can be reduced to a maintenance level. Most importantly future research should focus on translating the research into practice.

7.7 Closing comments

There are proven benefits of IRT in reducing and managing blood pressure in individuals who have prehypertension and stage 1 hypertension. Approximately only 50% of hypertensive individuals conduct the recommended aerobic exercise and strength training to aid in blood pressure management. Isometric handgrip exercise provides a simple, low cost alternative which can be conducted anywhere, and may increase exercise compliance. The Hypertension Clinical Practice Guideline 2017 has recognised this work and those of others working on IRT research as beneficial for blood pressure management (Whelton et al., 2017). The systematic review and meta-analysis in Chapter 2 and an earlier meta-analysis (see Appendix A) are both cited in the guidelines, confirming the impact that this research has had internationally.

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Appendix A: Chapter 2 Meta-analysis supplementary files

Supplementary Files

Figure 1. SEARCH STRATEGY

PUB MED SEARCH STRATEGY

Sensitive/broad search

[#8](#) Search (**Exercise/Broad[filter]**) AND (**#7**)

[#7](#) Search **#5** AND **#6**

[#6](#) Search **#4** OR **#5**

[#5](#) Search **#1** OR **#2** OR **#3** OR **#4**

[#4](#) Search (((**exercise[MeSH Terms]**) OR **exercise therapy [MeSH Terms]**) OR **aerobic exercise[Text Word]**) OR **exercise training[Text Word]**)

[#3](#) Search ((**physical activity [MeSH Terms]**) OR **physical training [Text Word]**)

[#2](#) Search (((**isometric exercise [MeSH Terms]**) OR **isometric training [Text Word]**)

[#1](#) Search (((((b>hypertension [MeSH Terms]) OR **high blood pressure[Text Word]**))

Figure 1. Egger Plot of Systolic Blood Pressure Analysis

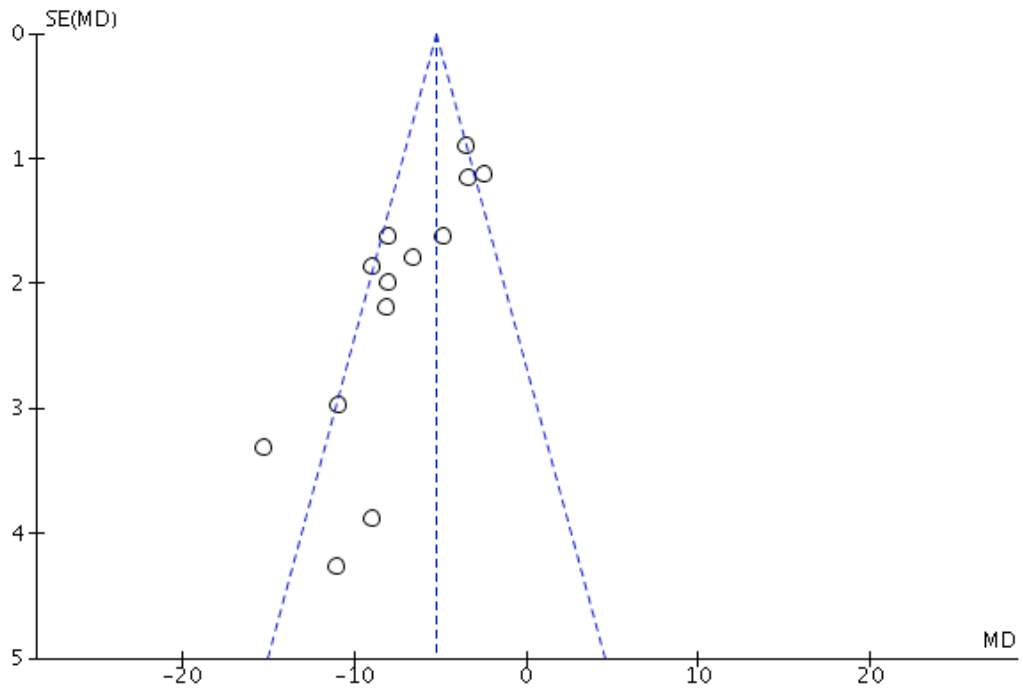


Figure 2. Egger Plot of Diastolic Blood Pressure Analysis

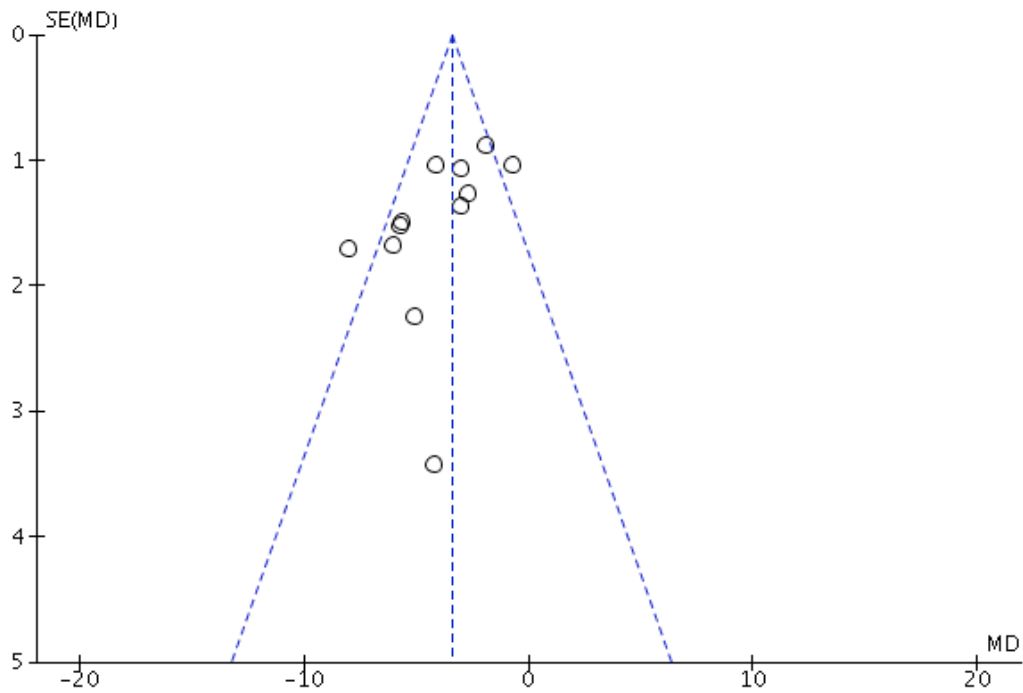


Figure 3. Egger Plot of Mean Arterial Pressure Analysis

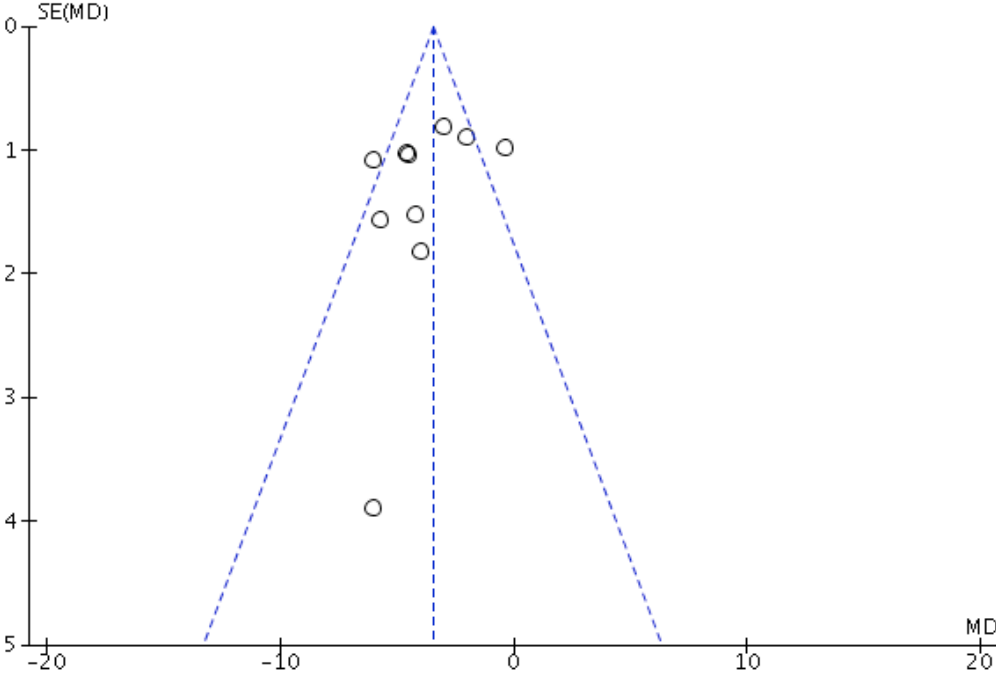


Table 1. Study Quality Assessment of Included Studies (using TESTEX Scale)

Study name	Eligibility Criteria specified	Randomly allocated participants	Allocation concealed	Groups Similar at baseline	Assessors blinded	Outcome	Intention to treat analysis	Reporting of statistical comparisons between group	Point	Activity Monitoring in Control Group	Relative Exercise Intensity Review	Exercise Volume & Energy Expended	Overall TESTEX
						Measures assessed >85% of participants#			measures & measures of variability reported*				
Badrov (2013a)	YES	YES	Unclear	YES	NO	YES (2)	NO	YES	YES (2)	NO	YES	NO	9
Badrov (2013b)	YES	YES	Unclear	YES	NO	YES (2)	YES	YES	YES (2)	NO	YES	NO	10
Baross (2013)	YES	YES	NO	YES	NO	YES (2)	YES	YES	YES (2)	NO	YES	NO	10
Devereaux (2012)	YES	Unclear	NO	YES	NO	YES (2)	YES	YES	YES (2)	NO	YES	NO	9
Gill (2015)	YES	YES	NO	YES	NO	YES (2)	YES	YES	YES (2)	NO	YES	NO	10
Miller (2008)	YES	YES	NO	YES	NO	YES (2)	YES	YES	YES (2)	NO	YES	NO	10
Stiller (2012)	YES	YES	Unclear	YES	NO	YES (2)	NO	YES	YES (2)	NO	YES	NO	9
Taylor (2003)	YES	YES	NO	YES	NO	YES (2)	YES	YES	YES (2)	NO	YES	NO	10
Wiles (2010)	YES	YES	NO	YES	NO	YES (2)	YES	YES	YES (2)	NO	YES	NO	10
Wiley (1992)	YES	YES	NO	YES	NO	YES (2)	NO	YES	YES (2)	NO	YES	NO	9

Total out of 15 Points

Legend: # Three points possible – 1 point if adherence >85%, 1 point if adverse vents reported, 1 point if exercise attendance is reported

*Two points possible – 1 point if primary outcome is reported, 1 point if all other outcomes reported

NR – not reported

Appendix B: Published articles, relevant to the thesis, ineligible to be included as individual chapters

The following two published journal articles were not part of the main body of my thesis; however, they provided crucial background for my doctoral research topic. I conducted a meta-analysis prior to commencement of my PhD to determine the viability of conducting isometric resistance training in my research. The research in the published article by Dr Nicole Hess, was used to determine the feasibility of utilising low impact isometric resistance training instead of a sedentary control in my research model.

1. **Carlson, D.J.**, Dieberg, G., Hess, N.C., Millar, P.J. and Smart, N.A. (2014). Isometric exercise training for blood pressure management: A systematic review and meta-analysis. *Mayo Clinic Proceedings*, 89(3), 327-334.
<http://dx.doi.org/10.1016/j.mayocp.2013.10.030>
2. Hess, N.C.L., **Carlson, D.J.**, Inder, J.D., Jesulola, E., McFarlane, J.R. and Smart, N.A. (2016). Clinically meaningful blood pressure reductions with low intensity isometric handgrip exercise. A randomized trial. *Physiological Research*, 65(3), 461-468.



Isometric Exercise Training for Blood Pressure Management: A Systematic Review and Meta-analysis

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Abstract

Objective: To conduct a systematic review and meta-analysis quantifying the effects of isometric resistance training on the change in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure in subclinical populations and to examine whether the magnitude of change in SBP and DBP was different with respect to blood pressure classification.

Patients and Methods: We conducted a systematic review and meta-analysis of randomized controlled trials lasting 4 or more weeks that investigated the effects of isometric exercise on blood pressure in healthy adults (aged ≥ 18 years) and were published in a peer-reviewed journal. PubMed, CINAHL, and the Cochrane Central Register of Controlled Trials were searched for trials reported between January 1, 1966, and July 31, 2013. We included 9 randomized trials, 6 of which studied normotensive participants and 3 that studied hypertensive patients, that included a total of 223 participants (127 who underwent exercise training and 96 controls).

Results: The following reductions were observed after isometric exercise training: SBP—mean difference (MD), -6.77 mm Hg (95% CI, -7.93 to -5.62 mm Hg; $P < .001$); DBP—MD, -3.96 mm Hg (95% CI, -4.80 to -3.12 mm Hg; $P < .001$); and mean arterial pressure—MD, -3.94 mm Hg (95% CI, -4.73 to -3.16 mm Hg; $P < .001$). A slight reduction in resting heart rate was also observed (MD, -0.79 beats/min; 95% CI, -1.23 to -0.36 beats/min; $P = .003$).

Conclusion: Isometric resistance training lowers SBP, DBP, and mean arterial pressure. The magnitude of effect is larger than that previously reported in dynamic aerobic or resistance training. Our data suggest that this form of training has the potential to produce significant and clinically meaningful blood pressure reductions and could serve as an adjunctive exercise modality.

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Current National Health and Nutrition Examination Survey data suggest that the prevalence of hypertension varies with ethnicity and sex but is between 25% and 43% in the US population, with an upward trend noted over the past 3 surveys.¹ Hypertension, or the long-term elevation of resting arterial blood pressure (BP) above 140 mm Hg systolic (SBP) and/or 90 mm Hg diastolic (DBP) remains one of the most significant modifiable risk factors for cardiovascular disease (eg, coronary artery disease, stroke, heart failure).² In light of the prevalence of hypertension,³ the associated economic health care costs are considerable. Additionally, although antihypertensive medications generally have minimal adverse effects, they are efficacious in perhaps 50% of those who are prescribed treatment.⁴ Both national

and international treatment guidelines for primary and secondary prevention of hypertension recommend nonpharmacological lifestyle modifications as the first line of therapy, including increasing levels of physical activity.⁵ There is class I, level B evidence that 150 minutes of physical activity weekly offers an alternative that may be used to complement antihypertensive medication,⁶ although the optimal exercise training prescription remains unclear.

One important factor that may impact the effectiveness to lower BP is the type of exercise performed. Recent analyses suggest that isometric exercise may elicit BP reductions greater than those seen with dynamic aerobic and resistance exercise.^{7,8} Currently, dynamic aerobic endurance activity is the preferred exercise modality for BP management. Aerobic exercise often



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requires access to a gymnasium or suitable equipment; moreover, considerable energy expenditure is required to elicit BP reductions, which is also time-consuming. For these reasons, adherence to aerobic exercise is often sub-optimal. Isometric exercise involves sustained contraction against an immovable load or resistance with no or minimal change in length of the involved muscle group. Low- to moderate-intensity isometric activity can be performed anywhere, requires relatively inexpensive equipment, and does not elicit the same level of cardiovascular stress (eg, rate-pressure product) as aerobic activity. Isometric activity has previously been associated with exaggerated hypertensive responses, but recent work has suggested that isometric handgrip activity may become a new tool in the nonpharmacological treatment of high BP.^{9,10} Relative to aerobic activity, isometric exercise has the potential for superior adherence due to simplicity, lower cost, and perhaps less exercise time. Previous meta-analyses have examined the effects of endurance training,¹¹ dynamic resistance training,^{12,13} and isometric resistance training¹⁰ on BP. The findings revealed that isometric resistance exercise does lower BP; however, the sample sizes of the trials to date are generally small. Recently, several isometric exercise training trials have been reported that necessitate an updated analysis of data from randomized, controlled, and crossover trials.

