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Ambulatory blood pressure variability: a conceptual review

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Ambulatory blood pressure (ABP) has long been recognized by researchers as the gold standard of blood pressure (BP) measurement. Researchers and clinicians typically rely on the mean measure of ABP; however, there is considerable variability in the beat-to-beat BP. Although often ignored, this variability has been found to be an independent predictor of cardiovascular disease and mortality. The aim of this paper is to provide a conceptual review of ABP variability (ABPV) focusing on the following: associations between ABPV and health, whether ABPV is reliable, how to calculate ABPV, predictors of ABPV, and treatments for ABPV. Two future directions are discussed involving better understanding ABPV by momentary assessments and improving knowledge of the underlying physiology that explains ABPV. The results of this review suggest that the unique characteristics of ABPV provide insight into the role of BP variability in hypertension and subsequent

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Introduction

Ambulatory blood pressure (ABP) has long been recognized as a superior predictor of cardiovascular disease and mortality, independent of clinic measurements [1–3]. Largely, researchers and clinicians have focused on the ABP mean – the average of all ABP measurements over a given time period. This paper reviews the risk factor status for a heretofore understudied dimension of ABP – variability, a measurement of the oscillation of ABP measurements taken over a specified period of time (often calculated as the SD or average real variability; see [4,5]). We will review the current status of this putative risk factor for cardiovascular disease with a focus on the following five areas: associations between ABP variability (ABPV) and indicators of health and well-being; whether ABPV is reliable; how to calculate ABPV; predictors of ABPV; and how to reduce and/or treat ABPV. Future directions are then discussed, citing the need to better understand ABPV by momentary assessments and to better understand the underlying physiology that explains ABPV and in turn how ABPV relates to cardiovascular disease and mortality.

Advantages of ambulatory blood pressure as a measure of pathology

The advent of ABP monitoring provided the means for researchers and clinicians to measure patients' blood pressure (BP) at multiple points during his or her self-selected activities (including sleep). Most of this work has been carried out in three areas: first, finding that ABP is more reliable and/or valid than clinic measures or

measurements taken with a home monitor [6]; and that it is more predictive of essential hypertension, coronary heart disease, stroke, and cardiovascular and all-cause mortality [7,8]; second, ABP has been used to study measurement issues, particularly that measurements taken in the physician's office may not be representative of the diurnal pattern of BP measured across awake and sleep periods. Thus, clinic BP may be higher than the patient's 'true' BP when taken by a physician (i.e. white coat hypertension [9,10]) or may be lower (i.e. masked hypertension [11]). Third, ABP provides the only means currently available for the measurement of nocturnal BP dipping. A failure for BP to decrease in purportedly healthy samples ($\geq 10\%$ mmHg is considered the criterion [12]) has been shown to be an independent predictor of cardiovascular and all-cause mortality, over and above the clinic mean BP, compared with daytime BP levels [7].

Almost all of this work has focused on the mean ABP levels. This seeming over-reliance on ABP mean is perplexing, given that the observation that BP varies from one moment to the next has been researched for nearly as long as ABP monitoring has been performed [13–15]. Moreover, for at least the past two decades, researchers have suggested an independent role of ABPV as a predictor of cardiovascular illness and all-cause mortality [16, 17]. Below, the current knowledge of the manner in which ABPV relates to cardiovascular disease is reviewed, along with whether ABPV is stable over time, how to calculate ABPV, what are the known psychosocial, demographic, biomedical, and other predictors of ABPV,

and, to the extent that ABPV is indeed an independent risk factor, how it can be reduced. Discussion is focused mostly on what is described as short-term BP variability – hour-to-hour variability in BP over a 24-h period, for example – as this aspect has been researched more consistently using ABP monitoring and similar devices (for a larger discussion of other types of BP variability, see [18]). We also note evidence that comes from visit-to-visit variability (V_{VV}), which is the change in variability across measurements taken in the physician's office. Evidence from V_{VV} is informative for understanding long-term patterns in variability, albeit V_{VV} is less likely to reflect the impact of one's environmental factors and responses to situations that can be captured with ABPV.

