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C Venkata S Ram

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Guest Editors:
Edward Barin, Alberto Avolio

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Editorial Office

Editor-in-Chief

C Venkata S Ram

Hypertension Journal
R-003, Great Value Sharanam, Sector 107, Noida-201301, Uttar Pradesh, India
Contact No.: (+91) 8527814605
e-mail: editor@hypertensionjournal.in

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AIMS & SCOPE

Hypertension Journal is a peer-reviewed journal which highlights epidemiology, health implications and cardiovascular risk from hypertension in India/South-Asia. Hypertension is much more common than diabetes. It is vastly under diagnosed and poorly treated in India/South-Asia. There are excellent therapeutic options to treat hypertension, but the available resources are not fully utilized by doctors therefore neglecting this disorder. The journal will hereby promote the significance of hypertension and the urgent need to bring it under control. The medical community should be educated on hypertension evaluation, diagnosis, workup and management simultaneously bringing up the literature, research, guidelines and scientific advances related to hypertension and its disorders. We are hereby starting a high-quality journal dedicated solely to hypertension and thus promoting the awareness, evaluation and effective management in India/South-Asia. Dr C Venkata S Ram is a world authority on hypertension with lifelong work (research, clinical and publications).

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Welcome Editorial

Deputy Vice-Chancellor (Medicine and Health) and Executive Dean, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia

I welcome readers and trust you will enjoy reading this special edition of the Hypertension Journal which has been prepared, written, and edited by clinicians and scientists from MQ Health – the Macquarie University Health Sciences Centre in Sydney, Australia. Over recent years, MQ Health has developed a close relationship with the Apollo Hospital Group in India, in particular the Apollo Health City in Hyderabad. At the core of this relationship are arrangements for senior medical students studying in Macquarie University's 4-year graduate entry MD medical degree to engage in extended clinical placements at Apollo Hospital, Hyderabad. The Macquarie MD is Australia's newest medical degree; it commenced and took in its first cohort in 2018 and has been designed to graduate doctors equipped for future practice within the health systems of a globalized world. In many ways, the Macquarie MD was designed to be a pioneering and emblematic "global medical degree" recognizing the increasing trans-national nature of much of modern clinical practice. By embedding Macquarie MD students in a different health system and in a culturally different country, our aim is to use these immersive experiences to graduate doctors with strong capability in cultural sensitivity and health system awareness by deeply experiencing a contrast to their home country and health system.[1]

MQ Health is a unique enterprise in Australia constituting the nation's only university-owned and -led academic health care system. It operates as a not-for-profit facility within Australia's private health-care sector and comprises a modern 150-bed Macquarie University Hospital plus a wide range of ambulatory services spanning general practice (primary care), specialist tertiary and quaternary care, digital mental health care, and allied health care. MQ Health was established and is fully owned by Macquarie University and has been modeled on successful university health-care systems in the United States such as the University of Pennsylvania's Penn Medicine or the University of California San Francisco (UCSF) Medical Centre. Similar examples of university-led academic health centers also exist beyond North America including Mahidol University's Siriraj Hospital in Bangkok, Thailand, and the Karolinska University Hospital in Sweden. A common theme is creating the virtuous cycle of the "learning health system" where clinical care is continuously improved by the outcomes of embedded clinical research. At MQ Health, we define our purpose as "Heal-Learn-Discover" to emphasize the integration of academic medicine with clinical care.

It is from this integrated academic health environment that the contributors of this Special Edition have been chosen. The authors represent great examples of MQ Health in action either being clinician scientists who practice their craft informed by research or who are researchers guided by practice and who aim to translate their discoveries to make impacts into clinical care. All are teachers of Macquarie MD medical students. I commend this edition to readers and express my deep thanks to Professor C Venkata Ram, Editor-in-Chief for inviting Macquarie University and MQ Health to compile this Special Edition.

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Dr. H Patrick McNeil is the Deputy Vice Chancellor (Medicine and Health) and the Executive Dean of the Faculty of Medicine, Health and Human Sciences at Macquarie University, Australia.

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Guest Editorial

Hypertension Journal – MQ Special Issue

Edward Barin[1], Alberto Avolio[2]

[1]MQ Health Cardiology, Faculty of Medicine, Health and Human Sciences, Macquarie University, [2]Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW 2109, Australia

The importance of the arterial blood pressure pulse has been recognized since ancient times, and from then to the present, the interaction of the observer and the patient has progressed in gradual steps. It evolved from the presence of a palpable arterial pulse, being accepted as a sign of life and health condition, to the registration of the features of the arterial pulse as the first ever graphical representation of any physiological parameter in medicine, culminating in the quantification of the tension in the arterial wall as a measurement of arterial "blood pressure."[1]

The current acceptance of high blood pressure (hypertension) as a major cardiovascular risk can claim to have part of its origins in the actuarial and data gathering endeavors of life insurance companies.[2] The ubiquitous use of the brachial cuff sphygmomanometer in the early 20th century enabled collection of numerical data on blood pressure over long periods. The accumulation of blood pressure measurements also enabled data to be collected across the whole human life span. This demonstrated that in the otherwise healthy population, that is, in the normal population with no symptoms of overt ill health, there was a wide range of blood pressure values. Systolic blood pressure varied much more than diastolic blood pressure but increased with age. Since blood pressure was thought to be related to (and drive) tissue and organ perfusion, the marked increase in blood pressure was thought to be essential for adequate blood flow, as is required for efficient organ function. Hence, the concept of "essential hypertension"[3] was used to describe this condition of elevated blood pressure as being due to the essential readjustment of the cardiovascular system to accommodate age-related changes that occur in the vasculature (such as reduced capillary density with sequelae of increased peripheral resistance, hence requiring a higher pressure for adequate tissue perfusion). However, calculations of risk of morbidity and mortality (perhaps related to the forecasting of life insurance premiums) showed that those with elevated diastolic pressure were at higher risk of clinical and multiorgan complications affecting their health.

Hence, the accepted notion of how to qualitatively understand elevated blood pressure was that it was essential that mean blood pressure would increase with age (leading to essential hypertension, with no overt symptoms or identifiable cause), that systolic pressure was mainly related to the strength of cardiac contraction (and so related to stroke volume), and that hypertension-related health complications were mainly associated with high diastolic pressure,[4] presumably as diastolic pressure was thought to be more closely associated with total peripheral vascular resistance. However, with accumulation of information from many large epidemiological studies in the latter part of the 20th century, and in particular with longitudinal and generational data from the Framingham Heart Study,[5] it is now accepted that systolic pressure is the major blood pressure component that is related to cardiovascular risk of morbidity and mortality.[6] Systolic pressure shows a much more pronounced increase with age compared to diastolic pressure, and that, in fact, diastolic pressure actually tends to decrease in the latter two decades of life, with the majority of hypertension in the elderly being categorized as "isolated systolic hypertension." This implies that it is the pulse pressure that shows the most pronounced increase with age, in particular after the sixth decade of life.[7] This marked increase in pulse pressure is not related to changes in stroke volume, which can also show a slight reduction with age, but rather to the known increase of arterial stiffness with age; and arterial stiffness itself has been shown to be an independent factor of cardiovascular risk.[8]

While arterial blood pressure is perhaps the most widely measured physiological parameter in clinical medicine, with methods that have essentially not changed since the inception of the brachial sphygmomanometer in late 19th and early 20th century, it still presents formidable challenges in how to improve the understanding of the effects of high blood pressure on end-organ damage leading to health complications. It is some of these important challenges that are addressed in the series of comprehensive review articles and commentaries in this Special Issue of Hypertension Journal presented by investigators and

Address for correspondence:
Alberto Avolio, Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW 2109, Australia. E-mail: alberto.avolio@mq.edu.au

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clinicians from the Faculty of Medicine, Health and Human Sciences and Macquarie University Hospital, from Macquarie University, Sydney, Australia.