The aims of this study were (1) to conduct a systematic review and meta-analysis quantifying the effects of isometric resistance training on the change in SBP, DBP, and mean arterial pressure (MAP) in subclinical populations and (2) to examine whether the magnitude of change in SBP and DBP was different with respect to BP classification.

PATIENTS AND METHODS

Search Strategy

Potential studies were identified by conducting a systematic search using PubMed for randomized controlled trials lasting 4 or more weeks that investigated the effects of isometric exercise on blood pressure in healthy adults (aged ≥ 18 years) and were published in a peer-reviewed journal between January 1, 1966, and July 31, 2013. The PubMed search strategy

is presented in Supplemental Figure 1 (available online at <http://www.mayoclinicproceedings.org>). CINAHL and the Cochrane Central Register of Controlled Trials were also searched for the same period. The search strategy included the terms *hypertension*, *blood pressure*, *isometric exercise*, *isometric resistance training*, *physical training*, and *exercise training*. These terms were combined with a sensitive search strategy to identify randomized controlled and crossover trials. Reference lists of selected articles were scrutinized for new references. All identified articles were assessed independently by 2 reviewers (G.D. and D.J.C.), and a third reviewer (N.A.S.) was consulted to resolve disputes. The latest editions of relevant journals (through July 31, 2013) were also examined.

Study Selection

Randomized controlled trials and crossover studies of isometric exercise training in adults were included. There were no language restrictions. Animal studies, review articles, short-term exercise studies, and nonrandomized controlled trials were excluded. Studies that did not have any of the desired outcome measures or a sedentary control group were excluded. Several authors were contacted to provide missing data or to clarify whether data were duplicated in multiple publications. Incomplete data, or data from an already included study, were excluded. Studies using interventions other than pure isometric exercise (eg, aerobic or dynamic resistance exercise) were excluded.

Our initial search identified 1288 articles, and examination of the latest editions of relevant journals yielded 1 more article. Of the 1289 studies, 368 were excluded at first inspection as duplicates, 152 were removed after reading titles or abstracts, and 598 studies were not trials of isometric exercise therapy in adults, leaving 171 studies; 159 of the 171 studies were not randomized controlled trials with a duration of 4 weeks or longer, and 3 others were excluded because of data duplication, leaving 9 studies for analysis (Figure 1) that included 223 participants (127 who underwent exercise training and 96 controls).

Data Synthesis

Information on outcome measures was archived in a database. The outcome measures were SBP, DBP, MAP (which was calculated by

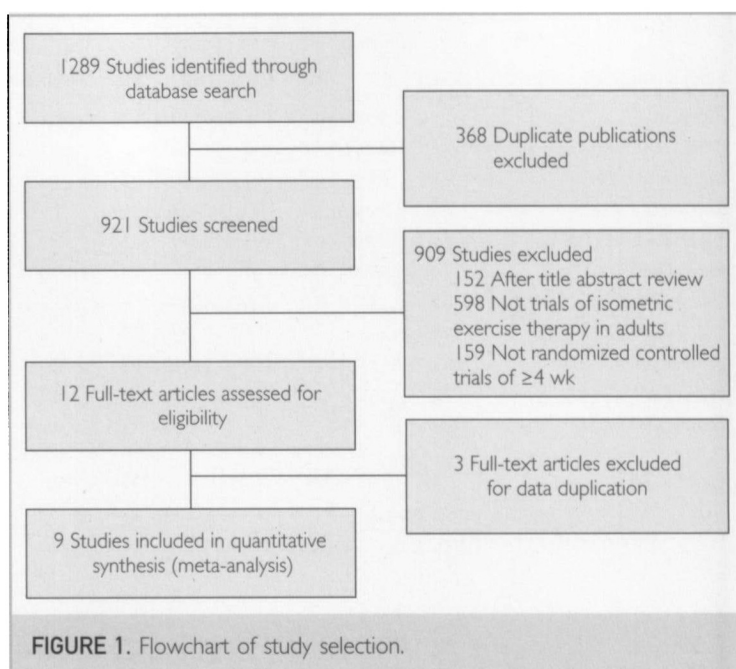
adding DBP plus one-third pulse pressure), and resting heart rate (RHR).

Statistical Analyses

Meta-analyses were completed for continuous data by using the change in the mean and SD of outcome measures. It is an accepted practice to use only postintervention data for meta-analysis, but this method assumes that random allocation of participants always creates intervention groups matched at baseline for characteristics such as age and disease severity. Change in postintervention mean was calculated by subtracting baseline from postintervention values. Change in the SD of postintervention outcomes was calculated using the Review Manager (RevMan) computer program, version 5.0 (Nordic Cochrane Centre). Data required were: (1) 95% CI data for baseline-postintervention change for each group; (2) if 95% CI data were unavailable, we used actual *P* values for baseline-postintervention change for each group; and (3) if only the level of statistical significance was available, we tried to obtain precise *P* values (eg, $P=.034$) or 95% CIs from authors. We attempted when possible to obtain these precise data, but if these data were not forthcoming, we used default *P* values, eg, $P<.05$ becomes $P=.049$ and $P=NS$ (not significant) becomes $P=.05$. A random effects inverse variance was used with the effects measure of MD. Heterogeneity was quantified using the Cochrane *Q* test.¹⁴ Egger plots were provided to assess the risk of publication bias. Study quality was assessed using a modified Physiotherapy Evidence Database (PEDro) scale¹⁵ score (0-9) because blinding is difficult in exercise training studies. Significance was considered at $P<.05$ with 95% CIs; figures were produced using RevMan 5.

RESULTS

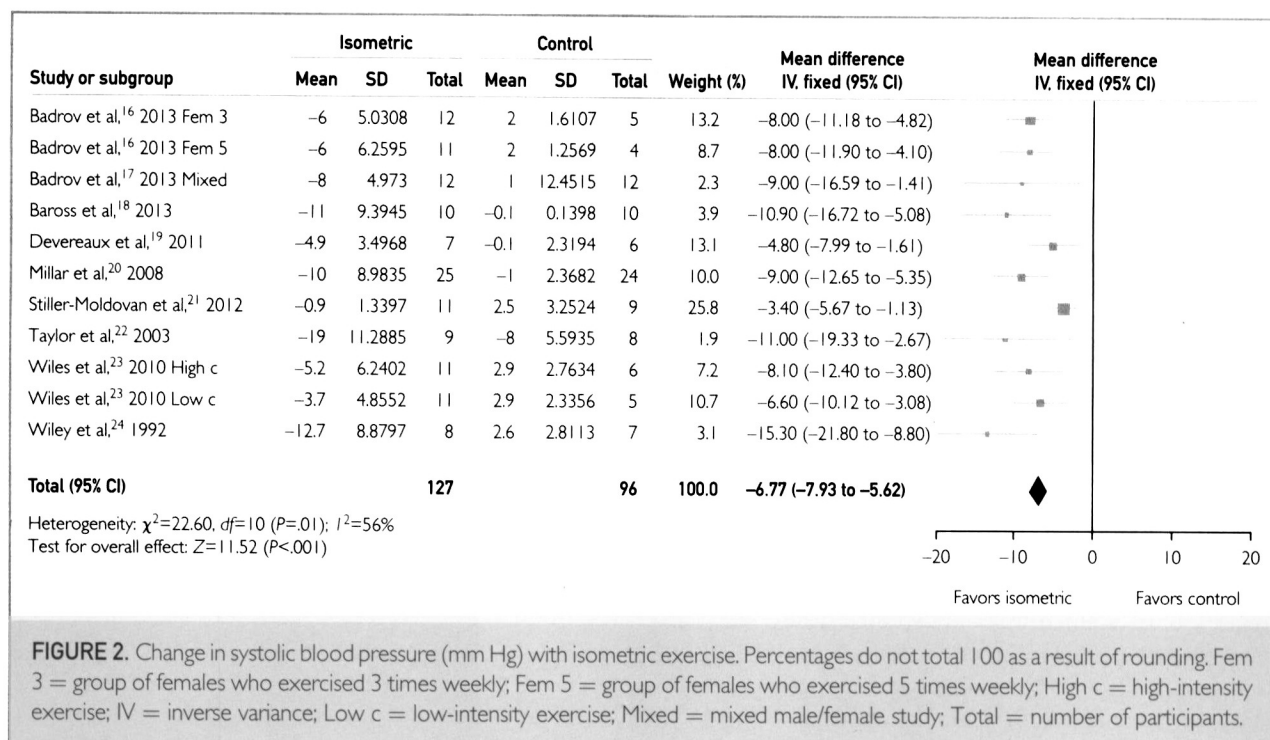
Nine studies were included in our analysis,¹⁶⁻²⁴ with a total of 223 patients (Supplemental Table 1, available online at <http://www.mayoclinicproceedings.org>). Six studies used hand-grip, and 3 studies used leg exercise. None of the studies reported any adverse events from isometric exercise. Four studies used automated BP measurements, 2 others collected waveform analyses, and 3 used auscultation, but methods were not otherwise standardized. Systolic blood



pressure was significantly reduced in all participants, with an MD of -6.77 mm Hg (95% CI, -7.93 to -5.62 mm Hg; $P<.001$) (Figure 2). Hypertensive participants, who were all on medication, had a smaller reduction in SBP (MD, -4.31 mm Hg; 95% CI, -6.42 to -2.21 mm Hg; $P<.001$) than normotensive participants (MD, -7.83 mm Hg; 95% CI, -9.21 to -6.45 mm Hg; $P<.001$) (Supplemental Figures 2a and 2b, respectively; available online at <http://www.mayoclinicproceedings.org>).

Diastolic blood pressure was significantly reduced, with an MD of -3.96 mm Hg (95% CI, -4.80 to -3.12 mm Hg; $P<.001$) (Figure 3). Hypertensive participants had a larger reduction in DBP, with an MD of -5.48 mm Hg (95% CI, -7.93 to -3.03 mm Hg; $P<.001$) than normotensive participants (MD, -3.08 mm Hg; 95% CI, -3.88 to -2.27 mm Hg; $P<.001$) (Supplemental Figures 3a and 3b, respectively; available online at <http://www.mayoclinicproceedings.org>).

MAP was reduced, with an MD of -3.94 mm Hg (95% CI, -4.73 to -3.16 mm Hg; $P<.001$) (Figure 4). Medicated hypertensive participants had a larger reduction in MAP, with an MD of -6.01 mm Hg (95% CI, -8.04 to -3.97 mm Hg; $P<.001$) than normotensive participants (MD, -3.58 mm Hg; 95% CI, -4.43 to -2.73 mm Hg;

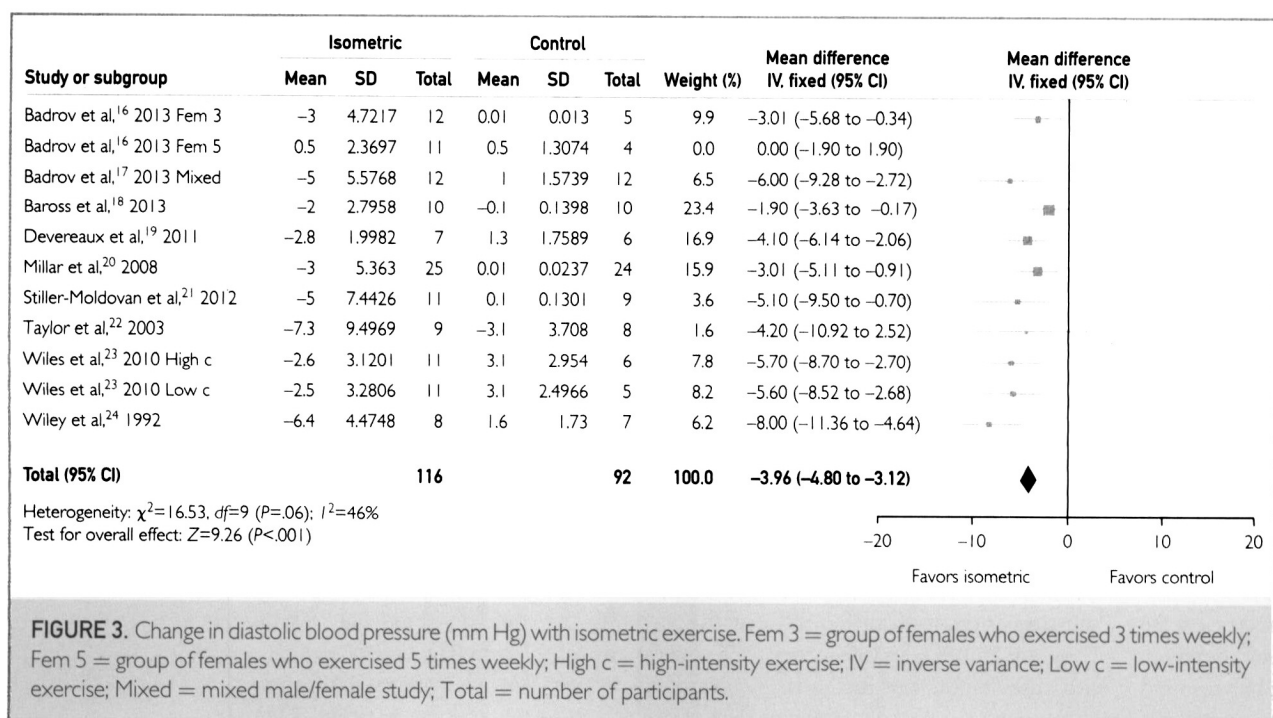


$P<.001$) (Supplemental Figures 4a and 4b, respectively; available online at <http://www.mayoclinicproceedings.org>).

A slight reduction in RHR was noted, with an MD of -0.79 beats/min (95% CI, -1.23 to -0.36 beats/min; $P=.003$) (Figure 5).

Study Quality Assessment

The median modified PEDro score was 6 on a scale of 0 to 9. Five studies scored 6, 2 scored 5, and 2 scored 4 (Supplemental Table 2, available online at <http://www.mayoclinicproceedings.org>).



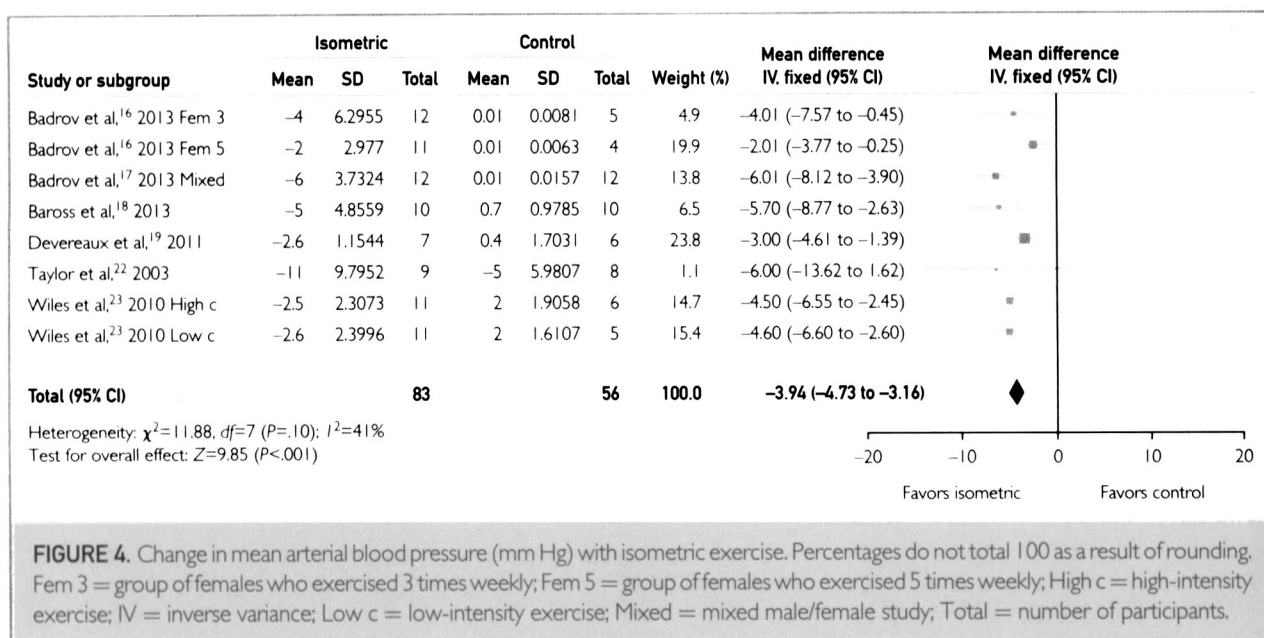


FIGURE 4. Change in mean arterial blood pressure (mm Hg) with isometric exercise. Percentages do not total 100 as a result of rounding. Fem 3 = group of females who exercised 3 times weekly; Fem 5 = group of females who exercised 5 times weekly; High c = high-intensity exercise; IV = inverse variance; Low c = low-intensity exercise; Mixed = mixed male/female study; Total = number of participants.

