Age and Ageing 2020; **49:** 168–170
doi: 10.1093/ageing/afz155

EDITORIALS

Heterogeneity in the reporting of blood pressure variability: high time for methodological consensus

Keywords: cerebrovascular disease, hypertension, blood pressure variability, stroke, cardiovascular disease, statistics, older people

Key Points

- Intra-individual blood pressure variability (BPV) signifies compromised vascular autoregulatory processes.
- A systematic review of 63 BPV studies, with data from 550,437 individuals, found substantial heterogeneity in the reporting of BPV in relation to cardiovascular and mortality outcomes.
- Significant heterogeneity in the reporting of BPV poses as a substantial barrier to quantifying the extent to which BPV contributes unique prognostic utility over and above mean blood pressure.
- Concerted efforts should be made to standardise BPV reporting, alongside mean blood pressure, to better understand the pathophysiological mechanisms underlying high BPV and target organ damage.

A degree of diurnal and postural variation in arterial blood pressure is part of normal circadian and homeostatic processes regulated by the heart and brain. A rich body of work demonstrates that arterial blood pressure oscillates within individuals, over repeated observations, and time; from beat-to-beat intervals to minutes, hours, weeks and even years [1]. One line of investigation indicates that higher and sustained intra-individual blood pressure variability (BPV) signifies compromised vascular autoregulatory processes [1, 2]. In their seminal papers, Rothwell and colleagues [3, 4] demonstrated that higher BPV was associated with an increased risk of stroke in blood pressure-lowering randomised controlled trials, independently of the level of mean blood pressure. This pivotal work, highlighted the significance of BPV to stroke, extended earlier research [5], and the potential prognostic utility has since been applied to other areas of medicine and epidemiology [6–8]. In this issue, Sillito and Myint [9] systematically reviewed literature on BPV in relation to cardiovascular and mortality outcomes, retaining 63 studies with data from 550,437 individuals.

Unlike prior reviews [10, 11], the authors restricted the scope of their review [9] to BPV calculated over 24-h to several days, thereby excluding beat-to-beat BPV and long-term visit-to-visit BPV. One valid reason for restricting the review to these timeframes is that BPV quantified over 24-h likely represents pathophysiological mechanisms related to central cardiovascular regulatory instability, with less influence of antihypertensive medication adherence [1]. Most studies in Sillito and Myint's [9] systematic review (42/63 studies) reported a composite cardiovascular endpoint, 26 examined cardiovascular mortality, and 25 investigated all-cause mortality. One drawback of the predominant focus on cardiovascular and mortality endpoints is that the utility of BPV metrics is partly determined by the association with disease outcomes, potentially leading to publication bias. Heterogeneity was cited as prohibiting an aggregate meta-analysis with the authors noting '*the evidence surrounding BPV is challenging to interpret due to variation in assessment based on population, measurement assessment and setting*.' Substantial methodological heterogeneity, even within the reporting of 24-h ambulatory blood pressure monitoring, remains an obstacle to understanding the causes and the clinical importance of BPV [11–16].

For BPV to offer incremental clinical utility, BPV must predict adverse outcomes over and above mean blood pressure [17], and relatedly, BPV metrics should be calculated independent from mean blood pressure. Yet two of the most common BPV metrics reported by Sillito and Myint [9] incorporate mean blood pressure in its calculation (e.g. the coefficient of variation and standard deviation methods). High multicollinearity between BPV and mean blood pressure is problematic for any endpoint modelling, which may spuriously under- or overestimate the risk of disease. Thus, BPV metrics with variance independent from mean blood pressure (e.g. variance in residuals and variance independent of the mean) seem better candidates. However, these measures seem best suited to longer-term or visit-to-visit variability [17] with less consensus on how to model BPV independent from mean blood pressure over 24-h [16].

This is especially important, as 24-h ambulatory monitoring captures hypertension phenotypes such as non-dipping, morning surge, masked hypertension and white-coat hypertension.

To address these unanswered questions on BPV, we set up the VARIAbility in BLood pressurE and BRAIN health consortium (VARIABLE BRAIN) to study the relationship between different BPV metrics with mean blood pressure on cardiovascular and cerebrovascular diseases as well as dementia [18, 19]. One of our aims is to analyse and compare different BPV metrics, taking into consideration the amount of shared variance with mean blood pressure. A second key focus is identifying common comorbidities associated with BPV, with the caveat that epidemiological studies seem limited in scope to clarify whether BPV is a cause or consequence of cardiovascular disease and related comorbidities [17]. Nonetheless, we aim to jointly model the effects of BPV and mean blood pressure with pertinent outcomes such as mortality, cardiovascular disease, stroke and cognitive decline.

