Current Hypertension Reports (2019) 21: 19
https://doi.org/10.1007/s11906-019-0919-x

BLOOD PRESSURE MONITORING AND MANAGEMENT (JOHN COCKCROFT, SECTION EDITOR)

Incorporation of Novel Vascular Measures into Clinical Management: Recent Insights from the Framingham Heart Study

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Published online: 21 February 2019

Abstract

Purpose of Review The review discusses evidence from the Framingham Heart Study that supports the assessment and utility of novel vascular and blood pressure measures to inform clinical management of blood pressure–related cardiovascular disease.

Recent Findings Recent Framingham Heart Study investigations provide new insights into the associations of novel and traditional vascular and blood pressure measures, such as measures of aortic stiffness, components of blood pressure waves, and orthostatic change in blood pressure, with cardiovascular disease events and brain structure and function. Novel vascular measures provide opportunities for additional investigation and potential development of new interventions that are more precisely targeted at underlying pathophysiology.

Summary Inclusion of novel vascular measures should be considered in clinical practice to screen for early, subclinical disease and to stratify high-risk individuals for targeted therapies.

Keywords Blood pressure · Aortic stiffness · Vascular hemodynamics · Orthostatic hypotension · Cardiovascular disease · Cognition

Introduction

Blood pressure (BP) is a well-known modifiable risk factor for cardiovascular disease (CVD). Many years passed before the first studies implicating the role of elevated BP on CVD risk became widely accepted and implemented into clinical practice [1]. By the mid-twentieth century, CVD accounted for about half of all deaths and was the primary cause of mortality in the USA [2]. At the time, prevention of CVD was inconceivable and CVD-related premature deaths were inevitable since clinical management was poorly understood. Exemplifying the case management of the period, physicians for US President Franklin D. Roosevelt largely ignored his progressive hypertension for years until shortly before his premature death from heart disease and cerebral hemorrhage [3, 4]. Three years later, the US Congress passed the National Heart Act, which established the National Heart Institute (now the National Heart, Lung, and Blood Institute) and contributed to the founding of the Framingham Heart Study (FHS) [1].

The FHS was the first long-term observational study established to elucidate the pathophysiology of CVD and provide clues to potential effective interventions. The original cohort was recruited from 1948 to 1952 and consisted of 5209 residents of Framingham, Massachusetts [5]. Since then, FHS has added an Offspring Cohort (1971), the First-generation Omni Cohort (1994), the Third Generation Cohort (2002), a New Offspring Spouse Cohort (2003), and a Second-generation Omni Cohort (2003). In 2018, the FHS marked its seventieth anniversary. Over the decades, FHS has contributed immensely to our understanding of the epidemiology of CVD and its risk factors, including BP. The purpose of this review is to discuss recent contributions from the FHS that examined novel BP and vascular measures, offered

This article is part of the Topical Collection on *Blood Pressure Monitoring and Management*

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insights into the pathobiology of CVD, and provided a rationale for inclusion of these novel vascular measures in clinical practice.

Blood Pressure as a Novel Index

In one of their first major findings, FHS researchers observed that hypertension (defined at the time as BP ≥ 160/95 mmHg) was related to a higher incidence of coronary heart disease [6] and stroke [7] and established that systolic BP (SBP) was a novel risk factor for CVD events. Despite evidence that SBP was related to CVD events, clinically acceptable SBP continued to be indexed to age. Designated as "benign essential hypertension," concordant rise in BP with age was thought to provide beneficial tissue perfusion as distal arteries within the systemic vasculature progressively narrowed [8]. Clinicians hypothesized that this ostensibly compensatory mechanism was perhaps more important among the elderly, contributing to the widely held clinical pearl that normal SBP should be calculated as age plus 100 mmHg [8]. However, attempts to normalize the observation that average SBP increases with age obscured the maladaptive contribution of age-related changes in systemic arteries, particularly age-related aortic stiffening, to the pathophysiology of hypertension and CVD.