Publication Bias

Egger plots illustrated minimal evidence of publication bias (Supplemental Figures 5-7).

DISCUSSION

Our updated systematic review and subsequent meta-analysis confirms previous findings that isometric resistance training reduces BP. The magnitude of reduction is similar, perhaps even greater, than benefits reported from other exercise modalities. The BP reductions were observed in SBP, DBP, and MAP and were consistent across included trials. Blood pressure reductions were seen in both medicated hypertensive and normotensive participants from secondary analyses, with medicated hypertensive participants experiencing a greater reduction in DBP and MAP. To date, the impact of antihypertensive medication class on the capacity of isometric exercise to reduce BP has not been examined. The magnitude of BP-lowering effects is likely to translate into a reduction in clinical events.

We found that SBP was lowered by almost 7 mm Hg in response to isometric training, an effect size similar to the 10-mm Hg SBP decrease in our previous meta-analysis.⁸ Although the inclusion of the recently published trials increases the statistical power of the current analysis, there is a small decrease in absolute effect size compared with our earlier work.⁸ Nevertheless,

the effect size remains highly significant with a relatively small CI and substantiates the recent inclusion by the American Heart Association of isometric exercise as a potential nonpharmacological therapy to lower BP.²⁵ Furthermore, the effect size lends weight to the notion that isometric exercise training is comparable or superior to dynamic exercise training (aerobic or resistance) or combined dynamic exercise for reducing SBP. Although the reductions in DBP and MAP are smaller than those seen in SBP, the effect sizes are comparable to changes observed with other exercise modalities.⁷ A novel finding of the current analysis is a slight statistical reduction in RHR, although the small effect size suggests it is unlikely a factor in mediating the changes in BP.

The mechanisms responsible for these BP effects remain equivocal. Similar to dynamic aerobic exercise training,²⁶ the BP-lowering effects of isometric exercise training are most likely mediated through changes in systemic vascular resistance. Limited evidence suggests that isometric exercise training may be associated with reduced vascular sympathetic modulation,²² while a larger body of research has investigated potential beneficial adaptations in vascular function. Specifically, isometric exercise training has been reported to increase endothelial-dependent (eg, nitric oxide-mediated) vasodilation in response to reactive hyperemia in

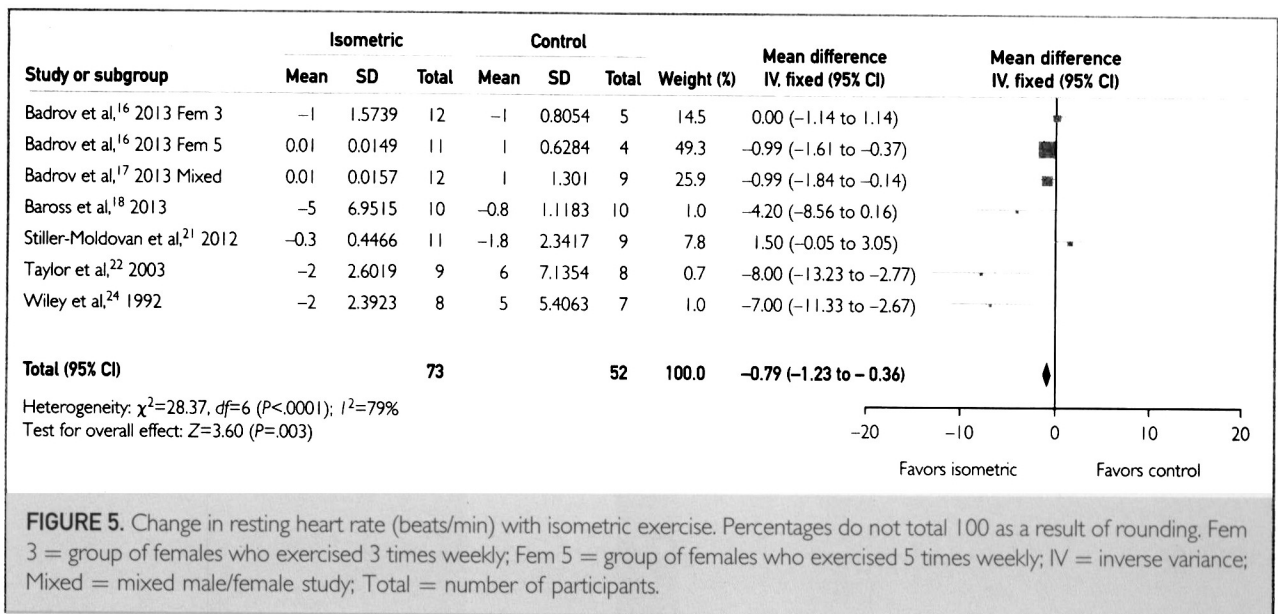


FIGURE 5. Change in resting heart rate (beats/min) with isometric exercise. Percentages do not total 100 as a result of rounding. Fem 3 = group of females who exercised 3 times weekly; Fem 5 = group of females who exercised 5 times weekly; IV = inverse variance; Mixed = mixed male/female study; Total = number of participants.

medicated hypertensive patients²⁷; however, this effect was only noted in the trained limb (not the untrained limb) and was not found in normotensive individuals, even though BP was reduced.²⁸ More recently, isometric exercise training has been found to increase resistance vessel endothelial function¹⁶ and increase training limb artery diameter, blood velocity, and blood flow in concert with reduced vascular conductance.²⁹ These findings are important because BP is primarily regulated at the level of the resistance vessels, and increased blood flow/velocity may increase the shear stress-mediated basal production of endothelial-dependent vasodilators such as nitric oxide. Isometric exercise training has also been reported to increase antioxidant concentrations.³⁰ Unfortunately, most mechanistic studies appear powered only to assess the primary variable of BP and not possible mechanistic pathways. Future robust trials are required to elucidate the role of isometric exercise training on neurohormonal (eg, sympathetic activity), inflammatory (eg, reactive oxygen species), and vascular (eg, endothelial function, arterial compliance) pathways as potential mechanisms for the reductions in BP.

Nevertheless, in the absence of a mechanistic explanation, health practitioners and individuals with hypertension can perhaps benefit from the simplicity and relatively low cost of isometric resistance exercise. The most common protocols have utilized a handheld dynamometer and four

2-minute isometric efforts at low to moderate intensity (30%-50% of maximal voluntary contraction), interspersed with 1 to 3 minutes of rest. The relatively short training session duration and flexibility of venue are obvious advantages of isometric exercise and may produce superior exercise adherence compared with aerobic or resistance training programs. It is possible that improved adherence may partially explain the relatively larger effect sizes that have been achieved almost without exception in isometric trials compared with other exercise modalities. In many cases, health care professionals turn immediately to pharmacological treatment of hypertension because exercise adherence is poor. In light of the effect sizes reported in our analysis and the removal of many common exercise barriers that may prevent good adherence, isometric resistance exercise has enormous potential for people with prehypertension and stage 1 hypertension. Moreover, as the only appreciable cost is a simple hand dynamometer, isometric training may be more cost-effective than antihypertensive medication.

It is important to remember that isometric exercise (as with dynamic aerobic exercise) immediately increases BP. However, as with dynamic resistance exercise, it is known that low- to moderate-intensity resistance exercise produces safe and minimal hemodynamic responses.³¹ Thus, given the low intensity employed in current isometric exercise training studies, it is not surprising that the reported immediate mean \pm

SD increases in SBP (16 ± 10 mm Hg), DBP (7 ± 6 mm Hg), and heart rate (3 ± 4 beats/min) are modest.³² As a result, it is generally recommended that at low intensities (<40% of maximum), patients in whom dynamic aerobic exercise is considered appropriate should be permitted to complete equivalent-intensity isometric exercise.³³ Additionally, given the high prevalence of ischemic heart disease in patients with hypertension, the immediate hemodynamic differences between dynamic aerobic and isometric exercise warrant further clarification. Physiologically, isometric exercise may be associated with reduced myocardial oxygen demand due to an attenuated increase in heart rate and increased DBP (ie, coronary perfusion pressure).³⁰ In support, the addition of isometric exercise to dynamic aerobic exercise has been shown to attenuate the ST-segment depression observed with dynamic aerobic exercise alone,³⁴ while other studies have reported that dynamic lifting elicited higher heart rate, BP, and rate-pressure product responses than sustained handgrip contraction and that ischemic ST-segment depression and clinically important ventricular arrhythmias were infrequent with static effort.³⁵ In general, it would be helpful if studies continuously recorded BP during the performance of isometric activity to establish normal responses and categorize potential risk of adverse events in various populations.

Our analyses exhibit moderate to high evidence of between-study heterogeneity. Although most comparisons of exercise training studies reveal variations in study duration and exercise modality, the commonality of protocols renders differences negligible in this analysis. While the investigators performing assessment measures were aware of group assignment, this was not necessarily a limitation since we chose to modify the PEDro scale to assess study quality because all studies would have found it difficult to blind participants and investigators to the allocation of isometric exercise training or sedentary control. The median PEDro score was 6, suggesting a moderate study design and reporting. Future studies should employ sham isometric training (such as suboptimal intensity) to permit studies to use a stronger double-blind design. The Egger plots showed minimal evidence of publication bias, which is understandable because studies demonstrate consistent improvements and authors are apt to

emphasize the antihypertensive benefits. It is therefore unlikely that unpublished negative or neutral data sets exist for most of our outcome measures, and the level of significance suggests that unpublished data would not change our findings. The major limitation of this field of study is that several desired measures such as continuous BP monitoring, neurohormonal and blood vessel compliance, and flow are unavailable, making it difficult to unravel the mechanistic interpretation of these antihypertensive findings.

CONCLUSION

Our findings document that isometric resistance training has the ability to significantly reduce resting BP. Interestingly, these antihypertensive responses are similar (if not larger) than those previously reported with aerobic or resistance exercise alone, even though they require a markedly smaller time commitment. Moreover, the relatively low cost and simplicity of delivery are likely to enhance exercise adherence. Our data suggest that this form of training has the potential to elicit significant and clinically meaningful BP reductions and may serve as an important adjunct to current exercise recommendations of dynamic exercise training.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>.

Abbreviations and Acronyms: BP = blood pressure; DBP = diastolic BP; MAP = mean arterial pressure; MD = mean difference; PEDro = Physiotherapy Evidence Database; RHR = resting heart rate; SBP = systolic BP

Potential Competing Interests: Dr Millar has received (2010-2012) speaking and travel honoraria from Zona Health.

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Clinically Meaningful Blood Pressure Reductions With Low Intensity Isometric Handgrip Exercise. A Randomized Trial

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Received July 2, 2015

Accepted January 8, 2016

On-line April 12, 2016

Summary

There exists no examination of what is the minimum anti-hypertensive threshold intensity for isometric exercise training. Twenty two normotensive participants were randomly assigned to training intensities at either 5 % or 10 % of their maximal contraction. Twenty participants completed the study. Clinically meaningful, but not statistically significant, reductions in systolic blood pressure were observed in both 5 % and 10 % groups -4.04 mm Hg (95 % CI -8.67 to $+0.59$, $p=0.08$) and -5.62 mm Hg (95 % CI -11.5 to $+0.29$, $p=0.06$) respectively after 6 weeks training. No diastolic blood pressure reductions were observed in either 5 % -0.97 mm Hg (95 % CI -2.56 to $+0.62$, $p=0.20$) or 10 % MVC $+1.8$ mm Hg (95 % CI -1.29 to $+4.89$, $p=0.22$) groups respectively after training. In those unable to complete isometric exercise at the traditional 30 % intensity, our results suggest there is no difference between 5 and 10 % groups and based on the principle of regression to the mean, this could mean both interventions induce a similar placebo-effect.

Key words

Blood pressure • Isometric exercise • Hypertension

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Introduction

Hypertension is considered to be the greatest modifiable risk factor pertaining to CVD (Hajjar and Kotchen 2003). Health professionals recommend lifestyle

modifications such as exercise for the prevention and treatment of hypertension in both normotensive and hypertensive individuals (James *et al.* 2014), traditionally, aerobic exercise training that targets cardiovascular fitness has been the first line exercise prescription for managing hypertension.

Isometric exercise training (IET) involves a single sustained muscle contraction against an immovable load or resistance with no, or minimal, change in length of the involved muscle group. Whilst the physiological mechanisms elicited by IET are not entirely clear there is a growing body of evidence that supports the role of IET to accommodate significant reductions in resting systolic and diastolic blood pressures in both hypertensive and normotensive men and women (Millar *et al.* 2008, Wiles *et al.* 2010, Devereux *et al.* 2011, Badrov *et al.* 2013a,b). Results of a recent meta-analysis reported that compared to dynamic aerobic endurance training, dynamic resistance training, and training comprising both dynamic endurance and resistance work, IET elicited the greatest reductions in resting SBP (Cornelissen and Smart 2013, Carlson *et al.* 2014). The effect size is similar to that of monotherapy with beta-blockade (Wong and Wright 2014).

The isometric training stimulus, responsible for the reductions in resting blood pressure, probably relates to a combination of intensity (% MVC), muscle mass (IHG vs. double-leg) and program length (number of weeks). Moreover similar blood pressure responses to isometric arm and leg exercise are observed (Williams 1991), however it is intuitive to assume that the smaller active muscle mass in arm compared to leg isometric

exercise may induce a greater blood pressure response. Whilst the effects of different IET intensities have been investigated across a number of hemodynamic measures such as systolic, diastolic and mean-arterial blood pressures, heart rate and total peripheral resistance, there are currently only three randomized controlled trials (RCT) that have directly compared the effects of different IET intensities on resting BP (Wiles *et al.* 2010, Baross *et al.* 2012). Baross *et al.* (2012) and Gill *et al.* (2015) compared the effects of isometric bilateral leg extensions (four sets of 2 min contractions) at a lower maximal voluntary contraction (MVC) (~8 %) and a higher (~14 % MVC) intensity. Reductions in resting BP and concomitant vascular adaptations were observed in the high intensity group; whereas, no BP reductions or vascular adaptations were evident in the lower group suggesting the threshold for anti-hypertensive effect lies between 8-14 %, but Wiles *et al.* (2010) also compared the effects of isometric bilateral leg extensions on BP (four sets of 2 min contractions) at a lower (~10 % MVC) and a higher (~20 % MVC) intensity. At 4 weeks into the study no significant differences in resting BP were observed in either group, however, at the studies end (8 weeks) significant reductions in resting blood pressure were reported in each group. More recently, Gill *et al.* (2015) compared the effects of low (~23 % MVC) and moderate (~34 % MVC) IET over a 3 week period and reported a reduction in SBP in the moderate intensity group only. In our recent meta-analysis of IET to manage BP (Carlson *et al.* 2014) two studies utilized an intensity of 10 % MVC as a lower intensity comparison. One of these studies (Wiles *et al.* 2010) used leg exercise and another (Wiley *et al.* 1992) used handgrip exercise. The data from Wiles *et al.* leaves open the possibility that there may be some anti-hypertensive effect from 10 % MVC (Wiles *et al.* 2010). Those who have participated in IET studies understand the physical and mental demands of sustaining four sets of isometric exercise at 30 % MVC for 2 min. Moreover the frail or elderly, who may initially struggle with IET at 30 % MVC, are more likely to be hypertensive and therefore derive most benefit from IET. The primary reason we are conducting this study is to establish if there exists an anti-hypertensive effect when conducting MVC at intensities of 10 % or as low as 5 %. Our hypothesis is that we can show an anti-hypertensive effect with IET at 10 % MVC, but not 5 % MVC, in normotensive people, as we particularly wished to avoid conducting this initial study in populations exposed to potent vasoactive

agents. If we can show an anti-hypertensive effect in normotensive participants, then intuitively these effects are also likely in older hypertensive patients. In addition, in the interests of scientific validity it would be valuable to truly establish if 10 % MVC or even 5 % MVC elicit placebo or anti-hypertensive effects. Our secondary aim was to examine if sampling blood pressure for longer periods eliminated the 'white coat hypertension' effect.