The series of 10 articles spans aspects of methodology, specific effects of blood pressure and the brain, association of blood pressure and end-organ function, and the treatment and strategies in relation to overall cardiovascular risk.

The article by Butlin *et al.* addresses aspects of the conventional auscultation and oscillometric method of blood pressure measurement using the brachial cuff sphygmomanometer. It provides a comprehensive historical description of the advances made to date, important issues regarding sources of error and device calibration, and a view of the future with methods enabling continuous measurement of blood pressure using cuffless technology. Tan *et al.* extended the description of measurement of blood pressure to include the pulse waveform. With detection of the pulse waveform in a peripheral location (radial or brachial artery), the calibrated pressure waveform can be mathematically processed to provide an estimation of central aortic pressure. This is of interest, as with similar peripheral pressure values, central systolic pressure can be quite different, and so can potentially improve discrimination of pressure-dependent effects on the heart. Simultaneous detection of pulse waveforms at separate locations enables calculation of pulse wave velocity providing a non-invasive measure of arterial stiffness. The article addresses the current state of clinical utility of the estimation of central aortic pressure and arterial stiffness. The article by Mihailidou addresses the important aspect of ambulatory blood pressure and its variation in individuals as a means of identifying those with enhanced cardiovascular risk. This is significant, since the use of office blood pressure is being reassessed in relation to ambulatory blood pressure. There is an increasing trend where office blood pressure might be relegated to screening and ambulatory blood pressure to be used for reliable clinical diagnosis of hypertension.

Investigations of the effect of blood pressure on the brain are gaining significant interest with respect to vascular associations with cerebral function. The article by Neville and Savage examines the complex array of evidence of the effect of high blood pressure on cognition and Alzheimer's disease. They also address the mixed evidence of the effect of hypertensive treatment in early life on the development of cognitive impairment in later life, and the effect of blood pressure lowering on cerebral perfusion and clearance of toxins. Additional evaluation of hypertension and the broad spectrum of dementia is addressed by the article of Fuller *et al.* in the context of the long-term effects of aerobic and resistance training exercise on lowering the risk of the development of dementia and cognitive decline. The article also highlights the fact that the mitigation of factors involved in the development of dementia is a multifactorial process and assesses the impact of pharmacological and non-pharmacological approaches to slow down the late age development of cognitive impairment associates with vascular dementia and Alzheimer's disease. The effect of hypertension on cerebral dysfunction is examined in the article of Kim *et al.* where blood pressure is considered a major factor involved in microvascular damage. The authors discuss a range of vascular and neurogenic mechanisms that predispose to stroke and cerebral small vessel disease. In particular, they emphasize the important role of cerebral autoregulation mechanisms involved in regulating cerebral blood flow through vasomotion of large distributing and small perfusing blood vessels.

An important sequela of high blood pressure is the effect on end-organ function. The article by Li *et al.* addresses the relationship between blood pressure and kidney function. Specifically, it assesses the use of renal denervation for the treatment of resistant hypertension in the presence of chronic kidney disease, a condition for which the benefits of renal denervation can be varied but may also provide additional benefits beyond blood pressure reduction in terms of improving kidney function. The effect of blood pressure on the heart is addressed by the article of Barin and Avolio. The interaction between the heart and the arterial load is described as a continuum in which the decline of optimum cardiovascular function initiated by elevated blood pressure and neurohumoral changes leads to the development of the left ventricular hypertrophy and heart failure involving positive feedback mechanisms. The associations of blood pressure and vessels in the eye as an end organ are reviewed by Graham and Schultz in the context of hypertensive retinopathy. The importance of the ocular vasculature is that it enables quantitative assessment of the microcirculation and its associated organ function through the use of optical techniques for the measurement of vessel properties in relation to blood pressure and intraocular pressure, such as the development of glaucoma.

The final article by Shalaby and Lin provides a closing bookend to the series of articles in the Special Issue by examining the treatment of hypertension and overall cardiovascular risk. Undoubtedly, the association of high blood pressure and coronary artery disease is a major contribution to total risk. However, as explained by the contributions in this series, total cardiovascular risk involves a broad spectrum of compromised vascular and organ function, and while the measurement of blood pressure might be a rather simple procedure, the association of its optimum treatment and management for improved health of the individual patient still presents formidable challenges.

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Review Article

Blood Pressure, Cognition, and Dementia

Rachael Neville, Greg Savage

Department of Psychology, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney NSW, Australia

Abstract

This review synthesizes findings from studies that investigate the impact of blood pressure on cognition and the development of Alzheimer's disease (AD), while highlighting research limitations that add to variability. To properly capture this relationship, we review findings from a neuropsychological perspective, considering the effect of blood pressure on different aspects of cognition (e.g., processing speed, memory, and executive function) rather than cognition as a unitary construct. Hypertension in mid-life is associated with worse cognitive outcomes in later life, particularly in the areas of executive functioning and processing speed. Findings are mixed in late-life studies; however, with several lines of research demonstrating that either high or low blood pressure is associated with worse cognition. Much of this variability may be due to greater incidence of dementia for those with low blood pressure in late-life. The effect of blood pressure levels on attention, visuospatial skills, and language skills is scarcely investigated and requires further examination. The effectiveness of antihypertensive agents for slowing cognitive decline or reducing dementia risk is still debated. There is strong evidence, however, that blood pressure treatment for at least 12 years or for people aged <75 may be effective in preserving cognitive function, reducing risk for AD, and may facilitate clearance of toxic AD-related biomarkers in the brain.

Key words: Alzheimer disease, antihypertensive agents, blood pressure, cognition, dementia

Introduction

Hypertension poses important public health issues, affecting 30% of people worldwide.[1] It is one of several risk factors for cerebrovascular disease and is frequently observed in the context of neurodegenerative diseases such as Alzheimer's disease (AD) and vascular dementia (VaD).[2,3] As blood pressure (BP) can be successfully managed and treated in clinical contexts, current investigations have focused on whether (a) hypertension contributes to cognitive impairment and (b) whether treatment for hypertension can slow or halt cognitive decline in aging or in people at risk for dementia. This review will discuss recent perspectives in these two main areas.

Hypertension is generally defined as >90 mm Hg diastolic blood pressure (DBP) or >140 mm Hg systolic blood pressure (SBP). Both SBP and DBP are considered important for clinical outcomes,[4] but systolic hypertension is usually associated with greater stroke risk and mortality.[5,6] SBP and DBP follow different trajectories across the lifespan, emphasizing the importance of treating them separately. DBP and SBP naturally increase until mid-life, after which DBP typically lowers and SBP continues to rise.[7] This means that SBP hypertension (considered as isolated systolic hypertension) is most common among elderly[8] and frequently the focus of modern hypertension research. The difference between SBP and DBP is termed pulse pressure (PP). Widening of PP caused by increases in SBP and decreases in DBP in late life is considered to be an indirect measure of arterial stiffness and a predictor of adverse vascular outcomes.[9]

Blood Pressure and Cognition

The effects of elevated blood pressure on cognition have been investigated widely, predominantly since the early 1990s.