Current knowledge of ambulatory blood pressure variability

Ambulatory blood pressure variability as a risk factor for cardiovascular disease

The value of identifying a new index from ABP data lies largely in its ability to (better) predict health and well-being. As such, most research on ABPV has examined its associations with cardiovascular health, finding that ABPV is associated with hypertension [19–21], carotid artery damage [22,23], progression of small vessel disease [24], left ventricular hypertrophy [25,26], cardiovascular events [27,28], and cardiovascular and all-cause mortality [29]. In addition, increased ABPV has been associated with cognitive dysfunction and quality of life among the elderly [30]. Similarly, V_{VV} is also associated with hypertension [19,31], small vessel disease [32], cardiovascular events [33], dementia [34], cognitive decline in Alzheimer's patients [35], and mortality [36]. For an extensive review of associations of ABPV with disease, see [18].

Despite this wealth of evidence, there are notable gaps in understanding these associations. For instance, it is not clear whether ABPV offers unique information over and above the ABP mean [17], despite some initial evidence suggesting relative independence [24,27]. Moreover, comparisons between systolic and diastolic ABP, and especially between daytime and night-time ABP, are lacking. Given that daytime and night-time ABP mean may offer unique information in predicting cardiovascular disease and mortality [7,37], it is plausible that such associations may also exist for ABPV. Indeed, some evidence suggests that daytime ABPV is independent from night-time ABP mean levels [38], and yet, more work is needed to further elucidate these relationships.

Is ambulatory blood pressure variability reliable?

Another question concerns the extent to which ABPV can be measured reliably. Test–retest correlations of ABP mean levels are stable, with correlations around 0.90 [39]. In contrast, less is known about whether ABPV is reliable over time. Some initial work in the area suggested

relatively low levels of reliability in the short term ($r_s = 0.16–0.36$ [39]). Given that ABPV can be influenced by contextual factors, a follow-up study had participants perform a series of similar activities (e.g. eating lunch, walking outdoors) across 2 days 1 week apart. Test–retest correlations of around 0.50 were found, and yet, the measurement of ABPV was limited to a few hours [40]. In longer-term tests, ABPV decreased over a 5-year period in one study [41], but increased over a 10-year period in another [42]. Across these two studies, ABPV at baseline accounted for a moderate amount of variability at follow-up, again suggesting some levels of reliability (e.g. 30% [41]). Thus, there appears to be some evidence showing that ABPV is stable over time. Yet, this evidence is limited in some respects. In the short term, evidence appears to be limited to a highly controlled study with measurements taken over a short period of time. It is unclear whether the test–retest correlations of ABP variabilities would be present when individuals engaged in a more diverse range of activities, in other words, testing whether ABPV is almost exclusively influenced by contextual factors or also has some more stable tendencies within an individual. In the long term, although baseline ABPV predicted a moderate level of the variance in ABPV 5 and 10 years later, these overall levels of ABPV changed over time. It is unclear what factors predicted this change; it has been speculated that age, for example, can explain in part differing patterns of change [42].

How to calculate ambulatory blood pressure variability?

BP changes with every heartbeat, and is thus potentially highly variable even over short periods of time. Yet, not all measures of variability may be the same. Traditionally, ABPV has been calculated as the SD of all BP observations over the measurement period. This measure, however, only looks at one's BP levels in relation to the ABP mean and does not consider the order in which the measurements were obtained. Ignoring this order can result in individuals with very different patterns of BP changes over time having the same variability in terms of SD [4]. For example, an individual who had elevated BP for the first five measurements of the day and normotensive levels for the next five would have the same SD as an individual who vacillated between high and normal levels across successive measurements. Thus, a measure called the average real variability has been proposed that looks at the absolute differences of consecutive measurements to capture true variability from measurement to measurement [4]. Average real variability has been shown to be a superior predictor to other measures of ABPV in predicting cardiovascular events [4], morbidity [5], and organ damage [43]. Future work should continue to compare these different measures of variability with an eye to adopting the average real variability as the standard measure of variability.