The purpose of the present study is to compare the effect of two isometric handgrip training programs performed at different intensities.

Materials and Methods

Participants

Twenty two participants, 13 males and 9 females, aged 38.8 ± 11 years, with resting BP within the normal range ($>90/>60$ mm Hg to $<139/<90$ mm Hg) volunteered to participate in the study. All participants were staff or students of the University of New England. Two participants (one male and one female) were unable to complete the study; both due to family circumstances. Participants were assessed as eligible if they were normotensive, had no significant visual or motor impairments, could follow verbal instructions and were between the ages of 25 and 65 years. At a screening session prior to commencement of the isometric exercise program all potential volunteers were asked to complete a participant history and medical questionnaire, an adult exercise screening questionnaire, and a written consent. At this time it was determined that participants were able to exercise and were not taking any medication that could affect the hemodynamic variables being investigated or their ability to perform IHG exercise. Baseline BP measurements were taken on 3 consecutive days, at the same time each day, prior to the commencement of training. Baseline participant characteristics are displayed in Table 1.

To minimize the influence of external variables on BP measurements, participants were asked to refrain from vigorous exercise and alcohol for 24 h prior to each scheduled continuous blood pressure measurement, to abstain from caffeine for 12 h prior and fast for 4 h prior. Prior to the commencement of BP measurements and IHG exercise participants were familiarized with the all equipment and IHG and BP measurement procedures. All study protocols were approved by the research ethics committee of the University of New England, HREC Approval Number HE14-047.

Study design

Based upon the mean difference for change in SBP in our meta-analyses (Carlson *et al.* 2014) we calculated that 10 participants in each group were required to detect a 5 % significant change with 80 % power. Participants were randomly allocated to either IHG training at 10 % MVC (n=10) or IHG training at 5 % MVC (n=10). Blind randomisation of participants was done using Microsoft Excel 2007 random number generator. Following group allocation all participants were instructed on the correct usage of the IHG equipment. Subsequent to group assignment all participants underwent baseline cardiovascular measures (systolic, diastolic and mean arterial blood pressure, heart rate) which were repeated each week for the duration of the training program.

Arterial BP and heart rate

Arterial BP and heart rate were continuously monitored using the Finometer (FMS, Amsterdam, Netherlands) Model-2 blood pressure monitor. The Finometer is considered to provide blood pressure information which is robust unless potent vasoactive agents are administered (McAuley *et al.* 1997). A wrap around finger cuff equip with, air bladder, light source (LED) and light detector (photo diode) was placed around the middle finger of the dominant hand. Care was taken when selecting and fitting an appropriate size cuff for each participant. The cuffed digit was maintained near heart level and the hydrostatic height correction unit of the Finometer compensated for any further hydrostatic pressure differences. Prior to recording cardiovascular measures the Finometer measurement of the finger arterial pressure was calibrated until the physical repetition rate recorded 40 beats or more. The Finometer provided a beat to beat estimate of the arterial waveform.

IHG training protocol

Participants in both groups completed four sets of 2 min IHG contractions 3 days per week for 6 weeks with the aid of a programmed dynamometer (DHD-3 Digital Hand Dynamometer, Saehan Corp, South Korea). Isometric contractions were performed using the non-dominant hand at either 10 % or 5 % MVC separated by a 1 min rest period. A direct-reading light box was attached directly to the dynamometer to provide visual feedback to assist participants in maintaining the desired contraction force. The light box was calibrated to either 5 % or 10 % MVC for every participant every session, furthermore, the dynamometer display was monitored by

an investigator each time. In terms of force exerted, our participants were able to exert a maximal handgrip force of between 30-50 Nm, so at 10 % MVC this equated to 3.0-5.0 Nm and at 5 % MVC this was 1.5-2.5 Nm.

To avoid Valsalva manoeuvres participants were instructed to breathe at a normal rhythm and depth. Participants were seated in an erect position so that the shoulder was adducted and neutrally rotated, the elbow was flexed at a 90° angle and the forearm and wrist were in a neutral position. The dynamometer was arranged in the participants' hand to ensure that it fitted comfortably, where necessary, the handle of the dynamometer was adjusted to the desired fit. Participants were instructed to apply grip force gently and smoothly and were advised by the researcher to hold their contraction once they had reached the desired IHG intensity. Participants trained every other weekday (Monday, Wednesday and Friday) with rest days in between. MVC was determined at the beginning of each training session (*via* imbedded electronic linear load cells contained within each handgrip); participants were asked to perform three MVCs with their non-dominant hand. The three measurements were then averaged to arrive at the MVC. On the third day of training each week, and prior to commencement of IHG training, resting BP measurements were recorded; continuous BP measurements were also recorded throughout the duration of these training sessions. Before resting BP measures were taken participants were asked to sit quietly for at least 10 min. All resting BP measurements were conducted within 2 h of the initial baseline testing time of day. All sessions were supervised in the exercise physiology laboratory at the University of New England, Armidale, Australia.

Data handling and statistical analysis

The Finometer device computed all hemodynamic variables online and stored the data in result files on a hard disk. Calibration of all pressure transducers was maintained throughout the study. Waveform filtering and level correction protocols corrected arterial hemodynamic measures. BeatScope 1.1a software (FMS, Amsterdam, Netherlands) was used to integrate participants' gender, age, body mass and weight; this information was further integrated to compute beat-to-beat SBP and DBP values. Finometer non-invasive arterial pressure was averaged over 120, 60, 30, and 15 s to account for the effects of BP variability due to different sampling durations. All processed data were transferred to Microsoft Excel (Microsoft

Corporation, Redmond, WA, USA) spread sheets.

Prior to statistical analysis all data were assessed for compliance with parametric test assumptions, where assumptions were violated transformations were applied (Tabachnick and Fidell 2013). Specifically a lower than expected outlying case was detected for a participant's post systolic blood pressure from the 10 % group. To reduce the impact of the univariate outlier the deviant result was reduced to reflect a measurement one unit larger than the next most extreme score. Statistical analysis was performed using Microsoft Excel and SPSS Statistics (IBM Corporation, Armonk, NY, USA) software, version 22. We used independent sample t-tests to compare baseline BP and post intervention BP between groups and paired sample t-tests were performed to determine within groups variations from baseline to post intervention blood pressure, in addition Cohen's *d* statistics were calculated to classify effect size. Two-way ANOVA with co-variates was performed to determine between group differences over time.

The magnitude of change in BP has been associated with initial resting values (Millar *et al.* 2007) to assess whether changes in resting BP following IHG training were influenced by the initial baseline BP values. Similarly in a separate analysis, age was added as a co-variate. An alpha level of <0.05 was determined as representing statistical significance, and the Bonferroni *post-hoc* procedure was used to further explore any significant differences that were detected.

Results

The adherence to IHG was 100 % in the 20 participants who completed the 6 week study. Groups were matched at baseline for age (range 27-61 years), gender, body mass, SBP (range 105-134 mm Hg), DBP (range 64-84 mm Hg) and BMI (range 23-46) (Table 1).

As we collected 120 s of resting BP data we chose this as the default for our primary aim which was to see if BP was reduced. In Table 2 we have also reported 60, 30 and 15 s rolling sample data in order to address our secondary aim of examining effect of sample duration on BP change.

Systolic blood pressure

Reductions in baseline versus post-intervention SBP were not significantly different in the 5 % MVC group, -4.04 mm Hg (95 % CI -8.67 to $+0.59$, $p=0.08$), Cohen's *d* for this test was 0.56 which can be described

as a medium to large effect size. There was no significant baseline versus post-intervention reductions in the 10 % MVC group, -5.62 mm Hg (95 % CI -11.5 to $+0.29$, $p=0.06$), Cohen's *d* for this test was 0.78 which can be described as large. Post-intervention SBP was similar between the 5 % MVC and 10 % MVC groups 116.3 ± 6 mm Hg vs. 114.8 ± 2.6 mm Hg respectively $F(1,17)=0.45$, $p=0.51$. No interaction effects were observed.

Diastolic blood pressure

Changes in baseline versus post-intervention DBP were not significantly different in the 5 % MVC group, -0.97 mm Hg (95 % CI -2.56 to $+0.62$, $p=0.20$), $d=0.18$. Similarly, there were no significant baseline versus post-intervention difference in the 10 % MVC group, $+1.8$ mm Hg (95 % CI -1.29 to $+4.89$, $p=0.22$), $d=0.26$ which can be described as small. Post-intervention DBP was similar between the 5 % MVC and 10 % MVC groups 68.5 ± 4 mm Hg vs. 69.4 ± 7 mm Hg respectively $F(1,17)=0.72$, $p=0.41$. No interaction effects were observed.

Heart rate

There were no significant changes in heart rate during the 6 week study. Heart rate did not increase during IHG exercise >10 beats.min⁻¹ in any participant during any session.

Effect of sampling duration

ANOVA showed that using 120 s produced significantly higher SBP and DBP than using 15, 30 or 60 s sampling durations (Table 2).

Table 1. Resting baseline data.

	5 % (n=10)	10 % (n=10)
<i>Age (years)</i>	38.8 ± 10.5	38.7 ± 12.6
<i>Male (n)</i>	6	6
<i>Female (n)</i>	4	4
<i>Height (m)</i>	1.72 ± 0.1	1.75 ± 0.1
<i>Weight (kg)</i>	83.3 ± 21.4	85.3 ± 26.9
<i>BMI</i>	28.4 ± 7.7	27.7 ± 7.4
<i>RSBP (mm Hg)</i>	120.3 ± 8.1	120.5 ± 11.8
<i>RDBP (mm Hg)</i>	69.5 ± 6.4	67.6 ± 6.4

All values are reported as means. BMI – body mass index, RSBP – resting systolic blood pressure, RDBP – resting diastolic blood pressure. All $p>0.05$.

Table 2. Mean difference scores for continuous blood pressure measurement.

	Blood pressure at 120 s			
	Pre SBP	Post SBP	Pre DBP	Post DBP
<i>Blood pressure</i>				
60 s	0.57 ± 0.75	0.02 ± 1.81	0.39 ± 0.54	-0.09 ± 1.25
30 s	0.91 ± 1.76	-0.09 ± 3.46	0.48 ± 0.95	0.03 ± 2.88
15 s	1.44 ± 2.35	0.01 ± 4.0	1.07 ± 1.44	0.17 ± 4.21

t statistic: * $p < 0.05$, ** $p < 0.01$. Data are means ± SD.

Age as a covariate

An ANOVA indicated that 20 % of the variance in post training SBP was explained by the participant ages, $F(1,17)=4.30$, $p=0.05$, partial $\eta^2=0.202$. Furthermore, 20 % of the variance in post training DBP was also explained by participant ages, $F(1,17)=4.31$, $p=0.05$, partial $\eta^2=0.202$.

Discussion

Our work examines the effects of the lowest isometric training intensities that have been explored. Our primary finding was that IHG training performed at either 5 % MVC or 10 % MVC elicited no statistically significant reduction on either SBP or DBP after 6 weeks of training in normotensive adult men and women. However, our results did show a reduction in SBP in both the 5 % and 10 % groups and this was supported by medium to large effect sizes suggesting that IHG training at both intensities has an anti-hypertensive effect. In the current study, after 6 weeks of IHG training, reductions in SBP were similar to the antihypertensive effects observed in monotherapy of 5-7 mm Hg (Wong and Wright 2014). Reductions in SBP and DBP of ≥ 2 mm Hg can significantly reduce the incidence of CVD in both hypertensive and normotensive individuals, subsequently small reductions of this magnitude are considered clinically meaningful (Collaboration 2003, Wong and Wright 2014). We identified one other published RCT that did not detect statistically significant reductions in resting BP yet were able to report clinically meaningful reductions in ambulatory SBP and night-time SBP (~ 3 -4 mm Hg) (Stiller-Moldovan *et al.* 2012). Our secondary finding was that there was minimal effect of different sampling durations for rolling averages (assessed over 120, 60, 30 and 15 s) on pre- or post-blood pressure values.

Our primary finding was no statistically

significant effect on either SBP or DBP after 6 weeks of training in normotensive adults. If one assumes for arguments' sake that there exists a 2/3 relative intensity of isometric handgrip (IHG) exercise to Double Leg (DL) isometric exercise, then the comparison of our data (non-significant changes after 6 weeks of IHG at 10 % MVC) might actually be showing similar results as Wiles *et al.* (2010) who used 10 % MVC DL for 8 weeks. Thus, Wiles *et al.* (2010) used a slightly higher intensity (comparing 'like-for-like' IHG to DL, but in a longer program). This interpretation is further confirmed by the 4-weeks to 6-weeks comparison between the data of Wiles *et al.* (2010) and the current data (both being non-significant). However, it should be noted that Wiles *et al.* (2010) did report significant reductions in resting BP at ~ 10 % MVC after 8 weeks, but not after 4 weeks of training.

Contrary to the findings of Wiles *et al.* (2010), Howden *et al.* (2002) observed statistically significant reductions in SBP after 3 weeks of isometric leg exercise at ~ 20 % MVC and after 4 weeks of isometric arm training at ~ 30 % MVC. Furthermore, Gill *et al.* (2015) hypothesized that reductions in resting BP from IET would be intensity dependent, they compared the effects of low (~ 23 % MVC) and moderate (~ 34 % MVC) IET over a 3 week period and reported a reduction in SBP in the moderate intensity group only. Baross *et al.* (2012) found that ~ 14 % MVC, but not ~ 8 % MVC elicited BP reductions after 8 weeks of isometric bilateral leg extension exercise. Collectively, these studies highlight a relationship between IET intensity, time (study duration) and reductions in resting BP. They suggest that the magnitude and rate at which resting BP is reduced increases as exercise intensity increases and that where present these reductions will continue to increase over time, with 8-10 weeks being the longest durations investigated so far. Subsequently, in terms of the current study, it could be the case that at intensity levels as low as

5 % and 10 % MVC that 6 weeks of IHG training is not a sufficiently long enough training period to elicit statistically significant results, but may elicit clinically significant results. Whilst the relationship between IET intensity, time and BP reductions are not fully understood, together, our findings and those of others suggest an anti-hypertensive threshold that may be well below 10 % MVC.

The precise mechanism(s) of the anti-hypertensive effect(s) of isometric exercise remain unclear; however, it appears likely that the true stimulus is probably a result of the competing drives of reduced blood flow (from external compression of the blood vessels and sympathetic vasoconstriction) in the face of a vasodilator stimulus from metabolite accumulation. The variation in individual adaptation rates to IET are probably due to the individual variations in plasma noradrenaline levels, which exist prior to training (Esler 2011). Indeed, plasma noradrenaline levels have been shown to be linked to training-induced reductions in resting blood pressure (especially in hypertensives, who seemingly have higher levels of plasma noradrenaline) (Cornelissen and Fagard 2005).