BP is composed of both mean and pulsatile components: mean arterial pressure (MAP) and pulse pressure (PP), respectively [9]. MAP is determined by cardiac output and total peripheral resistance whereas PP is determined by ventricular ejection characteristics (i.e., stroke volume and ejection rate) and aortic stiffness. In a Framingham sample, higher aortic stiffness was observed to accompany a rise in PP [10]. With age, elastic fiber fragmentation contributes to the stiffening of the proximal aorta as a result of deposition and engagement of collagen fibers within the arterial wall. Thus, older individuals generally have higher central PP and higher direct measures of aortic stiffness (i.e., characteristic impedance and carotid-femoral pulse wave velocity (CFPWV)). Among individuals ≥ 50 years, SBP rises and diastolic BP (DBP) falls with age, which leads to a progressively higher PP; therefore, PP represents a surrogate measurement of aortic stiffness particularly among the elderly [10]. In addition, several studies have shown that higher aortic stiffness and pulsatility (as evaluated by peripheral and central PP and aortic stiffness measures) are predictive of CVD events [11–19]. In multivariable models adjusted for CVD risk factors, higher CFPWV—the reference standard measure for aortic stiffness—was associated with increased incidence of first major CVD event in models that adjusted for known CVD risk factors including SBP [11, 20], while other vascular measures (i.e., augmentation index, central pulse pressure, and pulse pressure amplification) were not. Additionally, FHS investigators and others have shown that aortic stiffness among normotensive individuals preceded incident hypertension [15, 21–23], and in a recent FHS analysis, researchers observed greater aortic stiffness in the young, normotensive offspring of parents with hypertension [24•]. Thus, novel measures, like CFPWV, identify high-risk individuals and represent potentially modifiable novel targets for prevention or treatment of high BP as a risk factor for CVD.

Blood Pressure Components and CVD Risk

Several studies have suggested that central (vs. peripheral) pressure may be superior at predicting CVD outcomes [25–27]. Some of these studies, however, have important limitations that should be considered. First, investigators overlooked pressure amplification between the brachial and radial arteries, which leads to an underestimation of central PP [28]. In addition, central pressure calibration used to estimate MAP (with an unmeasured fixed shape factor) was derived from the brachial artery [28]. Since the brachial shape factor is variable and may be traditionally underestimated [29, 30], the error in the central pressure calibration in these studies was underestimated. Recently, FHS investigators observed that central BP measures derived using a generalized transfer function were not predictive of CVD risk after considering standard risk factors, including brachial SBP [31••]. Although central BP measures provided no incremental value after considering brachial pressures, when brachial SBP was added to a model that included central SBP, an improvement in model fit was observed (i.e., lower −2 log likelihood) [31••]. Although strong correlations between central and peripheral BP measures were observed in the sample ($r = 0.88$–0.98) [31••], these data do not support the hypothesis that central SBP provides additional predictive information beyond that provided by peripheral SBP. In addition, peripheral BP measurements are acquired more easily during clinic visits through traditional sphygmomanometer or arterial tonometry methods and remain an appropriate method to assess risk. Ongoing investigations that seek to measure central pressure directly with calibration methods that are independent of peripheral BP waveforms may provide incremental improvement of risk prediction beyond traditional risk factors but require further development and investigation. In addition, other existing methods that non-invasively measure novel vascular measures in the peripheral circulation, such as peripheral arterial tonometry, may be predictive of CVD risk. For example, a recent cross-sectional FHS analysis examined the relation between peripheral artery flow reversal during diastole and vascular function [32•]. Greater diastolic flow reversal was related to lower conduit and microvascular vasodilation, impaired flow-mediated dilation, higher CFPWV, and higher forearm vascular resistance [32•]. Since flow patterns in the peripheral arteries may be easily assessed non-invasively in

the clinic using pulsed Doppler [33], brachial flow reversal may emerge as a novel marker of endothelial and vascular dysfunction. However, further longitudinal studies are needed.