Predictors of ambulatory blood pressure variability

It is important to consider what common and potentially malleable factors relate to ABPV. This has been a common approach when studying ABP mean levels. For example, work has suggested that higher levels of depression [44], trait anger [45], trait anxiety [46], and trait pessimism [46] predict higher mean levels of ABP. In contrast, higher social support are associated with lower ABP compared with less socially connected individuals [47]. Other work has suggested the importance of momentary factors impacting individual-level variables. For instance, individuals with higher trait hostility tend to experience higher mean ABP while under stress [48], rumination is associated with increases in mean ABP compared with nonruminative periods [49], and higher pain experiences are related to higher ABP means [50]. Behavioral factors have also been found to predict mean ABP, including dietary changes [51] and increased aerobic exercise [52]. Finally, studies have identified important demographics, such as age [53] and race/ethnicity [54], as predicting higher ABP mean levels.

In contrast to ABP mean, less work has examined demographic and other psychosocial predictors of ABPV. One study found that anger, hostility, and depression were related to ABPV [55]. Other work has shown that ABPV is higher in older individuals [37,56,57]. Finally, it has been found that posture and physical activity are predictors of ABPV [58], as well as weather and environmental changes [59]. Thus, although this work is suggestive of potential relationships between psychosocial and contextual factors and ABPV, a more systematic understanding of the psychosocial and environmental predictors of ABPV is largely lacking.

Although less work has been carried out in the psychosocial domain, there is a fast-growing literature exploring associations between ABPV and a number of known medical conditions. For example, patients with autonomic neuropathy in cases of diabetes [60,61] and Parkinson's disease [62] often experience increased ABPV. Recent work has found that in patients with hypertension, long-term VVV may serve as a determinate of renal function decline [63]. Similarly, increased chronic BP variability in kidney transplant patients is often associated with poor outcomes, and patients with chronic kidney disease do in some cases show a small increase in VVV, a relationship that may provide further insight into the connection between renal function and cardiovascular concerns [64]. In other work, ABPV was indeed higher in those with kidney disease, but with an effect that became nonstatistically significant when controlling for mean ABP [65]. Overall, given these associations, work has begun to consider BP variability (both ABPV and VVV) as a prognostic tool (see [66] for a review). In sum, there is promise in using ABP to uncover new relationships between variability and chronic diseases; some important next steps include exploring whether

daytime versus night-time ABPV, along with nocturnal dipping, produce similar or differential associations.

Potential interventions to reduce ambulatory blood pressure variability

A final question concerns whether ABPV can be reduced and/or treated. Animal models, for example [67], have shown that it is possible to reduce ABPV and that these reductions resulted in lower levels of end-organ disease (see [18] for an extensive review). In light of this evidence and the importance of ABPV in predicting cardiovascular disease and mortality, it has been speculated that physicians should also attempt to treat ABPV when it is detected [68]. From a pharmacological perspective, there is evidence that some BP-lowering medications, including β -blockers, calcium-channel blockers, and diuretics, have effects not only on the mean BP but on ABPV and VVV as well [18,21,69,70]. Promising retrospective analyses have suggested that reduction of VVV by pharmacological means was associated with fewer cardiovascular events in hypertensive patients [71]. Although the effectiveness of drugs to treat both ABP mean and variability has shown some promise, evidence is still premature to recommend for clinical practice. Most notably, a systematic review and meta-analyses of 389 trials testing the effect of antihypertensive drugs on BPV suggested differential effects of medications [72]. Of the treatments tested, calcium-channel blockers appeared to have the greatest effect in reducing variability, whereas angiotensin receptor blockers and β -blockers showed an opposite pattern. More work is needed to better understand when and how pharmacological interventions should be used. For instance, in a trial treating 2780 hypertensive patients, calcium-channel blocks and diuretics proved to be an especially potent combination for lowering short-term variability [73], suggesting the potential for combinations as having additive effects. Yet, it is still unclear whether it is necessary and beneficial to focus on the treatment of both ABP mean and variability, and if that is not possible, whether mean or variability should primarily be targeted [74]. Moreover, long-term studies testing the potential for sustained salubrious effects on short-term and long-term variability are needed.