Previous work has suggested that blood flow is fully occluded at approximately 55-75 % of MVC, but those able to exert more handgrip force will have higher occlusion thresholds (Barnes 1980). Intuitively even at lower percentage of MVC with arm or leg isometric exercise, partial occlusion of blood flow is likely. The reactive hyperemia may therefore be due to partial or full occlusion of the brachial artery during 2 min IHG efforts. Previous work has postulated that in response to ischemia induced by IHG activity a number of metabolites are produced; these include prostaglandins, beta-endorphins and HIF-alpha (Wong *et al.* 2015, Stiller-Moldovan *et al.* 2012, Wong and Wright 2014). It may be that the presence or absence of reactive hyperemia is determined by the MVC intensity during isometric exercise. Moreover, the results of our work and of others such as Wiles *et al.* (2010) and Baross *et al.* (2012) suggest that MVC intensities as little as 5-14 % may induce sufficient, albeit partial, occlusion to blood flow to induce ischemia and the subsequent metabolite production that may be contributing to BP reductions. Nonetheless, IET response rates are highly variable between individual participants whereby some respond to IET (in highly varying degrees) and others do not (McGowan *et al.* 2007, Stiller-Moldovan *et al.* 2012). Whilst the reasons for this are not fully understood there are a number of variables that are

likely to affect the magnitude of reduction in resting BP. For instance, the greatest isometric exercise reductions in resting BP have been observed in pre-hypertensive and hypertensive individuals (Wiley *et al.* 1992, Taylor *et al.* 2003) and magnitude of change in BP has been associated with initial resting BP values such that greater reductions are observed in individuals with higher pre-IET BP (Millar *et al.* 2007). In the current study participant age was also identified as a significant predictor of resting BP reduction in response to IET, this finding was not surprising as age is related to arterial stiffness and hypertension.

Our secondary aim was to assess whether different sampling durations for rolling averages affected BP values for continuous BP measurements. Due to the transient nature of blood pressure the recommended gold standard procedure for measuring blood pressure is *via* 24 h ambulatory monitoring, however, ambulatory means of BP measurement were unavailable to this study. In an attempt to attenuate the natural fluctuations of BP we used a continuous BP measurement and also measured baseline resting BP on three separate occasions for a 2 min period each time. We found that in all cases 120 s sampling data was significantly higher than for the other sampling durations. We believe that the longer 120 s sampling duration provides a more robust default for our primary analysis.

The lack of a non-exercising or 'sham IRT' control group was a limitation in this study.

Conclusion

This is the first threshold (MVC %) examination for antihypertensive responses to IET at intensities traditionally used as a control or placebo. In those people unable to complete IET at the traditional intensity of 30 % MVC, our results suggest that IET intensities of both 5 % and 10 % MVC may offer clinically relevant anti-hypertensive effects, despite the absence of statistically significant reductions in resting BP. As this is the first study of its kind, the study duration and the sample size may have been insufficient to demonstrate a statistically significant reduction in resting BP at these low intensities. Further research involving a larger participant cohort, conducted over a longer period of time is required to determine a minimum therapeutic threshold for antihypertensive response, this determination would aid in the design of future RCT's to determine if sham groups are truly that. Moreover, ascertaining the

minimum IET intensity for BP reduction may also be important in terms of designing exercise programs for the frail and elderly. Elderly people may struggle to complete IHG exercise at 30 % MVC, and why would we ask them to in light of our clinically significant findings.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

The authors thank Dr Gudrun Dieberg for her assistance with study design.

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Appendix C: Conference abstracts

Throughout my PhD, I attended local and international conferences to promote my research. The conference abstracts are attached in chronological order. In 2016 I submitted a symposium proposal to the American Congress of Rehabilitation conference, the proposal is not published; however, I have attached the proposal in the appendix, along with the conference proceedings.

Refereed conference presentations

1. **Carlson, D. J.**, McFarlane, J. R., Dieberg, G. & Smart, N. A. (2015) Isometric handgrip exercise to reduce hypertension for stroke prevention and recovery. American Congress of Rehabilitation Medicine Conference (25-30 October 2015) in Dallas, TX, U.S.A. *Archives of Physical Medicine and Rehabilitation*, 96(2): e25.
2. **Carlson D. J.**, Inder, J. D., McFarlane, J. R., Dieberg, G. & Smart, N. A. (2016). Blood pressure management – isometric handgrip exercise reduces hypertension. 37th Annual Scientific Meeting of the High Blood Pressure Research Council of Australia (2-4 December 2015) in Melbourne, Australia. *Hypertension* 67(5): e9.
3. **Carlson, D. J.**, Hess, N.C. J., Inder, J. D., Palanisamy, S. K. A., McFarlane, J. R., Dieberg, G. & Smart, N. A. (2016). Rate pressure product in healthy individuals during an acute bout of isometric handgrip exercise. Exercise and Sport Science Australia (ESSA) – Research to Practice 2016 (14-16 April 2016) in Melbourne, Australia. ESSA E-proceedings.
4. American Congress of Rehabilitation Conference (30 October-4 November 2016) in Chicago, IL, U.S.A. Not published due to being an oral symposium.
5. **Carlson, D. J.**, Dieberg, G., McFarlane, J. R. & Smart, N. A. (2017). Isometric handgrip exercise reduces 24hr ambulatory blood pressure. American Heart Association Scientific Sessions 2017 (11-15 November 2017) in Anaheim, Ca, U.S.A. *Circulation*. 136: A17175. Printed online, Retrieved from http://circ.ahajournals.org/content/136/Suppl_1/A17175

Setting: A stratified purposive sampling method was used to select five out of nine provinces in Zambia based on the highest percentage statistics of persons with disabilities and geographical and social-economic characteristics.

Participants: Seventy-five PWML using wheelchairs or crutches for ambulation aged 17-55 years were purposively recruited.

Interventions: N/A.

Main Outcome Measure(s): Study results will assist in informing government of the need to improve environmental access to enable equal rights for all citizens.

Results: Inaccessibility of education institutions, workplaces and spaces have contributed to reduced participation with negative implications for personal, family, social and economic aspects of participants. Government buildings, service buildings and transportation were universally identified as most important but least accessible.

Conclusions: Zambians with mobility limitations have been disadvantaged in accessing services and facilities provided to the public, depriving them and their families of full and equitable life participation because of reduced economic capacity.

Key Words: Inaccessible Spaces, Community Participation, Persons with Mobility Limitations, Impact, Disability

Disclosure(s): None Disclosed.

Research Poster 4952

WITHDRAWN

Research Poster 4968

High Level Mobility Task Analysis after Military Mild Traumatic Brain Injury Identifies Subtle Motor Control Impairments

Muhammet Balcilar (Yildiz Technical University), Oleg Favorov, Karen Leigh McCulloch

Objective(s): Quantitative evaluation of performance on sensory or motor tests, practical and objective measures, have the potential to be highly sensitive to even subtle neural abnormalities associated with mild brain injury. In this study we investigated whether two components of the Assessment of Military Multi-task Performance, the Illinois Agility Test (IAT) and Run-Roll-Aim (RRA) task, identified movement differences associated with mTBI.

Design: Cross sectional.

Setting: Fort Bragg, NC.

Participants: The IAT was administered to 18 healthy control subjects and 18 subjects diagnosed with mTBI with persistent symptom complaints, while the RRA test was administered to 37 healthy control and 37 mTBI subjects, all drawn from active duty soldiers.

Interventions: N/A.

Main Outcome Measure(s): The IAT, requires running of a series of short distances while navigating obstacles, requiring frequent turns, speed acceleration and deceleration. This task places high demands on the performance of the CNS sensorimotor system. In the RRA test, a service member runs while carrying a simulated weapon on a course that includes requires "trip wire" avoidance, 3-5 second rush with a rapid transition to prone, a directional Stroop cue, combat rolls, visual target seeking through a weapon scope, rapid lateral transition, rapid transition back to standing, and running backwards. Each subject was outfitted with two inertial sensors (tri-axial accelerometers and gyroscopes), one attached to a headband and another at the lumbar area of the torso. Time series values outputted

continuously by each of the 12 sensors during the test were used as quantitative measures of performance on each test.

Results: In the RRA test, the power spectrum of each subject's time series was computed separately for each sensor using Fast Fourier Transform (FFT). Using the leave-one-out cross-validation approach, the 300 most significant frequencies were used as the input to a linear Support Vector Machine (SVM), trained to distinguish between control and mTBI subjects. The SVM correctly classified 23 out of 37 control subjects (62%) and 31 out of 37 mTBI subjects (83.7%). In IAT, only the accelerometry data were used. To reduce the dimensionality of the data, Principal Component Analysis was implemented and first 2 principal components were used in FFT analysis. The 190 most dominant frequencies were used as the input to a linear SVM. Cross-validation was conducted using the leave-one-out approach. The SVM correctly classified 14 out of 18 control subjects (77.7%) and 17 out of 18 mTBI subjects (94.4%). The area under ROC curve was 0.817.

Conclusions: These results indicate that movement during RRA and IAT performance are affected by mTBI and, once further optimized on a more comprehensive sample, may be used as sensitive diagnostic tools.

Key Words: Concussion, Mild Traumatic Brain Injury, Accelerometry, High Level Mobility

Disclosure(s): None Disclosed.

Research Poster 4969

Isometric Handgrip Exercise to Reduce Hypertension for Stroke Prevention and Recovery

Debra Jane Carlson (University of New England), James R. McFarlane, Gudrun Dieberg, Neil A. Smart

Objective(s): To investigate the anti-hypertensive effect threshold of isometric handgrip training and suitability for stroke prevention and recovery.

Design: Randomized controlled trial.

Setting: Exercise physiology laboratory at the University of New England, Armidale, Australia.

Participants: Individuals previously diagnosed with mild or pre hypertension, men (n=6) and women (n=10), aged 52 ± 7.9 years; with a resting systolic blood pressure (SBP) ≥ 120 mmHg and/or a resting diastolic blood pressure (DBP) ≥ 80 mmHg, or receiving anti-hypertensive pharmacotherapy (69%). None refused or withdrew due to adverse effects.

Interventions: Participants trained 3 days per week for 8 weeks using a DHD-3 Digital Hand Dynamometer with their non-dominant hand, at either 5% or 30% of their maximum voluntary contraction (MVC). Participants completed 4 sets of 2 minute isometric handgrip contractions separated by 3-minute rest periods. Blood pressure was measured at baseline and on the last day.

Main Outcome Measure(s): Systolic and diastolic blood pressure.

Results: A significant reduction in SBP was seen in the 30% MVC group of -12mmHg from 134 ± 7.6 to 122 ± 12.4 ($p=0.02$), while the 5% MVC group reduced -5mmHg from 127 ± 13.8 to 122 ± 17.3 ($p=0.52$). Reductions of DBP in the 30% and 5% MVC groups were -5mmHg from 74 ± 5.7 to 69 ± 8.4 ($p=0.17$) and -6mmHg from 75 ± 9.5 to 69 ± 8.9 ($p=0.15$), respectively.

Conclusions: The significant reduction in SBP in the 30% group confirms previous findings. While reductions in SBP in the 5% group and changes in DBP in both 5% and 30% groups were not statistically significant, they achieved clinical significance (>3 mmHg). Further study is required to determine if 5% MVC is a suitable introductory intensity to achieve anti-hypertensive effects in people unable to begin at the desired 30% MVC intensity.

Key Words: Randomized Controlled Trial, Hypertension, Blood Pressure, Isometric Handgrip Training

Disclosure(s): None Disclosed.

skinfold thickness, waist and hip circumference were measured and a questionnaire administered. Multivariable logistic regression was used to determine factors associated with awareness, treatment and control.

Results: We recruited 272 individuals with hypertension. Awareness (42%), treatment (32%) and control (27%) of hypertension were poor. Percent body fat (OR=1.06, 95% CI=1.01–1.11) and having had BP measured within the past year (OR=4.69, 95% CI=2.68–8.24) were positively associated with awareness of hypertension, while living >5 km from a health service was associated with poor awareness of hypertension (OR=0.53, 95% CI=0.30–0.93). Factors associated with treatment of hypertension were age ≥ 65 (OR=2.01, 95% CI=1.02–3.95), physical inactivity (OR=2.26, 95% CI=1.20–4.27), greater percent body fat (OR=1.07, 95% CI=1.02–1.13) and having had BP measured within the previous year (OR=5.78, 95% CI=3.01–11.10). Furthermore, having greater percent body fat was the only factor associated with better control of BP (OR=1.06, 95% CI=1.01–1.11).

Conclusion: Improved geographic access and utilization of health services is important for improving awareness and treatment of hypertension. Further research is necessary to determine drivers of control.

BLOOD PRESSURE MANAGEMENT – ISOMETRIC HANDGRIP EXERCISE REDUCES HYPERTENSION

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Background: Hypertension is responsible for 45% of cardiovascular deaths due to heart disease and 51% due to stroke worldwide (WHO). According to the Australian Bureau of Statistics 31.6% of the Australian population had hypertension in 2011/2012. Our recent meta-analysis indicates that isometric exercise may be an effective treatment for those unable to conduct the recommended minimum 30 minutes per day of moderate aerobic exercise. The anti-hypertensive effect threshold of isometric handgrip training has not been established. Moreover, the usual handgrip intensity of 30% maximum voluntary contraction (MVC) used in most studies is initially challenging for some people.

Aims: To investigate the isometric handgrip intensity threshold for an anti-hypertensive effect, and the possibility of using a 5% MVC group as either a low intensity effect group or a true working control.

Methods: A randomized trial was conducted of 24 participants, aged between 30 and 70 years, diagnosed with mild or pre hypertension, men (n=9) and women (n=15), aged 51±8.2 years. Adherence to training was 100%. Groups were matched at baseline for age, gender, systolic blood pressure (SBP) and diastolic blood pressure (DBP). There were no reported changes in exercise, diet and medication throughout the study for any of the participants. Participants had a resting SBP ≥ 120 mmHg and/or a resting DBP ≥ 80 mmHg, or were receiving anti-hypertensive pharmacotherapy (71%). Participants trained 3 days per week for 8 weeks using a DHD-3 Digital Hand Dynamometer with their non-dominant hand, at either 5% or 30% of their MVC. Participants completed 4 sets of 2-minute isometric handgrip contractions separated by 3-minute rest periods. During one weekly training session resting and handgrip blood pressure was continuously recorded so that fluctuations of single measurements could be avoided. Data were analyzed using paired *t*-tests and two-way ANOVA in R (version 3.1.3).

Results: In the 30% MVC group, a significant reduction in SBP of -10 mmHg, from 133 ± 6.4 to 123 ± 12.3 mmHg ($P=0.007$), was seen, while in the 5% MVC group a reduction of -5 mmHg, from 125 ± 11.7 to 120 ± 15.1 mmHg ($P=0.33$), was noted. Reductions in DBP in the 30% and 5% MVC groups were -4 mmHg, from 75 ± 5.1 to 71 ± 7.6 ($P=0.07$), and -6 mmHg, from 74 ± 8.6 to 68 ± 9.1 ($P=0.05$), respectively.

Conclusions: The significant reduction in SBP in the 30% group and DBP in the 5% MVC group confirms previous findings. While reductions in SBP in the 5% group and DBP in the 30% group were not significant, they both indicated trends towards blood pressure reduction, particularly for the latter group. Our results suggest that 5% may be a suitable introductory intensity to achieve anti-hypertensive effects in people unable to begin at the desired 30% MVC intensity. Further studies, increasing the number of participants is required to clarify the efficacy of 5% MVC intensity.

MACROPHAGE-DERIVED INSULIN-LIKE GROWTH FACTOR 1 CONTRIBUTES TO VASCULAR FIBROSIS, AORTIC STIFFENING AND ELEVATED BLOOD PRESSURE IN HYPERTENSIVE MICE

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Background: M2 macrophages accumulate in the vessel wall during hypertension and are important mediators of vascular remodelling, fibrosis and stiffening. However, the mechanisms involved are yet to be defined. M2 macrophages are an important source of insulin-like growth factor 1 (IGF-1). In other disease settings, IGF-1 is known to contribute to fibrosis and tissue growth but its role in vascular remodelling during hypertension remains unknown.

Aim: To examine whether macrophage-derived IGF-1 contributes to vascular fibrosis, aortic stiffening and elevated blood pressure (BP) in hypertensive mice.