Isolated systolic hypertension (ISH) is the most common subtype of hypertension among the elderly [34]. In an FHS analysis, two distinct paths to ISH were observed: (1) younger people with essential hypertension transitioned to ISH as a result of age-related arterial stiffening (i.e., burned-out diastolic hypertension) or (2) individuals developed ISH without antecedent diastolic hypertension (i.e., de novo ISH) [35]. Importantly, about 59% of ISH cases did not have antecedent diastolic hypertension before developing ISH later in life [35]. Among older individuals with ISH, the relation between DBP and CVD risk is non-linear and is observed as a J-curve. At lower DBP (≤ 70 mmHg), CVD risk is higher, and significant debate continues about causes of the observed relation between DBP and CVD risk in these individuals [36]. Compared to SBP, PP becomes more predictive of CVD risk after midlife, thus prompting researchers to hypothesize that PP may contribute to the J-curve phenomenon [37]. Framingham investigators compared the combination of SBP + DBP vs. PP + MAP (as both linear and quadratic terms) in predicting CVD events among individuals without prevalent BP-lowering therapy [38]. Combined pressure measures were superior to single pressure measures, consistent with findings from the Multiple Risk Factor Intervention Trial [39]. Combined SBP + DBP and combined PP + MAP were equally predictive of CVD risk because each pair of variables is a linear combination of the other; thus, neither dual BP model was found superior (based on Akaike information criteria) [38]. However, DBP was the only measure that showed a non-linear, quadratic relation with CVD; when modeled with SBP, risk increased at both the high and low extremes of DBP [38]. Contrariwise, PP and MAP had more linear relations with risk, and this dual model could reveal the relative contributions of arterial stiffness vs. peripheral resistance to CVD risk [38]. Furthermore, the observation of the J-curve for DBP and CVD risk in this untreated sample suggests that BP-lowering medication did not contribute to lower DBP among higher risk individuals [40], but rather that another mechanism, such as aortic stiffness, causes elevation of PP and lower DBP in high-risk individuals. More recently, an FHS analysis among CVD event survivors with ISH showed that individuals with DBP < 70 mmHg (compared with individuals with DBP 70–89 mmHg) had a higher risk for recurrent CVD events regardless of hypertension treatment status [41]. Higher risk, in association with lower DBP, was observed only in individuals with a wide PP, consistent with a contribution of aortic stiffness to the observed excess risk. Investigations that consider the mechanisms by which concurrent low DBP and elevated pulsatility predisposes individuals with ISH to additional CVD events merit further study.

Novel Vascular Measures and Cognition

Several FHS analyses have shown associations of elevated pressure pulsatility and aortic stiffness with worse brain structural integrity and function [42, 43•, 44–46]. The brain is a high-flow, low-resistance organ. Low precapillary resistance allows excessive carotid pressure and flow pulsatility to penetrate into the brain's microcirculation, where it can cause damage [47]. When the aorta stiffens, central PP increases and wave reflection at the interface between aorta and conduit arteries decreases, resulting in transmission of excessive flow pulsatility into the carotid arteries. However, changes to vascular function and subsequent structural and functional changes are not limited to older individuals. For example, a recent study examined the cross-sectional associations of aortic stiffness with cognitive function and brain tissue injury in middle-aged participants within the FHS Third Generation Cohort [48•]. Higher aortic stiffness was associated with worse cognition (worse processing speed and executive function in the whole sample) and greater burden of subclinical markers of brain injury, such as larger lateral ventricular volumes among the younger participants (< 45 years) and more white matter hyperintensities among the older participants (age 45–65 years) [48•]. Thus, subclinical structural and functional changes manifest in the brain relatively early and are concurrent with midlife transition to a stiffer aorta.

In addition, recent FHS analyses have examined longitudinal relations between vascular measures and cognition. In a recent analysis, Framingham Offspring participants were followed for five consecutive exam visits (from mid-to-late life) to examine the association between duration of hypertension and incident dementia [43•]. Compared to individuals with normal BP, individuals with persistent hypertension from mid-to-late life had higher risk for incident dementia [43•]. Thus, lower SBP in midlife may have long-term cognitive benefits. The investigators also observed that a steep decline in SBP in late life was associated with a > 2-fold increase in dementia [43•]; however, this observation was likely attributable to reverse causation. These data suggest that a precipitous decline in BP in older adults may be a marker of dementia instead of a risk factor. An additional analysis examined prospective relations between aortic stiffness (CFPWV) and 10-year risk of mild cognitive impairment and dementia [49•]. Higher CFPWV, as a continuous measure, was associated with higher risk of mild cognitive impairment. When CFPWV values were dichotomized, participants in the highest two quintiles of CFPWV (> 11.4 m/s) had a > 2-fold higher risk of all forms of dementia, including Alzheimer's disease [49•]. Furthermore, in the Framingham Offspring Cohort, higher CFPWV and central PP contributed to longitudinal deterioration of executive function and processing speed, as evidenced by a greater reduction in cognitive test scores over the follow-up period [50••]. These data suggest that interventions that