Address for correspondence:
Greg Savage, Department of Psychology, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia.
E-mail: greg.savage@mq.edu.au

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Many investigations have employed cognitive screeners such as the Mini-Mental State Examination (MMSE),[10] which are relatively brief and easy assessments that amalgamate many aspects of cognition into a unitary measure, and have reported highly variable results.[11-13] This is not surprising, as vascular risk factors and cerebrovascular disease have greatest impact on attention, processing speed, and executive functions[14,15] which are not always observable with cognitive screeners.[16] Many advantages are gained, however, by investigating cognition using neuropsychological test batteries instead of cognitive screeners: They are sensitive to subtle changes across cognitive domains, they are less likely to be suffer ceiling effects, and they may correct for age, sex, and education status.

The cognitive areas most extensively investigated in hypertension research include executive function, memory, and processing speed. Executive function is a term used to describe a cluster of high-level cognitive processes associated with inhibitory control, selective attention, cognitive flexibility (set shifting), problem solving, planning, and generation of ideas.[17] In hypertension research, executive function is most frequently assessed with letter and semantic fluency tasks. Processing speed (cognitive efficiency measured in time) is usually assessed using the Digit Symbol-Coding subtest variants from versions of the Wechsler Adult Intelligence Scale or similar tasks. The tools used to assess learning and memory are highly variable, which complicate interpretation and adds to variability in findings, but typically involve list-learning or recall of prose passages.

Overall, it appears that the presence of mid-life (generally < 65 years) hypertension is especially predictive of cognitive impairment later in life, particularly for executive and processing speed tasks.[18-23] This can be compared with the highly variable findings in late-life studies.[24-27] This distinction suggests that degree of cognitive impairment is dependent on the duration of elevated blood pressure, an observation which is supported by longitudinal findings with longer follow-up times.[28]

In terms of executive function, there is ample evidence linking mid-life hypertension with worse letter and semantic fluency later in life.[20,22,29-31] The effect of hypertension has also been associated with worse performance in other areas of executive function, such as cognitive flexibility[20,25,32,33] and reasoning.[29] Reduced executive function is generally found even when controlling for the presence of other vascular risk factors.[20] The association is less robust for those with higher blood pressure in late-life,[25,34] however, and one study found that younger individuals within their sample of older people with high DBP performed *better* on fluency tasks.[25] For the latter study, as well as several other late-life investigations, cerebrovascular disease, and/or stroke were exclusion criteria for recruitment. As discussed in later sections, hypertension is strongly associated with the development of white matter lesions, stroke, and various other manifestations of cerebrovascular disease. Excluding these participants may, therefore, have biased the sample to include healthier individuals whose hypertension had not yet exacerbated breakdown of cerebral vasculature. As incidence of cerebrovascular disease increases with age, this may not pose an issue for mid-life studies. Similarly, in older age, hypertension is highly comorbid with other vascular risk factors (such as obesity, diabetes, and hypercholesterolemia),[35] which lowers the potential of finding independent hypertension-related effects. This is supported by Elias *et al.*[34] who found worse cognitive performance in individuals with both hypertension and obesity, than just hypertension alone.

In mid-life studies, hypertension is frequently found to be associated with worse performance on processing speed tasks;[20,22,23,30,31] however, this has not been demonstrated consistently across studies.[32,33] One study found a stronger effect for individuals with both diabetes and hypertension, suggesting an additive effect with other vascular risk factors.[36] A 30-year longitudinal study found worse performance on processing speed tasks for individuals who were hypertensive in mid-life and dropped below 139 mm Hg SBP after 30 years.[28] This suggests that late-life decrease in SBP in the context of pre-existing hypertension is especially predictive for reduced processing speed. Findings from late-life hypertension studies are less clear, partly due to the exclusion of processing speed tasks in the selected battery of cognitive tests,[27,34,36] highlighting the need for further investigation. Nevertheless, there is some evidence that elevated BP is associated with reduced processing speed in late-life.[37,38]

The effect of hypertension on memory is unclear and requires further investigation. Independent of whether blood pressure was measured in mid- or late-life, findings are mixed with some investigations finding clear associations between hypertension and worse memory performance,[25,28,29,31,34,37] and others finding no effect.[20,22,23,26,27,30,32,39] It is also possible that much of this variability is caused by failure to account for individuals who are in preclinical phases of dementia due to illnesses such as AD or VaD. As the presence of hypertension is a risk factor for both dementias, and AD and VaD together cause 80% of dementias worldwide,[40] it is probable that a high proportion of participants across all studies will go onto develop either of these illnesses. Individuals who go onto develop AD typically demonstrate greater and earlier memory impairments than those who develop VaD. Therefore, studies with a greater proportion of participants in preclinical phases of AD may observe an effect on memory, producing variability across studies. Merely excluding participants with a diagnosis of dementia is not enough; however, as high accumulation of the AD biomarker amyloid-β can be detected 15 years before dementia diagnosis, when memory deficits are prominent.[41-43] In support of this notion, one study found that hypertensives who experienced decline in BP showed greater levels of CSF p-tau (another AD biomarker) and worsening verbal memory performance.[44] Future investigations should include amyloid-β or tau as possible moderating variables, especially since hypertension along with other vascular risk factors are thought to play an important role in the pathogenesis of AD.

Another issue with memory research involves the frequent amalgamation of many memory outcome measures into one factor. While this makes sense for statistical reasons (reducing

the number of comparisons and simplifying the data), individuals who develop VaD are likely to show worse performance on learning and retrieval aspects of memory with good retention, whereas those who develop AD typically score poorly on all aspects of memory, and especially retention.[45] Amalgamating all memory components can hide these differences and produce unaccountable variability.

Other domains that are typically less thoroughly investigated include attention, working memory, language, and visuospatial skills. Attention and working memory are usually investigated together, using digit span tasks. Kilander, Nyman (20) reported an association between elevated blood pressure and impaired digit span performance, although this finding was not robust across other investigations.[25,27,32,34] In terms of language, hypertension has been associated with reduced word knowledge[29] and naming.[25] However, one late-life study observed that verbal skills assessed with a synonym task were better amongst Stage 1 hypertensives (140–159 mm Hg SBP or 90–99 mm Hg DBP) than in normotensives, but not for those with higher levels of hypertension (e.g., >160 mm Hg SBP).[37] Given that it is at odds with other findings, this could be an artifact. The effect of hypertension on visuospatial skills was either not observed in mid-life studies[20] or associated with better performance in late-life studies.[37]

Some investigations report a nonlinear association between cognition and blood pressure. Waldstein *et al.* observe that cognition is worst for individuals at the low and high ends of the blood pressure spectrum as opposed to mid-range BP in some areas of cognition.[25] For example, older participants with low education perform worse on executive function tasks at both the higher and lower range of BP as opposed to mid-range BP. Others who find this inverted-U shaped effect usually measured blood pressure and cognition in late-life.[26,46] One likely explanation for this (discussed in greater detail below) involves findings that late-life hypotension in the context of pre-existing hypertension is associated with greater cognitive impairment, higher dementia risk, and greater vulnerability to ischemia. This is complemented by previously discussed findings that conclude greater vulnerability to processing speed deficits for hypertensives that dropped below 139 mm Hg SBP in late-life. This raises a significant methodological flaw with late-life investigations that assume BP is static across the lifespan. Namely, either high or low BP can have deleterious outcomes in the context of pre-existing hypertension.