As Sillito and Myint [9] asked, what is the 'best method' for assessing BPV? Although we cannot definitively answer what is the 'best method', ideally, BPV should be calculated in a manner that results in low shared variance with mean blood pressure. BPV should be reported alongside mean blood pressure to quantify the amount of shared variance, and then modelled concomitantly to determine additive prognostic utility. In future systematic reviews, it will be imperative to extract effect size data concerning mean blood pressure alongside BPV to determine the incremental benefits of the latter.

Phillip J. Tully[1], Christophe Tzourio[2]

[1]School of Medicine, The University of Adelaide, Adelaide, SA, Australia
[2]Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, UMR 1219, F-33000 Bordeaux, France

Address correspondence to: Dr. Phillip J. Tully, Centre for Men's Health, School of Medicine, Level 6 AHMS Building; The University of Adelaide, Adelaide SA 5005, Australia. Tel: +61 8 8313 0514; Fax: +61 8 8313 0355; Email: phillip.tully@adelaide.edu.au

Declaration of Conflicts of Interest: None.

Declaration of Sources of Funding: None.

References

1. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. Nat Rev Cardiol 2013; 10: 143–55.
2. Diaz KM, Veerabhadrappa P, Kashem M *et al.* Relationship of visit-to-visit and ambulatory blood pressure variability to vascular function. Hypertens Res 2012; 35: 55–61.
3. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. Lancet 2010; 375: 938–48.
4. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke. Lancet 2010; 375: 906–15.
5. Meredith PA, Perloff D, Mancia G, Pickering T. Blood pressure variability and its implications for antihypertensive therapy. Blood Press 1995; 4: 5–11.
6. Ohkuma T, Woodward M, Jun M *et al.* Prognostic value of variability in systolic blood pressure related to vascular events and premature death in type 2 diabetes mellitus: the ADVANCE-ON Study. Hypertension 2017; 70: 461–8.
7. Alperovitch A, Blachier M, Soumare A *et al.* Blood pressure variability and risk of dementia in an elderly cohort, the Three-City Study. Alzheimers Dement 2014; 10: S330–7.
8. Lasserson DS, Scherpbier De Haan N, Wetzels JFM *et al.* Stroke risk markers of blood pressure variability: associations with chronic kidney disease (CKD) and identification in primary care. Cerebrovasc Dis 2013; 35: 119–20.
9. Sillito J, Myint PK. Association between blood pressure variability and incident cardiovascular disease, cardiovascular mortality and all cause mortality in long-term follow up studies: a systematic review. Age Ageing 2019; TBC.
10. Stevens SL, Wood S, Koshiaris C *et al.* Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. BMJ 2016; 354: i4098.
11. Tai C, Sun Y, Dai N *et al.* Prognostic significance of visit-to-visit systolic blood pressure variability: a meta-analysis of 77,299 patients. J Clin Hypertens (Greenwich) 2015; 17: 107–15.
12. Asayama K, Wei FF, Liu YP *et al.* Does blood pressure variability contribute to risk stratification? Methodological issues and a review of outcome studies based on home blood pressure. Hypertens Res 2015; 38: 97–101.
13. Krakoff LR. Fluctuation: does blood pressure variability matter? Circulation 2012; 126: 525–7.
14. Asayama K, Wei F-F, Hara A, Hansen TW, Li Y, Staessen JA. Prognosis in relation to blood pressure variability: Con side of the argument. Hypertension 2015; 65: 1170. doi: 10.1161/HYPERTENSIONAHA.115.04808.
15. Dolan E, It Daily O'BEI. Monthly, or yearly blood pressure variability that enhances cardiovascular risk? Curr Cardiol Rep 2015; 17: 93.
16. Taylor KS, Heneghan CJ, Stevens RJ, Adams EC, Nunan D, Ward A. Heterogeneity of prognostic studies of 24-hour blood pressure variability: systematic review and meta-analysis. PLoS One 2015; 10: e0126375.
17. Stergiou GS, Parati G, Vlachopoulos C *et al.* Methodology and technology for peripheral and central blood pressure and blood pressure variability measurement: current status and future directions - position statement of the European Society of Hypertension Working Group on blood pressure monitoring and cardiovascular variability. J Hypertens 2016; 34: 1665–77.

18. The VARIABLE BRAIN consortium. The association between blood pressure variability with dementia and cognitive function: a systematic review protocol. Syst Rev 2018; 7: 163.

19. de Heus RAA, Olde Rikkert MG, Tully PJ, Lawlor B, Claassen JAHR, Nilvad Study Group. Blood pressure variability and progression of clinical Alzheimer's disease. Hypertension 2019; 74: 1172–80.