reduce or prevent hypertension and abnormal arterial stiffness may attenuate cognitive decline with advancing age. Since multiple vascular risk factors may contribute simultaneously to cognition [51], FHS investigators analyzed four decades of data to assess the association between vascular risk burden (using the Framingham Stroke Risk Profile (FSRP)) and changes to brain volume [52•]. The FSRP is a validated measure that combines information on age, sex, smoking, prevalent CVD, prevalent atrial fibrillation, prevalent diabetes, presence of hypertension treatment, and SBP; higher FSRP indicates greater level of vascular risk burden [53]. Higher FSRP was associated with lower brain volume, and in the longitudinal analysis, the effect between FSRP and brain volume was stronger among younger participants [52•]. These data support the idea that targeting vascular risk earlier in life may prevent progression of vascular dysfunction before it manifests as structural injuries and cognitive impairment or dementia [54••].

Additional studies are needed to elucidate potential mechanisms by which elevated BP and excessive aortic stiffness contribute to cognitive decline. However, two recent cross-sectional analyses from FHS have provided insights into potential targets and pathways. Investigators assessed the association of arterial stiffness with the structure of white and gray matter of the brain using diffusion tensor imaging and magnetic resonance imaging [55•]. Using diffusion tensor imaging, investigators characterized microstructure and integrity of white matter tracts in the brain by determining the fractional anisotropy, which is a measure of directional constraints on water diffusion along axons [55•, 56]. Among FHS Third Generation participants, higher CFPWV (but not central PP, augmentation index, or MAP) was associated with white matter injury and regional gray matter atrophy, which were exacerbated among participants who were older or required treatment for hypertension [55•]. These data were consistent with previous findings that suggest that cerebrovascular damage and brain atrophy are associated with aortic stiffness [42, 57•]. In a follow-up, FHS investigators examined relations between aortic stiffness and markers of microvascular brain tissue injury (excess free water, reduced fractional anisotropy, and greater white matter hyperintensity volume) in an expanded cohort including both Offspring and Generation 3 participants [58•]. In contrast to higher fractional anisotropy (greater organization), higher free water content reflects a loss of restriction of diffusion by the surroundings (greater disorganization) and is a robust biomarker for subtle cerebral injury [59, 60]. Higher CFPWV was associated with higher free water, lower fractional anisotropy (higher disorder), and higher incidence of white matter hyperintensities [58•]. Although they performed a cross-sectional study, researchers performed a mediation analysis to determine whether hemodynamic alterations contributed to microvascular alterations in the brain and ultimately lead to brain injury [58•]. Consistent with previous studies [57•, 61, 62•], these data suggest that hypertension and abnormal arterial stiffness may initiate a pathological chain of events leading to target organ damage via a mechanism that includes microvascular dysfunction. However, longitudinal assessments, particularly among younger individuals, are warranted. For example, in a recent study among Framingham Offspring and Third Generation Cohorts, the association between aortic stiffness and incident CVD events, including ischemic stroke, was mediated by pathways that include markers of microvascular damage and remodeling [62•]. Thus, future studies that explore how elevated pressure and pulsatility and abnormal aortic stiffness trigger or contribute to the onset of cognitive deficits in the brain may produce interesting findings. In addition, further studies should continue to utilize available imaging technologies that may reveal novel metrics and biomarkers to detect early subclinical microvascular and structural changes to inform prevention and treatment.

Aging exacerbates BP variability and may further sensitize the brain to detrimental consequences of impaired autoregulation [63•]. Although BP initially falls when changing from supine to standing posture, baroreceptors quickly sense the change in arterial pressure and initiate an increase in heart rate and vascular resistance in order to increase MAP [64]. Age-associated alterations in the baroreflex response impair regulation of MAP upon standing and is associated with higher risk for stroke and syncope [65, 66]. Studies suggest that abnormal arterial stiffness contributes to greater orthostatic BP variability in the elderly [67, 68], possibly affecting BP homeostasis by attenuating baroreflexes [69–71]. In a sample of the FHS Third Generation Cohort, investigators assessed the relation between orthostatic change in BP measures and comprehensive hemodynamic measures [72•]. Higher values of aortic stiffness measures (CFPWV, forward pressure wave amplitude, and characteristic impedance) were associated with a blunted orthostatic increase in MAP [72•]. Since aortic stiffness is associated with impaired microvascular reactivity and blunted compensatory elevation of MAP upon standing, aortic stiffness provides a substrate for repeated episodes of cerebrovascular hypoperfusion, which may contribute to observed associations among aortic stiffness, brain microvascular lesions, and cognitive impairment. Subsequently, FHS investigators examined the interrelations of orthostatic MAP change, CFPWV, and brain structure and function [73•]. In the middle-aged sample, blunted orthostatic increase in MAP was associated with poorer executive function and smaller total brain volumes; moreover, they observed significant interactions by age and extent of aortic stiffness [73•]. These data suggest that older individuals, and particularly those with abnormal aortic stiffness, are more dependent on orthostatic increase in MAP [73•]. Taken together, these recent FHS data suggest that blunting of orthostatic increase in MAP may be an early

marker of and contributor to cognitive impairment and warrants further study.