Another likely cause of heterogeneity in late-life studies in general involves the failure to account for duration of exposure to hypertension, and age first diagnosed. As mid-life studies clearly demonstrate that both are important for predicting cognitive impairment, late-life studies should include at least one proxy measure of hypertension duration in attempt to account for these factors. Pulse pressure partly reflects arterial stiffness and is often considered a better measure of the long-term effects of hypertension when measured in late-life.[47] Some studies now use PP rather than any single BP component separately.[48] Recent studies find that PP is associated with cognitive decline,[32] dementia risk,[49] and greater atrophic changes in the brain.[50] One study observed that increasing PP was associated with decline in verbal learning, visual memory, and working memory.[51] Another study found that arterial stiffness, but not hypertension, was associated with worse performance in executive function, processing speed, and working memory.[32] Hypertension was only associated with worse executive skills when seen in conjunction with arterial stiffness. Therefore, late-life studies should arguably consider including a measure of arterial stiffness to better account for long-term exposure to hypertension.

Alzheimer's Disease

As mid-life hypertension influences cognitive performance later in life, elevated blood pressure has been investigated for its contribution to the development of dementia. Alzheimer's disease is the most common form of dementia, with the greatest global burden on resources, impacting a projected 100 million people by 2050.[52] AD is characterized by progressive cognitive decline, brain atrophy, and accumulation of amyloid-β as well as neurofibrillary tangles in the brain. However, vascular contributions to AD are now well recognized, as over 55% of autopsy-confirmed AD brains have at least one type of vascular pathology.[53] With no disease modifying therapy available, current investigations question whether management of blood pressure among other vascular risk factors could reduce dementia risk, slow pathogenesis, or slow AD-related cognitive decline.

In terms of dementia risk, a combination of various vascular risk factors, including hypertension, is often found to be associated with increased risk for AD.[54] Other research suggests the presence of vascular risk factors lowers a clinical threshold for diagnosis, essentially advancing inevitable AD dementia diagnosis earlier in life.[55] In terms of the effect of hypertension specifically, several large studies have observed that mid-life hypertension is associated with higher incidence of AD diagnosis later in life.[56,57] For example, one study found that untreated mid-life hypertension was associated with almost 4.5 times greater risk of AD.[57] Measures relating to late-life hypertension are mixed, with a recent meta-analysis concluding no difference in dementia risk between hypertensives and normotensives.[58] One reason for this finding may be that in late-life, the combination of multiple vascular risk factors, rather than hypertension alone, influences dementia risk.

Individuals who develop AD have a greater rise in BP from mid-life to late-life and a greater decrease in BP in the years before dementia diagnosis.[59,60] This same pattern is comparable to investigations of brain volume, which shows that for individuals with a history of mid-life hypertension, lower late-life BP is associated with smaller medial temporal lobe structures, including hippocampi, than any other pattern of blood pressure change.[61,62] In studies with shorter follow-up periods, a general association between higher blood pressure and greater atrophic changes are observed.[63,64] Interestingly, this deleterious pattern

of blood pressure described above is comparable to cognitive findings discussed previously, as both high and low BP in late life can be associated with worse cognitive outcomes.[52] It is likely that those with low BP and poor cognitive outcomes will later be diagnosed with AD.

There is considerable debate concerning the way changes in BP influence the pathogenesis of AD. One theory that has gained attention recently involves disruption to autoregulatory processes. The brain is dependent on a constant rate of cerebral blood flow. One process by which it protects from ischemic damage is through autoregulation, whereby the natural fluctuations in arterial pressure are corrected by relaxation and constriction of arteries.[65] In AD research, it is understood that prolonged hypertension disrupts cerebrovascular autoregulation so that higher perfusion pressures are necessary to maintain stable cerebral perfusion. The brain is then susceptible to the deleterious effects of ischemia once blood pressure drops in older age, as autoregulatory mechanisms fail to compensate for this change[66] causing vascular insufficiency and ischemia in vulnerable brain areas such as periventricular regions, which are supplied by end arteries.[67] Supporting evidence demonstrates that those who developed AD dementia had more extensive white matter lesions later in life and higher blood pressure in mid-life.[60] In addition, degree of periventricular white matter damage[68] is associated with the degree of autoregulation dysfunction.[69] These ischemic lesions appear to interact with AD pathology to enhance the manifestation of dementia.[70]

Another way the brain regulates cerebral blood flow is through functional hyperemia, diverting cerebral blood flow to areas with increased neural activity[65] and controlling clearance of metabolic by-products to maintain homeostasis of the cerebral microenvironment.[71] The downstream effects of hypertension cause failure of this mechanism to clear toxic amyloid-β deposits during synaptic activity.[72] This leads to amyloid-β accumulation in the brain and blood vessels, a condition termed cerebral amyloid angiopathy (CAA). The degree of either amyloid-β burden or CAA is predictive of cognitive impairment in AD.[73,74]

Antihypertensive Therapies

The effect of blood pressure reduction medications on cognition is still debated. Nevertheless, many randomized control studies have found that the use of antihypertensives is protective for cognitive impairment.[75,76] Antihypertensives are especially linked to improved or preserved executive function,[75] processing speed,[76] and memory.[77,78] Treatment of hypertension is also thought to lower the incidence of AD,[79-81] and a postmortem study found that brains of individuals using hypertensive medications had less AD-related neuropathology than normotensive subjects,[82] while the Honolulu Asia Aging Study found that use of antihypertensives lowered risk for hippocampal atrophy.[83] Mouse models have demonstrated that antihypertensives can facilitate amyloid clearance across the blood-brain barrier.[84] These findings provide support for the role of hypertension in cognitive impairment as well as the pathogenesis of AD.

On the other hand, many investigations have not found an effect of blood pressure treatment on cognition or incident dementia.[85-87] A systematic review of randomized, double-blind placebo-controlled studies of participants with no history of cerebrovascular disease found no clear evidence for the effectiveness of antihypertensives.[88] However, this may partly be due to methodological limitations. Namely, the average duration of follow-up was a short 3.3 years and ages of participants ranged between 60 and 89 years. Current evidence suggests that BP treatment for at least 12 years[89] and for people aged <75 years[80] are more likely to be efficacious. This is consistent with prolonged exposure to hypertension in mid-life being associated with cognitive decline, brain atrophy, and white matter lesions. In addition, the effectiveness of antihypertensives is likely dependent on the type of treatment used, as a recent systematic review found that angiotensin II receptor blockers were the most effective for preserving cognitive function, and especially memory, in older adults.[90] Therefore, additional longitudinal investigations with younger populations are required to assess the long-term effectiveness of antihypertensives on cognition and dementia.