Evidence for the potential of nonpharmacological interventions to lower ABPV, in contrast, is lacking. There have been various calls for behavioral interventions aimed at improving ABP levels [75,76]. These calls are bolstered by evidence indicating that some nonpharmacological interventions – including transcendental meditation and controlled breathing – have shown effectiveness in reducing BP mean [77,78]. Similarly, behavioral interventions, including exercise therapy, have been recommended for regimens to control mean BP [79]. Critically, these behavioral interventions appear to have additive effects to pharmacological treatment

[80]. Yet, it is unclear whether the improvements in ABP mean because of exercise and meditation would also generalize to reductions in ABPV.

Finally, ABPV has shown to be elevated in the presence of chronic disease, including diabetes and Parkinson's disease [60–66]. Yet, it is unclear whether this elevated variability is a contributor to the development and progression of the disease, a byproduct of the disease, or wholly epiphenomenal to it. Uncovering these relationships opens up new potential for diagnosis and treatment. For example, if high levels of ABPV prove to be a predictor of chronic disease, detection of high ABPV may allow physicians an additional avenue for treatment to prevent disease onset and progression. In turn, if ABPV is a symptom of a disease, it may potentially be one that manifests earlier than other symptoms, allowing for early detection and treatment of the underlying disease. Alternatively, if ABPV is a byproduct of a disease, physicians may wish to focus their efforts on treating the disease itself rather than expending resources on ABPV.

Future directions

Given the dearth of research on ABPV compared with ABP mean, countless next steps exist. In fact, several directions are alluded to in the above paragraphs. Beyond these areas, two critical future directions are identified. First, beyond looking at associations between trait variables (e.g. anxiety, job strain) and ABP, work is increasingly becoming common to examine how in-the-moment contextual variables and momentary perceptions relate to ABP levels. Notably, greater levels of socially evaluative threats [81], anxiety [82], rumination [49], negative social interactions [48,83], negatively valenced and high arousal affect [83,84], and task demand [83] have all been shown to relate to higher levels of momentary ABP levels. Although these in-the-moment contextual variables have not been linked to greater levels of ABPV, they likely will offer great insights as to why one may have higher ABPV from one day to another. In other words, studying momentary factors represents a departure from focusing on trait measures, and yet, may offer more promise in understanding the sources of ABPV. Indeed it is these properties of ABP – that is, the ability to capture the impact of stressors and other environmental factors that occur in daily life – which have been argued for why ABP is a superior predictor than clinic BP readings [9,10].

Second, more work is needed to better understand the underlying biology to what causes ABP levels to vary, and in turn, why higher levels of variability are predictive of cardiovascular disease and mortality. One possible factor may be the positive associations between increasing systolic ABPV and C-reactive protein (a key marker of inflammation) in healthy adults [85]. Interestingly, both decreased vagal function and increased heart rate variability have also been found to be strongly related to these inflammation markers [86], speaking potentially to the

role of inflammation in cardiovascular disease. Animal models have shown that large BP variability can result in chronic cardiac inflammation, leading to cardiac organ damage, potentially offering a pathway [87]. This inflammation in humans may mediate the relationship between cardiac organ damage and cardiovascular disease. Another factor to consider is the role of hormones, especially those regulated by the HPA axis and adrenal glands [88], and estrogen [89] as these hormones have been found to be related to BP variability.

Conclusion

ABPV offers great promise in better understanding the development and prognosis of cardiovascular disease. It has been identified as an independent risk factor compared with ABP mean levels and ABP in general is seen as a superior predictor of cardiovascular disease and mortality than clinic BP measurements. Critically, the factors that govern changes in ABPV may be different from those affecting ABP mean as ABPV has been found to change over time even when ABP mean levels remain stable [42]. These results show promise for better prevention and treatment of cardiovascular disease. However, these results also are cause for concern as physicians are likely not screening for ABPV as most physicians rely on clinic measurements rather than ambulatory monitoring. Thus, there is a need to expand the use of ABP monitoring at both the research and the clinical levels to better understand ABPV. This greater focus may point to innovative ways for the treatment of hypertension and the reduction of cardiovascular disease.

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Conflicts of interest

There are no conflicts of interest.

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