Implications for Management and Treatment Recommendations

A few recent FHS analyses have focused on BP management and treatment strategies. The current guidelines for hypertension treatment and management from the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 8) [74] have prompted an ongoing debate [75–77]. Compared to the previous guidelines (JNC 7) [78], the Committee endorsed more modest treatment targets for older individuals (≥ 60 years; SBP < 150 mmHg) and for individuals with prevalent diabetes and chronic kidney disease (BP < 140/< 90 mmHg) [75]. Together with the Jackson Heart Study, FHS investigators evaluated the CVD risk among individuals whose BP classification changed under the updated guidelines [79••]. In multivariable models adjusted for standard CVD factors, participants who were inadequately treated by JNC 7 but successfully treated by JNC 8 had the highest cumulative incidence of CVD in the FHS sample [79••]. Additionally, high risk for CVD events persisted even when older participants were treated to SBP 140–149 and DBP < 90 mmHg [79••]. These observations reveal that the discordances between JNC 7 and JNC 8 management strategies may lead to higher CVD burden by underestimating the prevalence of hypertension that warrants treatment. Indeed, a recent National Health and Nutrition Examination Survey report showed that the proportion of individuals classified as having uncontrolled hypertension was reduced under the updated guidelines from 16.6 to 12.8%, with most of the reclassification affecting females, older individuals, and diabetics [80]. The researchers observed that older age and presence of diabetes exacerbated the relation between treatment group and risk for incident CVD ($P < 0.01$ for both interactions), but effect modification was not observed by sex [79••]. These data empirically counter the Committee's rationale that insufficient evidence exists to support more aggressive treatment thresholds in prevention of BP-related CVD events. Consistent with the findings of the Systolic Blood Pressure Intervention Trial [81] and the recent American Heart Association/American College of Cardiology hypertension guidelines [82••], the FHS observations support a lower treatment target for SBP. Further work to define improved treatment strategies to reduce CVD risk in high-risk groups is warranted.

Defining optimal BP remains an ongoing interest. FHS investigators aimed to identify a BP threshold level after which rapid progression toward hypertension occurred [83••]. To that end, the natural history of BP elevation (long-term trajectories) was observed in the Framingham Original Cohort using a serial analysis of standardized BP measurements taken between 1948 and 2005 [83••]. Before hypertension, researchers observed that participants maintained a resting SBP < 120–125 mmHg, but above this threshold, resting SBP increased rapidly regardless of age or time of hypertension onset [83••]. These data are consistent with the investigators' hypothesis and reinforces the idea that appropriately timed and targeted interventions may prevent rapid progression to hypertension [83••]. In addition, if progression toward rapid blood elevation can be prevented regardless of age, these data also suggest that interventions targeting age-associated increases in arterial stiffness could help individuals maintain optimal BP [15]. Additional studies should further examine the mechanisms that underlie the association between vascular function and incident hypertension.

While many individuals are unaware of their hypertension status, those who are aware often receive suboptimal treatments that fail to control their BP [80], so despite treatment, these individuals remain at higher risk for CVD events. A recent investigation in the Framingham Offspring Cohort assessed the putative contribution of aortic stiffness on the residual CVD risk among treated hypertensives [84•]. Researchers assessed the relative CVD event risk among participants who were stratified into four groups according to the presence of hypertension (BP ≥ 140/90 mmHg or use of antihypertensive medications) and high vs. low aortic stiffness (defined by age- and sex-specific median CFPWV values) [84•]. A majority of treated hypertensives had elevated aortic stiffness, and the researchers observed the highest CVD cumulative incidence among participants with both prevalent hypertension and high aortic stiffness [84•]. Consistent with previous work [85], these data suggest that residual aortic stiffness contributes to residual event risk among treated hypertensives. Thus, concurrent reduction in aortic stiffness with lowering of BP through adequate treatment may significantly reduce CVD event risk among hypertensive patients.