Conclusion

Effective treatment for hypertension may be important for the preservation of cognition and brain health. Mid-life hypertension is associated with worse cognitive outcomes, particularly in the areas of executive function and processing speed. Mid-life hypertension is also associated with higher incidence of Alzheimer's disease later in life. Two mechanisms by which hypertension is thought to influence the pathogenesis of AD involve disruption to autoregulatory processes and poor clearance of amyloid deposits. While the effect of late-life hypertension on cognition and incidence of Alzheimer's disease is less clear, there is some evidence that low BP in late-life is also associated with cognitive impairment and the development of AD, but this requires further investigation. Research on the use of antihypertensive medications partially supports a causal relationship between mid-life hypertension and worse cognition, but variable methodologies, short follow-up periods, and inclusion of older participants complicate findings.

Greater attention needs to be given to the effect of hypertension in specific cognitive areas, using rigorous and consistent neuropsychological tools, particularly in the areas of attention, working memory, language and visuospatial skills, which are scarcely investigated, and can often underpin memory performance. Future late-life studies should include proxy measures of duration of exposure to hypertension (such as PP) to reduce variability.

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Review Article

Blood Pressure, Left Ventricular Hypertrophy, and Congestive Heart Failure: A Continuum

Edward S. Barin[1], Alberto Avolio[2]

[1]MQ Health Cardiology, Faculty of Medicine, Health and Human Sciences, Macquarie University, [2]Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University

Abstract

The left ventricular hypertrophy (LVH) predicts adverse outcomes in hypertension. However, it is a crude and imprecise index of risk occurring late in the evolution of complicated hypertension. Heart failure (HF) is a major complication of hypertension, but its onset and syndromes are heterogeneous, and clinical definitions and risk thresholds are imprecise. Once LVH occurs, the window to the development of HF has opened. Imaging techniques may provide early insights into the structural basis of HF and track ventricular remodeling. Ventricular-arterial coupling analysis techniques provide an added opportunity to understand how HF evolves within this window, and so inform tailored management of hypertension and adverse LV loading (hydraulic and myocyte afterload) conditions in the continuum from LVH to overt HF.

Key words: Arterial hemodynamics, arterial stiffness, heart failure, hypertension, left ventricular hypertrophy, ventricular-arterial coupling

Brachial Cuff Blood Pressure Provides Limited Insight into Heart Failure Mechanisms

Elevated blood pressure (BP) relates to long-term prognosis including the development of heart failure (HF),[1] and its control will effectively prevent HF.[2] In addition to absolute systolic and diastolic pressures, recording widened pulse pressure, patterns of variability, ambulatory BP phenotypes, and even non-linear patterns of pressure values provide mechanistic insights into the pathophysiology of complicated hypertension. Nonetheless, the brachial cuff BP can have limited value in informing the development of the left ventricular hypertrophy (LVH) and complex evolution of HF later in hypertension. HF is not always heralded by the presence of LVH despite the presence of impaired diastolic function.[3] Structural remodeling, which follows treatment of hypertension or HF, may occur within the myocardium as well as in large conduit arteries,[4] with limited structural and functional information provided by brachial cuff measurements.

Central aortic BP also relates to prognosis, ventricular remodeling, and complications of hypertension.[5] Its effects in hypertension can be seen through the differential influence of medications or heart rate.[6] Due to the heart rate dependence of pulse amplification between the aorta and brachial artery,[7] beta-blockers have been shown to have a reduced effect on regression of LVH compared to other antihypertensive agents for a similar decrease in brachial systolic pressure.[8,9] Being a more proximate measure of the ventricular-arterial (V-A) coupling interface, it may more closely reflect LV loading conditions; however, large cohort studies are awaited to establish the clinical value of central aortic pressure in treatment and management of hypertension and associated cardiac complications.[10]

The definition and onset detection of HF, which is a clinical syndrome, remains multifaceted[11] and cannot be evaluated by simply recording arterial pressures. Even though hypertension is a risk factor for the development of HF, a rise in BP accompanies clinical improvement and predicts a better prognosis in HF.[12] Despite the increased understanding of various phenotypes of hypertension,[13,14] it remains unclear which are the best parameters obtained from a 24 h ambulatory BP recording,[15] for example, which influence or promote LVH and predict the development of HF.

Address for correspondence:
Edward S. Barin, MQ Health Cardiology, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW 2109, Australia. E-mail: edward.barin@mqhealth.org.au

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Left Ventricular Hypertrophy is a Maladaptive Response

LVH is a well-defined structural biomarker for increased risk in hypertension, in particular for the development of HF.[16] Once HF occurs, it presages a poorer clinical outcome. Targeting LVH is appropriate and effective in hypertension.[8] It is useful to consider the finding of LVH as representing a failing heart, evidenced by deranged neurohumoral, microcirculatory, and inflammatory biomarkers which are recognized hallmarks of HF.[17]

Techniques such as cardiac magnetic resonance imaging, echocardiography, and positron emission tomography in LVH may show significant abnormalities consistent with myocardial dysfunction, which are not accompanied by symptoms.[18] The use of arterial and pulse wave analysis techniques[19] provides a further opportunity for HF to be more clearly understood and managed much earlier along the pathophysiologic continuum, as hypertension evolves to complicated forms.

"LV remodeling," a term used to describe structural heart changes without hypertrophy, may be an earlier marker for abnormal myocardial function which may warrant intervention.[20] Although LVH or remodeling may only be crude indicators of impaired LV performance, they mark prominent red flags along the risk continuum.

Assessing Ventricular-Arterial (V-A) Dynamics in Understanding HF

Assessing V-A coupling using various modalities provides more detailed understanding of mechanisms of HF and other cardiovascular disease. V-A coupling has also been proposed as a means to manage a variety of cardiovascular syndromes including HF,[21] providing insights into pathophysiology, energetics, fibrosis, and remodeling.

V-A coupling reflects the fundamental notion that the ventricle, aortic valve, aorta, and peripheral arteries are separate organs in series. Ventricular stroke volume affects arterial performance, and dynamic arterial characteristics affect ventricular function. BP is the result of flow generated by the heart meeting the resistance of the arterial tree. The development of LVH and HF (either HF with reduced ejection fraction [HFrEF] or HF with preserved ejection fraction [HFpEF]) is a result of the maladaptive interaction of the heart and the arterial tree.[22]

The "gold standard" technique of measuring ventricular performance is based on pressure-volume loop relationships within the ventricular chamber, which is load independent. This uses the ratio of effective arterial elastance (EA) to LV end-systolic elastance (EES).[23] However, this technique does not take into account the pulsatile characteristics of V-A coupling nor does it impart any information about the myocardium itself. It appears to be of limited value in assessing HFpEF. This has led to recent calls to include comprehensive measures of pulsatile arterial dynamics in assessing V-A coupling.[24] This seems to be useful in HFpEF, which happens to be the earliest manifestation of HF in hypertension.

Various hemodynamic modalities available to assess V-A coupling include pulse wave velocity (PWV) and reflection analyses, wave intensity analysis, wave power analysis, global longitudinal strain (GLS) and tissue Doppler echocardiography, measurement of characteristic impedance of the proximal aorta, and obtaining PWV to GLS ratios.[17,24,25] Fibrosis, inflammation, and oxidative stress are common biochemical pathways linking impaired V-A function.[26] Their direct evaluation requires detailed techniques which are not yet widely available in routine clinical use but can be inferred by current V-A modalities.