Methods and Results: In 10–12 week old male C57BL/6J mice, chronic infusion of angiotensin (Ang II) (0.7 mg/kg/d for 14 days, s.c.) elevated systolic BP (measured by tail-cuff) by >50 mmHg ($P<0.05$) and increased collagen content (Masson's trichrome) and stiffness (ultrasound measurement of pulse wave velocity) of the aorta, each by ~ 2 -fold ($P<0.05$). These changes were accompanied by a 6.8-fold increase in numbers of M2 macrophages (CD45⁺CD11b⁺Ly6G⁺F4/80⁺CD206⁺ cells) in the aortic wall ($P<0.05$), and, importantly, expression of the M2 macrophage marker, CD206, correlated strongly and positively with that of IGF-1 ($r^2=0.57$; $P<0.001$). Depletion of circulating monocytes (precursors of tissue macrophages) by treatment of mice with clodronate-containing liposomes (50 mg/kg, every 3 days, i.v.) reduced the Ang II-dependent influx of M2 macrophages into the aorta by 75% ($P<0.05$) and simultaneously inhibited aortic IGF-1 expression by 32%, collagen deposition by 34%, aortic stiffening by 43% ($P<0.05$), and systolic BP by 25 mmHg (all $P<0.05$). Finally, macrophage-specific IGF-1 deficient mice (LysM^{Cre/+} x IGF-1^{fl/fl}) that were treated with Ang II displayed reduced IGF-1 expression in the vessel wall (by $\sim 33\%$) compared to similarly treated control mice (LysM^{fl/fl} x IGF-1^{fl/fl}; $P<0.05$). Moreover, the IGF-1 deficient animals were protected from Ang II-induced increases in aortic collagen deposition, aortic stiffening and systolic BP (all $P<0.05$).

Conclusions: These results demonstrate that M2 macrophage-derived IGF-1 plays a crucial role in the aortic fibrosis that contributes to vascular stiffening and elevated systolic BP during Ang II-induced hypertension in mice. Thus, future studies aimed at unraveling the cellular targets and second messenger pathways activated by IGF-1 in the aortic wall have the potential to reveal new targets for novel antihypertensive therapies.

ROLE OF INFLAMMATION, VASOCONSTRICTION AND OXIDATIVE STRESS IN THE ENHANCED PRESSOR RESPONSE TO ANGIOTENSIN II IN AGED MICE

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Background: The prevalence of hypertension increases with age. Chronic low-grade inflammation commonly occurs with aging, and inflammasomes are important initiators of inflammatory responses. We tested whether aged mice exhibit an enhanced pressor response to angiotensin II (Ang II) and whether this is associated with inflammation, enhanced vasoconstriction and vascular oxidative stress. We also tested the effect of MCC950, a NLRP3 inflammasome inhibitor, on blood pressure (BP) in Ang II-treated aged mice.

Methods: Young (8–12 week old) and aged (24–30 month old) male C57BL/6 mice were left untreated, or treated with either vehicle or a "slow-pressor" dose of Ang II (0.28 mg/kg/d) for 28 days. Another group of aged mice were treated with either Ang II + saline or Ang II + MCC950 (10 mg/kg/d) for 10 days. We measured systolic BP, mRNA expression of inflammatory markers and components of the renin-angiotensin system, vascular contractile responses and superoxide levels.

Results: In young mice, Ang II caused a gradual increase in BP (from 108 ± 5 to 142 ± 8 mmHg; $n=8$), whereas the effect was much greater in aged mice (from 112 ± 4 to 155 ± 12 mmHg; $n=9$; $P<0.05$). Aging alone increased renal expression of AT1a receptors, NLRP3, caspase-1, IL-1 β , IL-33, CCR2, CCL7 and CCL8 by >1.5 -fold ($n=7-8$; all $P<0.05$). Maximum contractile responses to Ang II in mesenteric arteries were selectively enhanced (by 1.8-fold) in aged vs. young mice ($n=4$; $P<0.05$). In aged mice, contractile responses to Ang II were not affected by acute pre-treatment with the nitric oxide synthase inhibitor L-NAME (100 μ M/L; $n=4$) or the cyclo-oxygenase inhibitor indomethacin (3 μ M/L; $n=3$), but were reduced by the superoxide scavenger tempol by 1.3-fold (100 μ M/L; $n=3$; $P<0.05$). Aged mice exhibited increased Nox2-dependent superoxide production in mesenteric arteries (by 2.4-fold) and thoracic aorta (by 2-fold) compared to young mice ($n=6-10$, both $P<0.05$). Ang II-induced BP was unaffected by MCC950 vs. vehicle in aged mice (BP: 139 ± 7 vs. 145 ± 10 mmHg; $n=6-7$; $P>0.05$).

Conclusions: Aged mice have enhanced pressor responses to Ang II, in association with augmented inflammation, vasoconstriction and vascular oxidative stress. NLRP3 inflammasome activation does not appear to contribute to Ang II-induced hypertension in aged mice.

HUMAN AMNION EPITHELIAL CELLS REDUCE INFARCT VOLUME, SPLENIC ATROPHY AND LUNG INFLAMMATION FOLLOWING ISCHEMIC STROKE IN MICE.

Evans MA^a, Gardiner-Mann CV^a, Chan CT^a, Chu HX^a, Lim R^a, Wallace EM^a, Drummond GR^a, Sobey CG^a, Broughton BRS^a

^aCardiovascular Disease Program, Biomedicine Discovery Institute and Department of Pharmacology Clayton, Victoria, Australia; ^bThe Ritchie Centre, Monash Institute of Medical Research, Clayton, Victoria, Australia

Background: The outcome following ischemic stroke is influenced by the extent of brain injury and also the occurrence of bacterial infections within the lung. These infections are promoted by post-stroke immunosuppression, a phenomenon characterized by a marked loss of circulating and splenic leukocytes. Stem cells offer great therapeutic potential for stroke patients and may improve stroke outcome via multiple mechanisms. Human amnion

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Rate pressure product in healthy individuals during an acute bout of isometric handgrip exercise

Debra J. Carlson¹, Nicole C.L. Hess¹, Jodie D. Inder¹, Suresh K.A. Palanisamy¹, James R. McFarlane¹, Gudrun Dieberg¹, Neil A. Smart¹

¹University of New England, Armidale, NSW, Australia

Introduction: Meta-analyses have shown isometric resistance training (IRT) to produce a significant blood pressure lowering effect. Due to hypertensive responses during IRT some health professionals are reluctant to recommend IRT. Consequently moderate intensity aerobic exercise remains the preferred exercise modality for lowering blood pressure. Aerobic exercise at 60% max heart rate (HR) at 41 years, with HR 108 and systolic blood pressure (SBP) 140 would have a rate pressure product (RPP) of 15-20K.

Aims: To measure surrogate myocardial oxygen consumption using peak RPP during IRT conducted at 'control intensities' 5%, 10% and 'intervention intensity' 30% of maximum voluntary contraction (MVC).

Methods: A randomised trial was conducted of 32 healthy participants, men (n=19) aged 41 ± 12, height 173mm ± 10 and weight 80kg ± 21. Participants were randomised into a 5%, 10% or 30% MVC group. Participants conducted 4 x 2 min isometric handgrip exercises with their non-dominant hand, separated by either a 1 min (5% and 10%) or 3 min (30%) rest period. During the session beat-to-beat resting and handgrip blood pressure, and heart rate were continuously recorded.

Results: There were no significant differences between the 4 bouts of exercise in any of the groups for SBP, diastolic blood pressure, mean arterial pressure, HR or RPP. Mean peak RPP for each bout in the 5% group ranged from 8423-9055 p=0.62, 10% was 9026-9569 p=0.85, and 30% was 10429-11308 p=0.81. Comparison of peak RPP amongst groups was 5%vs10% p=0.48, 10%vs30% p=0.13, 5%vs30% p=0.02, indicating a significant difference between the 5% and 30% MVC groups.

Conclusion: The RPP response to isometric exercise at 30% MVC, in healthy 41 year old participants, is less than would be expected during moderate intensity aerobic exercise at 60% maximum predicted heart rate. These data suggest that isometric exercise induces smaller myocardial oxygen consumption than aerobic exercise while delivering anti-hypertensive benefits.

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A Comparison of Motivation Factors for Male and Female Track and Field Athletes Competing at the World Masters Games

Ian Heazlewood¹, Joe Walsh¹, Mike Climstein², Kent Adams³, Trish Sevene³

¹Charles Darwin University, Darwin, NT, Australia; ²University of Sydney, Sydney, NSW, Australia; ³California State University, Monterey Bay, California, USA

Introduction: Previous research has identified some factors considered by master's athletes to be significant in motivating their participation and adherence to sport. While this research may be useful in guiding strategies to combat inactivity it is important to identify any differences in factors motivating individuals to participate in track and field in general to develop strategies to motivate athletes in step with their motivation needs to enable evidence based marketing strategies to be effective.

Aims: Identify gender differences related to factors motivating master's athletes to compete in the 2009 World Masters Games (WMG).

Methods: The sample was male (n= 326) and female (n=213) participants with age range 30-85 years who completed the Motivations of Marathoners Scales (MOMS) self-report instrument with 56 items and 7 point Likert responses (1= not a reason; 7= a most important reason) representing nine motivating factors of health orientation, weight concern, personal goal achievement, competition, recognition, affiliation, psychological coping, life meaning and self-esteem. Unpaired t-tests assessed difference for gender and stepwise discriminant analysis to assess classification accuracy based on gender.

Results: Important factors for both genders in order were goal achievement, health orientation, self-esteem, weight concern, competition and affiliation. Life meaning, psychological coping and recognition were not important. T-tests revealed competition (p=.021) and affiliation (p=0.18) were significantly different for gender. Discriminant analysis using affiliation then competition indicated 64% classification rate.

Conclusion: The most important constructs for both genders were goal achievement, health orientation, self-esteem, weight concern, and competition for males and affiliation for females. Marketing track and field to master's athletes should "sell" these constructs to meet their motivational needs and to promote exercise engagement and adherence.

ACRM 2016 Symposia Proposal: The efficacy and Safety of Isometric Resistance Training for Blood Pressure Management.

Introduction

Hypertension is a major risk factor for cardiovascular disease as well as ischemic and hemorrhagic stroke; with a higher incidence of stroke associated with increasing systolic or diastolic blood pressure (Aronow, 2013). In 2008 approximately 40% of adults aged 25 years and over worldwide, had been diagnosed with hypertension (WHO, 2013). Hypertension is responsible for 45% of cardiovascular deaths due to heart disease and 51% due to stroke worldwide (WHO, 2013).

The American Heart Association (AHA) 2015 guidelines recommend that blood pressure (BP) should be reduced to less than 130/80mmHg in patients with coronary artery disease, post-myocardial infarction, stroke or TIA (Rosendorff et al., 2015). Small decreases in resting blood pressure could significantly reduce long-term morbidity and mortality, and population decreases of 2mmHg in DBP could prevent 34,000 deaths from stroke in the United States per year (Lawrence et al. 2015).

Prompt well-organized, multidisciplinary, effective rehabilitation interventions post stroke are recommended to enhance the recovery process (Duncan et al. 2005). A key point in rehabilitation is prevention of stroke recurrence, coronary vascular events and coronary heart disease-mediated death (Duncan et al. 2005).

Meta-analyses have shown isometric resistance training to be an effective BP management tool, indicating that it may be a suitable alternative for people who are unable to conduct the recommended exercise by the AHA (Carlson et al., 2014, Millar et al., 2014). The following presentations describe this type of therapy and evidence for its use in treating hypertension.

Presentations:

1. What we know, do not know, and need to know about Isometric Resistance Training

Presenter: Philip Millar, Assistant Professor, University of Guelph, Ontario, Canada

Research over the last 24 years has consistently established that isometric resistance handgrip or leg training is capable of lowering resting blood pressure in healthy and clinical populations. These results suggest a novel role as an adjunct therapy for the management of high blood pressure. Importantly, isometric resistance training protocols have been conventionally completed at low-intensity, alleviating concerns over excessive pressor responses. The mechanisms responsible for the reductions in resting blood pressure remain to be fully clarified, with individual studies reporting improvements in conduit and resistance vessel endothelium-dependent dilation, oxidative stress, and autonomic regulation. Although the clinical potential for isometric resistance training remains high, future work is required to demonstrate efficacy in a large-scale clinical trial, determine the confounding impact of anti-hypertensive medication classes, and the capacity to influence measurements of ambulatory blood pressure.

2. The Efficacy of Blood Pressure Management with Isometric Resistance Training

Presenter: Debra Carlson, PhD Candidate, University of New England, Armidale, NSW, Australia

A pilot study we conducted showed a 12mmHg reduction in SBP, and a 5mmHg reduction in DBP in participants who conducted isometric resistance training using a handgrip dynamometer, at an intensity of 30% of their maximum voluntary contraction (MVC) (Carlson et al., 2015). Reductions in SBP of 5mmHg, and 6mmHg in DBP were also seen in participants who conducted the same training at 5% MVC. Further research indicated reductions in the 30% MVC group of 7mmHg SBP, from 136 ± 12 to 129 ± 15 , and 2mmHg DBP from 128 ± 15 to 126 ± 16 . These data confirm that isometric resistance training can be effective in blood pressure management.

3. Comparison of Cardiovascular Responses to Acute Aerobic and Isometric Resistance Exercise Presenter: Neil Smart, Associate Professor, University of New England, Armidale, NSW, Australia

Due to hypertensive responses during isometric resistance training (IRT) some health professionals are reluctant to recommend IRT. Consequently, moderate intensity aerobic exercise remains the preferred exercise modality for lowering blood pressure. Surrogate myocardial oxygen consumption using peak rate pressure product (RPP) during IRT was analysed in 32 healthy individuals, men (n=19) aged 41 ± 12 . Participants were randomised into three groups conducting IRT using a hand dynamometer at 5%, 10% and 30% maximum voluntary contraction (MVC). Mean peak RPP for each bout in the 5% group had an index which ranged from 8423-9055 $p=0.62$, 10% was 9026-9569 $p=0.85$, and 30% was 10429-11308 $p=0.81$. More recently, 40 hypertensive participants, men (n=15) aged 53 ± 10 , were randomised into two groups conducting IRT using a hand dynamometer at 5% and 30% MVC. Mean peak RPP for each bout in the 5% group ranged from 10341-10679 $p=0.90$, and 30% was 11274-13077 $p=0.20$. This data suggests that isometric exercise induces smaller myocardial oxygen consumption than aerobic exercise while delivering anti-hypertensive benefits.

4. Isometric Resistance Training as a feasible BP-lowering treatment prescribed in primary care: Can we predict the patients it will work for, will health care providers want to prescribe it, and if so, will patients comply?

Presenter: Cheri McGowan, Associate Professor, University of Windsor, Ontario, Canada

Accumulating evidence suggests that SBP reactivity to a simple isometric handgrip task (IHGT) predicts who will respond best to isometric resistance training (IRT), such that those with the greatest post-training reductions in resting SBP have the highest pre-training SBP reactivity to an IHGT. This has been observed in both normotensive (Millar et al., 2009; Somani et al. 2015), and hypertensive (Badrov et al., 2013) populations, and thus may be a useful tool for health care providers from both a primary and secondary prevention perspective. With poor rates of BP control worldwide, there is an imperative need to translate additional and effective BP-lowering therapies into primary care. Despite its potential as a BP-lowering intervention, alone or as an adjunct to traditional treatments, IRT is not widely recognized or prescribed for BP management. Better understanding this gap in translation, from both a provider and patient perspective, together with the clinical effectiveness and tolerability of IRT in general practice, is an essential next step.

Presentations will each take 10 mins, followed by 5 mins for questions. A panel discussion will be held in the last 15 mins after all presenters have finished.

American Congress of Rehabilitation Medicine (ACRM) 93rd Annual conference 2016

Below is the program listing the symposium which I organised and spoke at during the ACRM conference in 2016. The Initial proposal contained four presenters including myself. Dr Phillip Millar was unable to attend at the last moment, so we adjusted the final presentation which is why he is not listed in the brochure.