Although higher PP confers greater CVD risk, the component of PP that confers higher risk remains debated. PP can be separated into forward and backward pressure waves using data from directly measured central aortic pressure and flow. Some studies that attempted to separate backward and forward pressure waves used a typical flow waveform or a pseudo-flow waveform derived from pressure data [12, 86, 87]. These studies were unable to provide accurate assessment of forward and backward wave amplitudes. In an analysis of data from the Framingham Offspring Cohort, investigators compared the association with incident CVD events of various mean and pulsatile components of BP [88]. In a multivariable model that adjusted for standard CVD risk factors, including SBP, greater forward pressure wave amplitude was associated with higher CVD risk [88]. Other hemodynamic variables, including MAP and measures of wave reflection (backward pressure wave amplitude and global reflection coefficient), were not associated with CVD events [88]. Traditional

Table 1 Blood pressure and vascular measures as potential novel biomarkers

Blood pressure or vascular measure	Related injury or functional measure	Recent FHS reference
↑ Diastolic brachial flow reversal	↓ Hyperemic flow velocity ↓ Flow-mediated dilation ↑ Forearm vascular resistance ↑ CFPWV	Breton-Romero et al. [32•]
↑ CFPWV	↑ Lateral ventricular volumes ↑ White matter hyperintensities ↓ Processing speed and executive function ↑ Risk of incident MCI and dementia	Pase et al. [48•] and [49•]
	↑ White matter injury ↑ Regional gray matter atrophy ↑ Free water (↑ subtle cerebral injury) ↓ Regional FA (↑ microstructural damage)	Maillard et al. [55•] and [58•]
↑ CFPWV and central pulse pressure	↓ Performance on executive function and abstraction tasks	Tsao et al. [50••]
↑ CFPWV and primary pressure wave*	↓ Hyperemic flow velocity ↑ CVD events	Cooper et al. [62•]
↓ Orthostatic increase in MAP	↓ Brain volume ↓ Executive function ↑ CFPWV	Torjesen et al. [72•] and Cooper et al. [73•]

CFPWV carotid-femoral pulse wave velocity, *SBP* systolic blood pressure, *MAP* mean arterial pressure, *MCI* mild cognitive impairment, *FA* fractional anisotropy

*Pressure-only surrogate for forward wave amplitude

approaches to hypertension treatment have focused primarily on small vessels and aimed to reduce peripheral resistance and MAP in order to lower BP and hopefully reduce CVD risk. In light of the foregoing analysis of relations of various BP components with CVD risk, MAP-focused approaches may be limited as they fail to address a major contributor to hypertension progression and CVD risk, as evidenced by the large proportion of people with excessive forward pressure wave amplitude leading to prevalent hypertension with wide PP (ISH) and higher CVD risk despite treatment [34, 35, 78, 89]. Thus, excess forward pressure wave amplitude as a result of mismatch between aortic stiffness, geometry, and flow may represent a key target to reduce BP-related morbidity and mortality.

Conclusions

FHS has contributed significantly to our understanding of relations between BP and CVD. Attitudes surrounding BP pathophysiology, treatment, and management have changed dramatically since the first FHS publications implicated elevated BP as a primary contributor to CVD progression and events. Accumulating evidence implicates abnormal pressure pulsatility and aortic stiffness as primary contributors to incident hypertension (particularly de novo ISH) and BP-related CVD events. Recent work suggests that consideration of the various components of BP better stratifies CVD risk and provides potential new targets for treatment. Additionally, FHS has shown strong associations of measures of abnormal aortic stiffness with brain injury, potentially mediated by microvascular damage, and cognitive decline. Novel BP measures have emerged as strong correlates of aortic stiffness and cognition (Table 1). These studies suggest that novel, potentially modifiable factors contribute to subclinical disease and represent early vascular targets that are complementary to traditional BP measures. Incorporation of novel and traditional indices into clinical practice may provide a comprehensive evaluation of BP-related CVD risk. Assessment of novel vascular measures can be utilized to improve BP control leading to a reduction of CVD burden in the community.

Compliance with Ethical Standards

Conflict of Interest Dr. Mitchell reports grants from National Institutes of Health and from Novartis, is a consultant to Merck and Servier, and is Owner and Employee of Cardiovascular Engineering, Inc. Dr. Cooper declares no conflict of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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