Arterial load consists of steady and pulsatile components. Total peripheral resistance is the measure of the *steady* component and depends on microvascular properties such as stiffness and reflectivity. The *pulsatile* component of LV afterload is influenced by the elastic properties of conduit vessels, which includes the aorta and distal muscular arteries, and wave propagation phenomena, including intensity and timing of peripheral wave reflection.[24] Pulsatile LV load may then be measured by the characteristic impedance of the proximal aorta, the magnitude and timing of wave reflections, and the total arterial compliance.

Furthermore, LV afterload should be distinguished from myocardial afterload. LV afterload is defined as the hydraulic load imposed on the LV by arterial pressure, and myocardial afterload is the wall stress imposed on myocytes to generate fiber shortening.[27] It is now understood that complex patterns of LV afterload and wall stress evolve as patients develop the syndrome of heart failure.[28-30] Carotid to femoral pulse wave velocity (PWV), aortic characteristic impedance, and the magnitude and timing of wave reflections during systole summate the impact of arterial load on LV function throughout the cardiac cycle, linked in turn to clinical syndromes and cardiovascular events.[21,27,31]

Dividing myocardial dysfunction syndromes into HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) by arbitrary cutoff values belie the variations and complexities of loading and structural conditions which provoke HF at the V-A interface, as well as the varied influence of neurohumoral, cellular, and biochemical alterations.[32]

While imaging techniques such as echocardiography, cardiac magnetic resonance, and isotopic techniques provide valuable information regarding structural changes and clinical risk in HF from hypertension,[33] novel techniques extending their use in assessing V-A coupling have emerged and now may also be applied to tailor treatment in heart failure syndromes.[23]

In HFpEF, arterial waveform indices (which are measures of pulsatile function) have been shown to match the ability of echocardiographic tissue Doppler parameters in establishing the diagnosis.[31] A recent study described the utility of tailoring heart failure therapy by measuring and adjusting aortic pulsatility in HFrEF[34] employing radial applanation tonometry to estimate the central aortic pressure. This is based on the idea that the true hydraulic load of a failing LV occurs at the level of

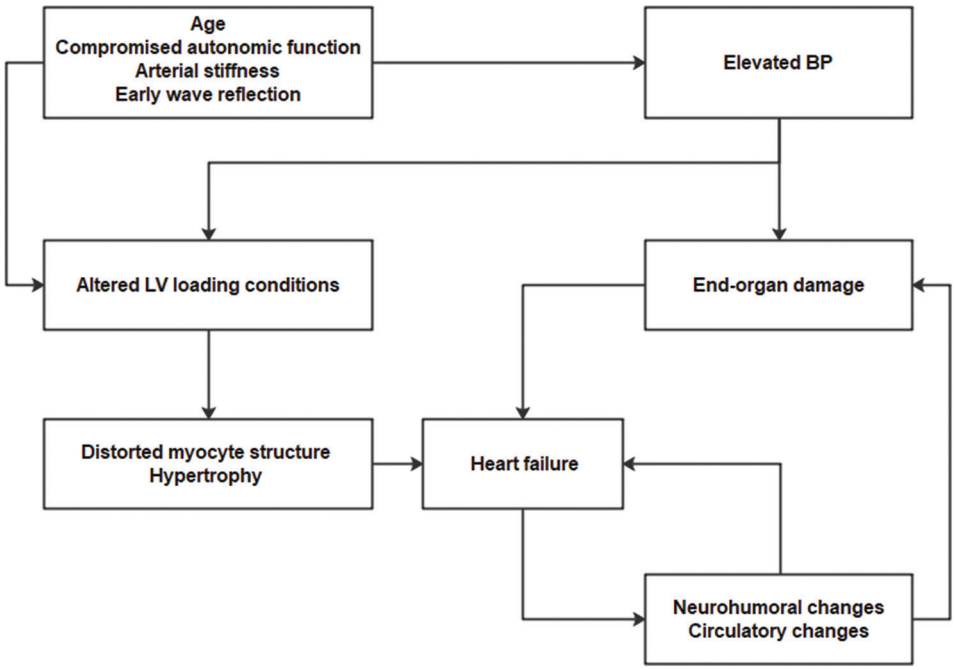

Figure 1: The continuum pathway for blood pressure, left ventricular hypertrophy, and heart failure

the central aorta and cannot be strictly assessed by peripheral BP cuff measurements. However, in HFrEF, it has been shown that effective treatment of HF with angiotensin receptor blockade and neprilysin inhibition is not associated with remodeling of the proximal aorta, as measured by applanation tonometry and echocardiography.[35]

Conclusions

As an adverse adaptation in hypertension, LVH may precede the clinical syndrome of HF, but is poorly predicted by brachial cuff pressure alone. Central aortic pressure may be a better predictor of the left ventricular hypertrophy and reflect ventricular loading conditions.

More refined assessment of arterial load at the V-A interface has the potential to translate into more effective and individualized management of HF and adds to the value of imaging and biomarker techniques.

Elevated BP initiates the progression from LV remodeling to failure through a process involving altered LV loading conditions, distorted myocyte structure or hypertrophy, neurohumoral, and circulatory changes [Figure 1]. Recognizing this continuum will enable the clinician to supplement brachial pressure readings with myocardial imaging techniques and newer modalities of dynamic arterial analysis for assessing severity and prognosis in hypertension.

The challenge is to find the best way to bring these novel techniques to the bedside in the least complex way.

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Review Article

Blood Pressure Measurement Methodologies: Present Status and Future Prospects

Mark Butlin[1], Isabella Tan[1], James Cox[1], Fatemeh Shirbani[1], Karen C. Peebles[2], Junli Zuo[1,3,4], Alberto P. Avolio[1]

[1]Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia, [2]Department of Health Professions, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia, [3]Department of Hypertension, Ruijin Hospital North, Shanghai Jiaotong School of Medicine, Shanghai, China, [4]Department of Geriatrics, Ruijin Hospital North, Shanghai Jiaotong School of Medicine, Shanghai, China

Abstract

The seminal advances of Riva Rocci made by introducing a brachial cuff with peripheral palpation, and of Korotkoff by auscultation of sounds associated with changes in arterial blood flow due to cuff pressure, have been the lynchpin of non-invasive measurement of blood pressure. Non-invasive quantification of blood pressure of the brachial artery has utility in risk prediction and hypertension management, despite inherent inaccuracies in the method, that an individual does not have a single blood pressure but a variability in blood pressure reflecting diurnal rhythm and physiological responses to daily life, and that brachial artery pressure may not be the precise pressure seen by the heart, kidney, and brain. This article discusses the inherent limitations of blood pressure measurement, the site of measurement, and currently largely ignored technical issues such as traceable calibration of blood pressure devices. The improvements in temporal resolution of blood pressure measurement with cuffless measurement of blood pressure are highlighted with the challenges of these techniques discussed. The future challenges are to obtain reliable continuous blood pressure measurements to quantify risk not only on blood pressure values but also on the entire beat-to-beat profile during daily living.

Key words: Aortic blood pressure, arterial pressure, brachial blood pressure, central blood pressure, cuffless blood pressure, measurement

Introduction

Arterial blood pressure, one of the most important clinical parameters, is also one that presents formidable challenges to obtain accurate non-invasive measurements. All non-invasive blood pressure quantification methods do not measure the actual blood pressure in arteries, but rely on factors that correlate with blood pressure to arrive at an estimate that has some correlation with, but is not equivalent to, the actual blood pressure. Blood pressure is also difficult to quantify as a single quantity as it is highly variable from day-to-day, throughout the day, minute-to-minute, and even from one cardiac cycle to the next. It is also difficult to quantify as arterial pressure varies throughout the vasculature such that there is no single blood pressure across the body at any 1 time. Despite these limitations, the current non-invasive methods of quantification of brachial artery systolic and diastolic blood pressure are highly useful in prediction of cardiovascular events and mortality.[1] As a result, non-invasive brachial artery systolic and diastolic pressure are the main measures guiding clinical decision on administration of antihypertensive therapy.