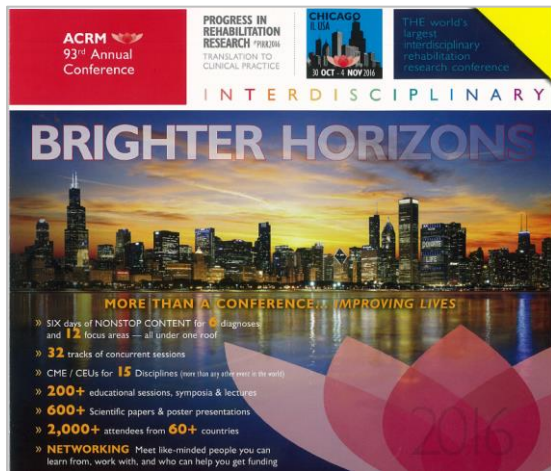


Figure 1: Front page of ACRM 2016 Program



Figure 2: Program page listing the Isometric Resistance Training symposium



Figure 3: Entire program page listing the Isometric Resistance Training symposium



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HYPERTENSION AND NEPHROLOGY

SESSION TITLE: NOVEL INSIGHTS INTO THE PATHOGENESIS OF HYPERTENSION

Abstract 17175: Isometric Handgrip Exercise Reduces 24hr Ambulatory Blood Pressure

Debra J Carlson, Gudrun Dieberg, James R McFarlane, Neil A Smart

Circulation. 2017;136:A17175

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Abstract

Introduction: Despite increased awareness, treatment and control of hypertension, it is still a major health concern with over 1 billion adults worldwide diagnosed with hypertension. The 2014 NHANES data indicates that only 50% of adults with hypertension meet the recommended aerobic exercise guidelines. Recent studies indicate that isometric exercise training (IET) has shown similar reductions in blood pressure to aerobic exercise studies. To date only 2 published IET studies, both of 8-week duration, have utilized ambulatory blood pressure (ABP) monitoring.

Hypothesis: We assessed the hypothesis that conducting isometric handgrip exercise for 12 weeks

would reduce 24hr ABP.

Methods: Twenty pre-mild hypertensive participants, men ($n=12$) and women ($n=8$) attended our laboratory 3 times a week for 12 weeks to conduct IET at either 5% or 30% of their maximum voluntary contraction (MVC). Prior to commencing the training, and upon completion of the 12 wk protocol, participants wore an ABP monitor for 24hrs. Blood pressure was recorded every 15mins during the day, and every 30mins whilst sleeping, the overall average was used for analysis.

Results: Isometric handgrip exercise at 30% MVC saw a significant reduction in SBP of -7mmHg from 154 ± 4.5 to 147 ± 3.3 (95% CI -14.3, 0.0; $p=0.05$) from baseline to post. No reductions in SBP were seen in the 5% MVC group with 148 ± 3.9 to 146 ± 1.9 (95% CI -9.1, 5.5; $p=0.59$) from baseline to post. Similar results were seen in DBP; with the 30% MVC group having a significant reduction of -5mmHg from 89 ± 2.8 to 84 ± 2.3 (95% CI -8.9, -1.1; $p=0.02$) from baseline to post. There was no reduction of DBP at 5% MVC which was 86 ± 1.8 to 84 ± 1.6 (95% CI -5.7, 2.5; $p=0.40$) from baseline to post.

Conclusions: In conclusion 12 weeks of IET saw significant reductions in 24hr ABP measurements of SBP and DBP in the 30% MVC group. There were no significant reductions of SBP and DBP in the 5% MVC group, confirming the suitability of its use as a working control.

Hypertension Exercise tests and training Blood pressure

Author Disclosures: **D.J. Carlson:** None. **G. Dieberg:** None. **J.R. McFarlane:** None. **N.A. Smart:** None.

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Article Tools

Appendix D: Research Documentation

The following appendices are the invitation to participate, information sheets, and consent forms provided to individuals who expressed interest in participating in my research program. The ESSA Adult pre-exercise screening tool was used to screen participants for inclusion eligibility. The form which I created to record each participants exercise and intensity is also included. This form is a generic one which was used for all participants irrespective of which group they were randomized into.



Associate Professor Neil Smart
School of Science and Technology
University of New England
Armidale NSW 2351
Phone: 02 6773 4076
Email: nsmart2@une.edu.au

Invitation to Participate in a Research Study

A feasibility study of isometric handgrip exercise for blood pressure management

This project has been approved by the Human Research Ethics Committee of the University of New England; approval no. HE14-209 valid to 30/11/2016.

I understand that you expressed an interest in participating in the above research study that is investigating the effects of performing isometric handgrip exercise for blood pressure management.

The study is being conducted by PhD student Ms Debra Carlson under the supervision of her University of New England supervisors Associate Professor Neil Smart, Dr Gudrun Dieberg and Associate Professor Jim McFarlane.

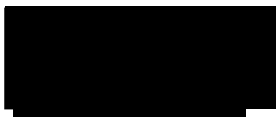
Participation in this study is voluntary and your health care will not be adversely affected in any way if you decide not to participate.

At this point, we would like you to read the enclosed *Information Sheet for Participants* to familiarise yourself with the research project and your involvement should you decide to participate.

Please bring the consent form with you when you attend your initial assessment interview.

We will be more than happy to answer any questions you might have.

Kind regards,



Associate Professor Neil Smart
Associate Professor Jim McFarlane
Dr Gudrun Dieberg
Debra Carlson

Please find enclosed the following documents:

- 1 – Information sheet for participants
- 2 – Consent form for participants

I wish to invite you to participate in my research project, described below.

My name is Debra Carlson and I am conducting this research as part of my PhD in the School of Science and Technology at the University of New England. My supervisors are Associate Professor Neil Smart, Dr Gudrun Dieberg and Associate Professor Jim McFarlane.

Research Project	A feasibility study of isometric handgrip exercise for blood pressure management.
Aim of the research	The research aims to explore if isometric handgrip exercise conducted 3 days per week is feasible for maintaining and/or reducing blood pressure. This is a randomised controlled study to determine at what level of maximum voluntary contraction (MVC) reductions in blood pressure occur.
Protocol	<p>Prior to starting the research study, we suggest that you see your doctor to help you decide whether this study is suitable for you.</p> <p>During your first screening visit we will explain this research study in detail, familiarise you with the equipment, and complete a pre-exercise screening questionnaire to ensure you are eligible to participate.</p> <p>Exercise Training Procedures:</p> <p>All participants will be randomly selected to exercise at either 5%, 10% or 30% of their MVC. As this is a controlled study you will not be told which group you are in; however, we can tell you afterwards if you wish to know. You will be asked to conduct isometric handgrip (IHG) exercise using a hand dynamometer three times per week; Monday, Wednesday and Friday, for twelve weeks.</p> <p>At each visit you will be required to perform initial testing with the hand dynamometer to assess your MVC. This will determine at what level you will exercise on that day. You will then rest for five minutes before commencing your IHG exercise. Participants will be asked to conduct 4 x IHG exercise, for 2 mins each time, with a three minute rest period between each IHG exercise. You will then rest for five minutes after completing the exercise program before you leave. The entire protocol should take no more than 30 minutes.</p>

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for
PARTICIPANTS

Once a week you will be connected to a finometer which will monitor your blood pressure whilst you are exercising. This is done by attaching a finger cuff on the hand which is not exercising, and works similar to an arm cuff used for taking your blood pressure.

During the exercise you will be seated in a comfortable chair in a quiet, temperature-controlled room. We request that prior to commencing your IHG exercise that you not eat for 4 hours, do not have caffeine for 12 hours, and not perform any vigorous exercise for 24 hours. You are still able to take any medications as per your normal routine.

There are minimal risks involved with performing isometric exercise, these are outlined as follows. Blood pressure will elevate whilst conducting the exercise but will drop to an acceptable level during the rest period. There will be minimal discomfort from the finger cuff, similar to having your blood pressure taken in your arm, which should dissipate within five minutes of cuff removal. There may be some slight discomfort from muscle tension in the forearm muscles conducting the exercise which should dissipate within an hour.

Confidentiality

Any information or personal details gathered in the course of the study will remain confidential. No individual will be identified by name in any publication of the results. All names will be replaced by pseudonyms; this will ensure that you are not identifiable.

Participation is Voluntary

Please understand that your involvement in this study is voluntary and I respect your right to withdraw from the study at any time. You may discontinue the study at any time without consequence and you do not need to provide any explanation if you decide not to participate or withdraw at any time.

Use of information

I will use information from the study as part of my doctoral thesis, which I expect to complete in April 2017. Information from the study may also be used in journal articles and conference presentations before and after this date. At all time, I will safeguard your identity by presenting the information in way that will not allow you to be identified.

Upsetting issues

It is unlikely that this research will raise any personal or upsetting issues but if it does you may wish to contact your local Community Health Centre on (02) 6776 9600 or Lifeline 13 1114

INFORMATION SHEET
for
PARTICIPANTS

Storage of information

I will keep hardcopy records and notes of the study in a locked cabinet at the researcher's office at the University of New England's School of Science and Technology. Any electronic data will be kept on a password protected computer in the same School. Electronic data will be backed up onto a USB which will be kept in a locked cabinet with the hardcopy records and notes. Only the research team will have access to the data.

Disposal of information

All the data collected in this research will be kept for a minimum of five years after successful submission of my thesis, after which it will be disposed of by deleting relevant computer files, and destroying or shredding hardcopy materials.

Approval

This project has been approved by the Human Research Ethics Committee of the University of New England (Approval No. HE14-209, Valid to 30/11/2016).

Contact details

Feel free to contact me with any questions about this research by email at dmaher7@myune.edu.au or by phone on 02 6773 1456.

You may also contact my supervisors. My Principal supervisors name is Associate Professor Neil Smart and he can be contacted at nsmart2@une.edu.au or 02 6773 4076 and my Co-supervisors names are Dr Gudrun Dieberg and she can be contacted at gdieberg@une.edu.au or 02 6773 2321, and Associate Professor Jim McFarlane and he can be contacted at jmcfarla@une.edu.au or 02 6773 3201.

Complaints

Should you have any complaints concerning the manner in which this research is conducted, please contact the Research Ethics Officer at:
Research Services
University of New England
Armidale, NSW 2351
Tel: (02) 6773 3449 Fax: (02) 6773 3543
Email: ethics@une.edu.au

Thank you for considering this request and I look forward to further contact with you.

Regards,



Ms Debra Carlson

**CONSENT FORM
for PARTICIPANTS**

Research Project: A feasibility study of isometric handgrip exercise for blood pressure management

I,, have read the information contained in the Information Sheet for Participants and any questions I have asked have been answered to my satisfaction. Yes/No

I agree to attend three times each week for the duration of my exercise program. Yes/No

I agree to complete two minutes of isometric exercise, four times, with a three minute rest period between each isometric exercise. I understand that the total time required for me to attend each visit will be 30 minutes. Yes/No

I agree to be connected to the finometer at one visit each week to monitor my blood pressure and cardiovascular measures whilst I am completing the exercise program. Yes/No

I agree that prior to blood pressure and cardiovascular measurements I will fast for four hours, will abstain from caffeine for 12 hours, and avoid vigorous exercise for 24 hours. Yes/No

I agree to participate in this activity, realising that I may withdraw at any time. Yes/No

I agree that research data gathered for the study may be published using a pseudonym Yes/No

I am older than 18 years of age. Yes/No

.....
Participant Date

.....
Researcher Date



Associate Professor Neil Smart
School of Science and Technology
University of New England
Armidale NSW 2351
Phone: 02 6773 4076
Email: nsmart2@une.edu.au

Invitation to Participate in a Research Study

Cardiovascular response to isometric resistance training in people with hypertension for blood pressure management

This project has been approved by the Human Research Ethics Committee of the University of New England; approval no. HE15-036 valid to 31/12/2016.

I understand that you expressed an interest in participating in the above research study that is investigating the effects of performing isometric handgrip exercise for blood pressure management.

The study is being conducted by PhD student Ms Debra Carlson under the supervision of her University of New England supervisors Associate Professor Neil Smart, Dr Gudrun Dieberg and Professor Jim McFarlane.

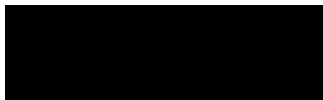
Participation in this study is voluntary and your health care will not be adversely affected in any way if you decide not to participate.

At this point, we would like you to read the enclosed *Information Sheet for Participants* to familiarise yourself with the research project and your involvement should you decide to participate.

Please bring the consent form with you when you attend your initial assessment interview.

We will be more than happy to answer any questions you might have.

Kind regards,



Associate Professor Neil Smart
Professor Jim McFarlane
Dr Gudrun Dieberg
Debra Carlson

Please find enclosed the following documents:

- 1 – Information sheet for participants
- 2 – Consent form for participants

I wish to invite you to participate in my research project, described below.

My name is Debra Carlson and I am conducting this research as part of my PhD in the School of Science and Technology at the University of New England. My supervisors are Associate Professor Neil Smart, Dr Gudrun Dieberg and Professor Jim McFarlane.

Research Project

Cardiovascular response to isometric resistance training in people with hypertension for blood pressure management.

Aim of the research

The research aims to explore the effect of isometric resistance training (IRT) conducted 3 days per week, on maintaining and/or reducing blood pressure and other cardiovascular measures. This is a randomised controlled study to explore the reductions in blood pressure which occur at varying levels of maximum voluntary contraction (MVC).

The primary aims are to:

- (i) assess the effect of isometric exercise on ambulatory blood pressure in participants aged 40-70 years who are either pre- or mild hypertensive; either un-medicated or taking medication to control their blood pressure.
- (ii) examine whether the size of blood pressure change is different in those people taking or not taking anti-hypertensive medication.
- (iii) determine the anti-hypertensive mechanism to IRT.
- (iv) establish the rate of de-training effects after participants have ceased IRT.

Protocol

Prior to starting the research study, we suggest that you see your doctor to help you decide whether this study is suitable for you.

During your first screening visit we will explain this research study in detail, familiarise you with the equipment, and complete a pre-exercise screening questionnaire to ensure you are eligible to participate.

Exercise Training Procedures:

All participants will be stratified into groups based on their medication status (unmedicated, Beta blocker, Angiotensin II receptor antagonist) then randomly selected to exercise at either 5% or 30% of their MVC. As this is a controlled study you will not be told which MVC

INFORMATION SHEET
for
PARTICIPANTS

group you are in; however, we can tell you afterwards if you wish to know. You will be asked to conduct isometric handgrip (IHG) exercise using a hand dynamometer three times per week, for up to twelve weeks.

At each visit you will be required to perform initial testing with the hand dynamometer to assess your MVC. This will determine at what level you will exercise on that day. You will then rest for five minutes before commencing your IHG exercise. Participants will be asked to conduct 4 x IHG exercise, for 2 mins each time, with a three minute rest period between each IHG exercise. You will then rest for five minutes after completing the exercise program before you leave. The entire protocol should take no more than 30 minutes. During the exercise you will be seated in a comfortable chair in a quiet, temperature-controlled room.

At baseline, end of IRT and end of detraining you will be asked to undergo a blood test which will be conducted by a fully trained phlebotomist, and provide a urine sample in a container which we will give you. Blood samples will be frozen and kept for further analysis when funding is available. You will also be asked to monitor your blood pressure for 24 hours. The researchers will provide you with a holter monitor which they will ask you leave on for 24 hours. The researchers will explain, demonstrate and connect the holter monitor to you and ask you to return in 24 hours to have it removed.

We request that prior to blood pressure measurements (not including the 24hr monitoring), blood and urine samples that you not have caffeine or eat for 4 hours, do not have alcohol for 12 hours, and not perform any vigorous exercise for 24 hours. You are still able to take any medications as per your normal routine.

At baseline, post IRT, and post detraining we will also assess your forearm blood flow. This will be done by placing a cuff on your forearm which will be inflated to 250mmHg for five minutes. For one minute prior to the cuff being inflated, and for two minutes after it is deflated an ultrasound Doppler will measure your forearm blood flow. After 10 minutes the artery will be measured manually via electronic callipers and assessed until it returns to baseline diameter.

There are minimal risks involved with performing isometric exercise, these are outlined as follows. Blood pressure will slightly elevate whilst conducting the exercise but will drop to baseline level within 30 seconds during the rest period. There may be some slight discomfort from muscle tension in the forearm muscles conducting the exercise which should dissipate within seconds.

There will be minimal discomfort from the blood test, the same as would be expected from any blood test. There may be some

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discomfort during the occlusion of the forearm when assessing vascular responsiveness which should dissipate immediately after the cuff is released.

Participants will be provided with their individual results upon request. Due to the various tests which will be conducted there is the slight possibility that during the study the researchers may become aware of medical conditions relating to your hypertension which may affect your health. This may prompt you to seek further medical advice, you may be required to report this to your health insurer which could affect your premiums.

The Department of Human Services provides Medicare and Pharmaceutical Benefits Scheme (PBS) data for participants enrolled in ethically approved health related studies. The use of Medicare and PBS, specifically their costs to the Australian Health Care System, are one of the outcomes which we are measuring in this study. We hope to try to show that our intervention has reduced Medicare and PBS costs (as an outcome measure) over the course of our study. In order to do this we will request your Medicare number so that we can access any data in your records relating to hypertension.

Confidentiality

Any information or personal details gathered in the course of the study will remain confidential. No individual will be identified by name in any publication of the results. All names will be replaced by pseudonyms; this will ensure that you are not identifiable.

Participation is Voluntary

Please understand that your involvement in this study is voluntary and I respect your right to withdraw from the study at any time. You may discontinue the study at any time without consequence and you do not need to provide any explanation if you decide not to participate or withdraw at any time.

Use of information

I will use information from the study as part of my doctoral thesis, which I expect to complete in April 2017. Information from the study may also be used in journal articles and conference presentations before and after this date. At all time, I will safeguard your identity by presenting the information in way that will not allow you to be identified.

Upsetting issues

It is unlikely that this research will raise any personal or upsetting issues but if it does you may wish to contact your local Community Health Centre on (02) 6776 9600 or Lifeline 13 1114.

Storage of information

I will keep hardcopy records and notes of the study in a locked cabinet at the researcher's office at the University of New England's



Associate Professor Neil Smart
School of Science and Technology
University of New England
Armidale NSW 2351
Australia
Phone 02 6773 4076
Fax 02 6773 3267
nsmart2@une.edu.au

INFORMATION SHEET
for
PARTICIPANTS

Disposal of information

School of Science and Technology. Any electronic data will be kept on a password protected computer in the same School. Electronic data will be backed up onto a USB which will be kept in a locked cabinet with the hardcopy records and notes. Only the research team will have access to the data.

All the data collected in this research will be kept for a minimum of five years after successful submission of my thesis, after which it will be disposed of by deleting relevant computer files, and destroying or shredding hardcopy materials.

Approval

This project has been approved by the Human Research Ethics Committee of the University of New England (Approval No. HE15-036 Valid to 31/12/2016).

Contact details

Feel free to contact me with any questions about this research by email at dmaher7@myune.edu.au or by phone on 02 6773 1456.

You may also contact my supervisors. My Principal supervisors name is Associate Professor Neil Smart and he can be contacted at nsmart2@une.edu.au or 02 6773 4076 and my Co-supervisors names are Dr Gudrun Dieberg and she can be contacted at gdieberg@une.edu.au or 02 6773 2321, and Professor Jim McFarlane and he can be contacted at jmcfarla@une.edu.au or 02 6773 3201.

Complaints

Should you have any complaints concerning the manner in which this research is conducted, please contact the Research Ethics Officer at:
Research Services

University of New England
Armidale, NSW 2351
Tel: (02) 6773 3449 Fax: (02) 6773 3543
Email: ethics@une.edu.au

Thank you for considering this request and I look forward to further contact with you.

Regards,



Ms Debra Carlson

**CONSENT FORM
for
PARTICIPANTS**

Research Project: Cardiovascular response to isometric resistance training in people with hypertension for blood pressure management

I,, have read the information contained in the Information Sheet for Participants and any questions I have asked have been answered to my satisfaction. Yes/No

I agree to attend three times each week for the duration of my exercise program. Yes/No

I agree to complete two minutes of isometric exercise, four times, with a three minute rest period between each isometric exercise. I understand that the total time required for me to attend each visit will be 30 minutes. Yes/No

I agree to attend once a week, for 12 weeks, after the exercise program has completed to have my blood pressure taken. Yes/No

I agree that prior to blood pressure and cardiovascular measurements I will fast and abstain from caffeine for four hours, will abstain from alcohol for 12 hours, and avoid vigorous exercise for 12 hours. Yes/No

I agree to undergo 24 hour ambulatory blood pressure measurements, blood tests, and provide a urine sample at baseline, 12 weeks and 24 weeks. Yes/No

I understand that blood samples will be frozen and kept for further analysis when funding is available. Yes/No

I agree to have an occlusion cuff placed on my forearm, my brachial blood flow monitored using an ultrasound Doppler, and brachial artery diameter measured at baseline, 12 weeks and 24 weeks. Yes/No

I agree to inform the researchers of any change to my exercise routine, nutritional intake and status, alcohol consumption, medications and adherence. Yes/No

I agree to participate in this activity, realising that I may withdraw at any time. Yes/No

I understand that if I request my results it is possible that a medical condition may be revealed which I would be required to report to my medical insurer. Yes/No

I agree to provide the researchers with my Medicare number to enable them to access my records so that they can assess the cost on the health care system of hypertension. Yes/No

I agree that research data gathered for the study may be published using a pseudonym Yes/No

I am older than 18 years of age. Yes/No

.....
Participant Date
.....

.....
Researcher Date
.....

ADULT PRE-EXERCISE SCREENING TOOL

This screening tool does not provide advice on a particular matter, nor does it substitute for advice from an appropriately qualified medical professional. No warranty of safety should result from its use. The screening system in no way guarantees against injury or death. No responsibility or liability whatsoever can be accepted by Exercise and Sports Science Australia, Fitness Australia or Sports Medicine Australia for any loss, damage or injury that may arise from any person acting on any statement or information contained in this tool.

Name: _____

Date of Birth: _____ Male Female Date: _____

STAGE 1 (COMPULSORY)

AIM: to identify those individuals with a known disease, or signs or symptoms of disease, who may be at a higher risk of an adverse event during physical activity/exercise. This stage is self administered and self evaluated.

Please circle response

1.	Has your doctor ever told you that you have a heart condition or have you ever suffered a stroke?	Yes	No
2.	Do you ever experience unexplained pains in your chest at rest or during physical activity/exercise?	Yes	No
3.	Do you ever feel faint or have spells of dizziness during physical activity/exercise that causes you to lose balance?	Yes	No
4.	Have you had an asthma attack requiring immediate medical attention at any time over the last 12 months?	Yes	No
5.	If you have diabetes (type I or type II) have you had trouble controlling your blood glucose in the last 3 months?	Yes	No
6.	Do you have any diagnosed muscle, bone or joint problems that you have been told could be made worse by participating in physical activity/exercise?	Yes	No
7.	Do you have any other medical condition(s) that may make it dangerous for you to participate in physical activity/exercise?	Yes	No

IF YOU ANSWERED 'YES' to any of the 7 questions, please seek guidance from your GP or appropriate allied health professional prior to undertaking physical activity/exercise

IF YOU ANSWERED 'NO' to all of the 7 questions, and you have no other concerns about your health, you may proceed to undertake light-moderate intensity physical activity/exercise

I believe that to the best of my knowledge, all of the information I have supplied within this tool is correct.

Signature _____

Date _____

EXERCISE INTENSITY GUIDELINES

INTENSITY CATEGORY	HEART RATE MEASURES	PERCEIVED EXERTION MEASURES	DESCRIPTIVE MEASURES
SEDENTARY	< 40% HRmax	Very, very light RPE# < 1	<ul style="list-style-type: none"> Activities that usually involve sitting or lying and that have little additional movement and a low energy requirement
LIGHT	40 to <55% HRmax	Very light to light RPE# 1-2	<ul style="list-style-type: none"> An aerobic activity that does not cause a noticeable change in breathing rate An intensity that can be sustained for at least 60 minutes
MODERATE	55 to <70% HRmax	Moderate to somewhat hard RPE# 3-4	<ul style="list-style-type: none"> An aerobic activity that is able to be conducted whilst maintaining a conversation uninterrupted An intensity that may last between 30 and 60 minutes
VIGOROUS	70 to <90% HRmax	Hard RPE# 5-6	<ul style="list-style-type: none"> An aerobic activity in which a conversation generally cannot be maintained uninterrupted An intensity that may last up to about 30 minutes
HIGH	≥ 90% HRmax	Very hard RPE# ≥ 7	<ul style="list-style-type: none"> An intensity that generally cannot be sustained for longer than about 10 minutes

= Borg's Rating of Perceived Exertion (RPE) scale, category scale 0-10

ADULT PRE-EXERCISE SCREENING TOOL

STAGE 2 (OPTIONAL)

Name: _____

Date of Birth: _____ Date: _____

AIM: To identify those individuals with risk factors or other conditions to assist with appropriate exercise prescription. This stage is to be administered by a qualified exercise professional.

RISK FACTORS

<p>1. Age _____</p> <p>Gender _____</p>	<p>≥ 45yrs Males or ≥ 55yrs Females +1 risk factor</p>																					
<p>2. Family history of heart disease (eg: stroke, heart attack)</p> <table border="0"> <thead> <tr> <th>Relative</th> <th>Age</th> <th>Relative</th> <th>Age</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/> Father</td> <td>_____</td> <td><input type="checkbox"/> Mother</td> <td>_____</td> </tr> <tr> <td><input type="checkbox"/> Brother</td> <td>_____</td> <td><input type="checkbox"/> Sister</td> <td>_____</td> </tr> <tr> <td><input type="checkbox"/> Son</td> <td>_____</td> <td><input type="checkbox"/> Daughter</td> <td>_____</td> </tr> </tbody> </table>	Relative	Age	Relative	Age	<input type="checkbox"/> Father	_____	<input type="checkbox"/> Mother	_____	<input type="checkbox"/> Brother	_____	<input type="checkbox"/> Sister	_____	<input type="checkbox"/> Son	_____	<input type="checkbox"/> Daughter	_____	<p>If male < 55yrs = +1 risk factor If female < 65yrs = +1 risk factor Maximum of 1 risk factor for this question</p>					
Relative	Age	Relative	Age																			
<input type="checkbox"/> Father	_____	<input type="checkbox"/> Mother	_____																			
<input type="checkbox"/> Brother	_____	<input type="checkbox"/> Sister	_____																			
<input type="checkbox"/> Son	_____	<input type="checkbox"/> Daughter	_____																			
<p>3. Do you smoke cigarettes on a daily or weekly basis or have you quit smoking in the last 6 months? Yes No</p> <p>If currently smoking, how many per day or week? _____</p>	<p>If yes, (smoke regularly or given up within the past 6 months) = +1 risk factor</p>																					
<p>4. Describe your current physical activity/exercise levels:</p> <table border="0"> <thead> <tr> <th></th> <th>Sedentary</th> <th>Light</th> <th>Moderate</th> <th>Vigorous</th> </tr> </thead> <tbody> <tr> <td></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>Frequency sessions per week</td> <td>_____</td> <td>_____</td> <td>_____</td> <td>_____</td> </tr> <tr> <td>Duration minutes per week</td> <td>_____</td> <td>_____</td> <td>_____</td> <td>_____</td> </tr> </tbody> </table>		Sedentary	Light	Moderate	Vigorous		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Frequency sessions per week	_____	_____	_____	_____	Duration minutes per week	_____	_____	_____	_____	<p>If physical activity level < 150 min/ week = +1 risk factor If physical activity level ≥ 150 min/ week = -1 risk factor (vigorous physical activity/ exercise weighted x 2)</p>	
	Sedentary	Light	Moderate	Vigorous																		
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																		
Frequency sessions per week	_____	_____	_____	_____																		
Duration minutes per week	_____	_____	_____	_____																		
<p>5. Please state your height (cm) _____</p> <p>weight (kg) _____</p>	<p>BMI = _____ BMI ≥ 30 kg/m² = +1 risk factor</p>																					
<p>6. Have you been told that you have high blood pressure? Yes No</p>	<p>If yes, = +1 risk factor</p>																					
<p>7. Have you been told that you have high cholesterol? Yes No</p>	<p>If yes, = +1 risk factor</p>																					
<p>8. Have you been told that you have high blood sugar? Yes No</p>	<p>If yes, = +1 risk factor</p>																					

Note: Refer over page for risk stratification.

STAGE 2 Total Risk Factors =

9. Have you spent time in hospital (including day admission) for any medical condition/illness/injury during the last 12 months?
Yes No

If yes, provide details

10. Are you currently taking a prescribed medication(s) for any medical condition(s)? Yes No

If yes, what is the medical condition(s)?

11. Are you pregnant or have you given birth within the last 12 months? Yes No

If yes, provide details. I am _____ months pregnant or postnatal (circle).

12. Do you have any muscle, bone or joint pain or soreness that is made worse by particular types of activity? Yes No

If yes, provide details

STAGE 3 (OPTIONAL)

AIM: To obtain pre-exercise baseline measurements of other recognised cardiovascular and metabolic risk factors. This stage is to be administered by a qualified exercise professional. (Measures 1, 2 & 3 – minimum qualification, Certificate III in Fitness; Measures 4 and 5 minimum level, Exercise Physiologist*).

	RESULTS	RISK FACTORS
1. BMI (kg/m ²)		BMI ≥ 30 kg/m ² = +1 risk factor
2. Waist girth (cm)		Waist > 94 cm for men and > 80 cm for women = +1 risk factor
3. Resting BP (mmHg)		SBP ≥ 140 mmHg or DBP ≥ 90 mmHg = +1 risk factor
4. Fasting lipid profile*		Total cholesterol ≥ 5.20 mmol/L = +1 risk factor HDL cholesterol > 1.55 mmol/L = -1 risk factor HDL cholesterol < 1.00 mmol/L = +1 risk factor Triglycerides ≥ 1.70 mmol/L = +1 risk factor LDL cholesterol ≥ 3.40 mmol/L = +1 risk factor
5. Fasting blood glucose*		Fasting glucose ≥ 5.50 mmol = +1 risk factor
		STAGE 3 Total Risk Factors = <input type="text"/>

RISK STRATIFICATION

Total stage 2
or
Total stage 3
Plus stage 2 (Q1 - Q4)



≥ 2 RISK FACTORS – MODERATE RISK CLIENTS

Individuals at moderate risk may participate in aerobic physical activity/exercise at a light or moderate intensity (Refer to the exercise intensity table on page 2)

< 2 RISK FACTORS – LOW RISK CLIENTS

Individuals at low risk may participate in aerobic physical activity/exercise up to a vigorous or high intensity (Refer to the exercise intensity table on page 2)

Note: If stage 3 is completed, identified risk factors from stage 2 (Q1-4) and stage 3 should be combined to indicate risk. If there are extreme or multiple risk factors, the exercise professional should use professional judgement to decide whether further medical advice is required.

IHG Exercise Record

Participant No: _____

Week	Date	MVC	5% MVC	10% MVC	30% MVC	Comments
1						
1						
1						
2						
2						
2						
3						
3						
3						
4						
4						
4						

IHG Exercise Record

Participant No: _____

Week	Date	MVC	5% MVC	10% MVC	30% MVC	Comments
5						
5						
5						
6						
6						
6						
7						
7						
7						
8						
8						
8						

IHG Exercise Record

Participant No: _____

Week	Date	MVC	5% MVC	10% MVC	30% MVC	Comments
9						
9						
9						
10						
10						
10						
11						
11						
11						
12						
12						
12						
12						