The following is a discussion on the current invasive and non-invasive methods of blood pressure quantification with a look toward the future of techniques in blood pressure quantification including continuous and cuffless approaches. It also covers issues that need to be addressed in quantifying blood pressure such as traceable calibration and addressing blood pressure variability.

Address for correspondence:
Mark Butlin, Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia. Phone: +61-2-9850-2888. E-mail: mark.butlin@mq.edu.au

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Invasive Blood Pressure Measurement

The first reported instance of the direct measurement of blood pressure was by Reverend Stephen Hales[2] in 1733, who observed the height of blood in a pipe inserted into the left crural artery of a conscious 14-year-old mare, tied down on her back [Figure 1]. The blood "rose in the tube 8 ft 3 in [185 mmHg] perpendicular above the level of the left ventricle of the heart" and did "rise and fall at and after each pulse 2, 3, or 4 in [4–7 mmHg].[2]" This was a direct measurement of pressure in the large arteries in relation to the reference level of atmospheric pressure and did not involve any principle of transduction with associated instrumentation and physical variables. All other reported blood pressures are either in some way transduced through a secondary surrogate measurement, as in the case of invasive blood pressure measurement, or estimated, as in the case of non-invasive measurement.

In humans, the closest measurement of direct blood pressure is obtained by placing a solid-state pressure sensor-tipped catheter in contact with the blood itself within the artery. With changing pressure, the transducer (usually a strain gauge) changes resistance (with the signal being an output voltage). Accuracy relies on reliable calibration of the transducer relating that change in resistance to a change in pressure. More common in the acute care scenario is the placement of a saline-filled line within the artery, and which is externalized to a pressure transducer and referenced to atmospheric pressure. Accuracy in this method also relies on reliable calibration of the transducer. Error can also be introduced by placement of the transducer as movement of the transducer upward or downward in relation to the artery will change the hydrostatic pressure within the fluid line, and thus the pressure measured. Even with correct calibration, errors can be introduced by the length of tubing between the signal (blood stream) and the pressure transducer, the compliance of the tubing, and/or microbubbles in the saline, all of which all have the potential to alter the frequency response of the manometer system as a whole. A survey of 300 blood pressure measurements using a fluid line found 31% were underdamped, resulting in an overestimation of systolic blood pressure (compared to invasive solid-state pressure catheter) of 28 ± 16 mmHg and underestimation of diastolic blood pressure of −2 ± 11 mmHg.[3]

Non-invasive brachial blood pressure estimation

Any quantification of blood pressure that is not invasive is estimation, by definition. All non-invasive methods use signals that can be correlated, with varying accuracy, to blood pressure. Non-invasive methods do not provide an actual measurement of blood pressure.

The *uncalibrated* pressure pulse waveform (sphygmography) was first transduced by Marey[4] and Mahomed.[5] The first non-invasive blood pressure estimation was reported in 1896 by Riva Rocci.[6,7] He reported using a pressurized cuff wrapped around the upper arm to occlude the brachial artery, then deflating the cuff and associating the cuff pressure with systolic pressure at the first appearance of the pulse palpated distal to the cuff. In 1905, Korotkoff extended this technique by application of the stethoscope to the brachial artery distal to the cuff to identify characteristic sounds associated with systolic and diastolic pressure.[8]

These methods of blood pressure estimation were not proposed because of their absolute correlation with invasive measurement of brachial artery blood pressure. Rather, the methods rely on logical assumptions that underlie all cuff-based blood pressure estimates:

1. That the pressure in the cuff is the pressure applied to the brachial artery.
2. That cuff pressures above systolic pressure collapse the artery and occlude blood flow.
3. That cuff pressure at, or, marginally below systolic pressure allows blood to intermittently flow in the artery, giving rise to characteristic sounds and a palpable pulse distal to the cuff.
4. That cuff pressure at, or marginally below diastolic blood pressure is reliably associated with the disappearance of sounds or characteristic muffling of the sounds.

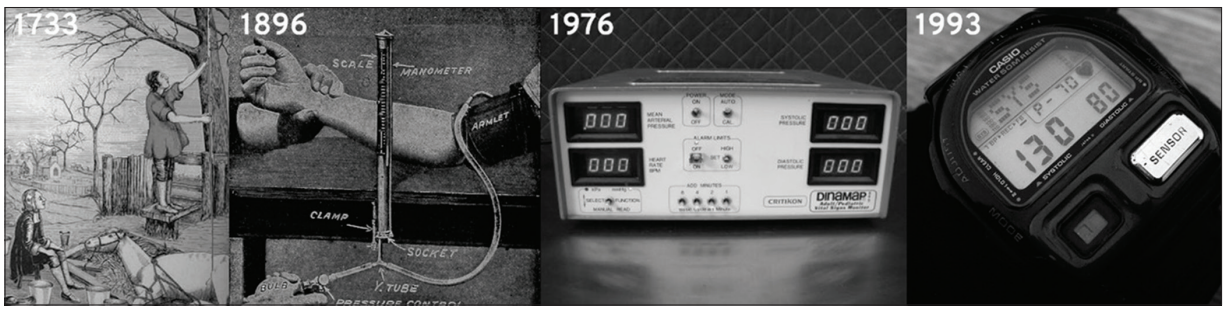

Figure 1: The evolution of blood pressure measurement. (1733) Adapted from Cuzzort's impression (printed in the Medical Times, 1944)[57] of Stephen Hales and assistant measuring the blood pressure of a horse, here shown taken from the left crural artery as described by Stephen Hales (original shown taken from the left carotid artery). (1896) Riva Rocci's method (later auscultation as described by Korotkoff) of relating pulse related phenomenon to the pressure within a cuff around the upper arm.[58] (1976) The first commercial oscillometric blood pressure devices were the Device for Indirect Non-invasive Automatic Mean Arterial Pressure (DINAMAP) 825. Model 845XT shown here. (1993) The first commercial device to measure blood pressure without a cuff was the Casio BP-100

Although the technique of brachial artery auscultation is the reference standard for non-invasive quantification of blood pressure, Korotkoff himself saw the limitations and difficulty of quantifying blood pressure, captured in the title of his seminal work proposing auscultation, "A *contribution to the problem* of methods for the determination of blood pressure."[8] There are varying theories as to the source of the Korotkoff sounds, especially during the supposed systolic pressure.[9] The more common theory is that the first Korotkoff sound is due to arterial wall movement when blood begins to flow through the previously occluded artery, and subsequent Korotkoff sounds are due to fluid (blood) turbulence.[9]

The characteristic sounds, first described by Korotkoff, do not correspond exactly with the systolic and diastolic pressure within the brachial artery. Systolic pressure is underestimated, on average, by 6 mmHg (95% CI −8 to −4 mmHg) and diastolic pressure overestimated by 6 mmHg (95% CI 4–8 mmHg).[10] This discordance between invasively measured blood pressure and non-invasively estimated blood pressure is not constant, varying greatly between people and within the individual under different physiological conditions.[11]

The reasons for this disparity between measured blood pressure and non-invasively estimated blood pressure are unknown but will relate to errors in the previously outlined assumptions. Modeling suggests that physiological differences in arterial wall properties can alter pressure estimates using a brachial cuff by up to 20%[12] due to transmission of the cuff pressure to collapse and occlude the artery. The transmission of cuff pressure to the artery is one of the potential causes for the historical inaccuracy of wrist cuff blood pressure devices with the radial artery being bordered by the ulna and radius bones. It has been suggested that accurate positioning of the cuff and scaling the cuff width to an individual's wrist diameter may overcome these problems.[13]

Due to ease of use, oscillometry is a highly popular method of non-invasive quantification of brachial blood pressure. The underlying principle is identical to that proposed by Riva Rocci, but relies on detection of small oscillations in the cuff pressure due to volumetric changes in the brachial artery[14] and association of changes in the amplitude or shape of those small oscillations with the systolic and diastolic pressure. The point of maximum oscillations will occur when the arterial wall is unloaded, that is, when the transmural pressure is zero and the cuff pressure corresponds to the mean arterial pressure. This has been demonstrated in an idealized model[15] but suffers from the same limitations as the auscultatory technique insofar that it assumes the cuff pressure is entirely and uniformly transmitted to the artery.

Relying on an algorithm (usually proprietary and unreleased by the device company, but sometimes published[16]) to estimate systolic and diastolic pressure, the technique has the advantage that it can be automated and the measurement itself is user-independent. However, the timing of measurements, positioning of the patient, and use of the automated device is not user-independent and is still subject to errors. A recent study evaluating medical students' ability to take blood pressure with an automated device found that on average less than 40% of the criteria for good blood pressure measurement were met.[17] Only 1 of the 159 students tested was able to take a blood pressure measurement correctly and according to guidelines.[17]

At the time of invention of oscillometric blood pressure devices, the use of auscultation for quantification of blood pressure was ubiquitous and long-standing clinical guidelines[18] using auscultation values of blood pressure were in place. Despite auscultation not accurately estimating invasive blood pressure, oscillometric devices were, and still are, validated against auscultation estimation of blood pressure so that the blood pressure values provided are consistent with those in guidelines. However, this also means that the oscillometric technique has the same error in estimating invasive blood pressure as auscultation does. The agreement between oscillometric and auscultation itself is highly variable, with a greater than 10 mmHg difference between oscillometric quantified blood pressure and auscultation quantified blood pressure in 15% of measurements for systolic blood pressure and 6% of measurements for diastolic blood pressure.[19]

Efforts were made in the last century to standardize validation of blood pressure quantification against auscultatory quantification of blood pressure measurement. Several guidelines on how to validate blood pressure devices were created.[20-22] All were largely similar and more recently an effort was announced[23] to consolidate the several guidelines into a single standard, ISO 81060-2:2018.[24] Not all blood pressure devices sold have been validated, and the Lancet Commission on Hypertension[25] has recommended that government regulatory authorities adopt a requirement for blood pressure devices to be validated.[26]

Validation studies are peer reviewed. However, these validation studies usually occur outside of the international measurement framework and in laboratories that do not have accreditation, and thus are not privy to the same scrutiny that is standard in other industries, sciences, and in retail,[27] with issues as fundamental as traceable calibration of references devices not addressed.

Validation occurs within the limits of variability of the technique. There is variability between oscillometric and auscultatory quantification of blood pressure.[19] In part, this is likely due to auscultation being highly variable in reliably quantifying brachial blood pressure as measured invasively.[11] The disparity between oscillometric and auscultation measurement may therefore be a result of the limitations of accuracy of auscultation for blood pressure quantification.

Calibration

Regardless of the method used to estimate blood pressure, pressure needs to be transduced. In the case of cuff techniques, it is the pressure of the air within the cuff that is transduced. Conventionally, this was done by coupling the bladder of air with a column of mercury, with the height of mercury within

that column giving the pressure. The high density of mercury as compared to water allows for the pressure to be read in an easy-to-handle device that can sit on a desk. This gave rise to the expression of blood pressure in mmHg rather than in *Système International* (SI) units (also accepting that SI units were proposed in the 20th century, after the advent of blood pressure measurement).

Mercury columns, often perceived as ground truth for pressure measurement, can deteriorate with age and give erroneous readings. In a 2002 inspection of mercury sphygmomanometers, 28% had an error of 4 mmHg or more and 7% an error of 6 mmHg or more.[28] The impact of such systematic errors is substantial. It is estimated that systematic errors due to non-calibrated devices are responsible for 28% of undetected hypertensive cases and 31% of false diagnoses of hypertension.[29]

Due to issues of safety, there is now a movement away from mercury devices. In general, a piezoelectric sensor is coupled with the air in the brachial cuff (non-invasive measurement) or a fluid line internalized to the artery (invasive measurement). When released from the factory, this sensor has been calibrated to provide an accurate transduction of pressure. With time, the sensitivity of the sensor can change, and recalibration is required. Annual calibration checks are recommended with the calibration check being performed with traceable measurement (documented, unbroken chain through national measurement institutes to the international standard) by an accredited laboratory.[30,31] This does not often occur. Of 271 general practices surveyed across England and Wales, one (0.4%) regularly calibrated their blood pressure devices and 34 (12.5%) had at some point had their blood pressure machines calibrated by a drug company representative.[32]

Site of blood pressure measurement

Historically, non-invasive blood pressure has been taken as an approximation of brachial artery blood pressure as a matter of convenience and feasibility. There is no reason that brachial artery blood pressure is more important than blood pressure elsewhere in the body. It could be argued that the arterial pressure near the heart or in the brain is of greater consequence as these are sites of cardiovascular events. However, the main arteries of the heart and brain are not superficial and external pressure cannot be applied to them in the same way that it can in the brachial artery. Techniques for non-invasively estimating pressure in the aorta is addressed in this issue[33], where a transfer function applied to the peripheral arterial pressure waveform combined with cuff-based measurement of brachial blood pressure calculates the aortic pressure.[34,35]

The site of blood pressure measurement is also important within brachial blood pressure measurements alone, with there being reported differences in blood pressure between the two arms, and this interarm difference being associated with greater cardiovascular risk[36] and with cognitive decline.[37] Interarm blood pressure difference does not appear to be associated with asymmetry in arm geometry, suggesting that it is not an artefact due to differences in the transmission of the cuff pressure to the artery.[38] It may be that the interarm difference is an artefact due to pulse-to-pulse variability in blood pressure, with small differences in the timing of "simultaneous" blood pressure measurement in both arms resulting in a difference in estimated blood pressure. This theory has circumstantial evidence in that the interarm difference is not reproducible within individuals[39], yet is associated with end organ damage.[36,37]

Blood pressure variability: What is someone's blood pressure?

Systemic arterial blood pressure changes acutely. Blood pressure has a diurnal variability, variability with different life activities and stressors, and variability from one pulse to the next. Even if blood pressure can be measured accurately, and it is decided at which vascular site blood pressure is most important, it is still impossible to state that someone's blood pressure is a set number due to the inherent and critical variability in blood pressure.

It is recommended in clinical evaluation of blood pressure that the blood pressure outside of the clinic be assessed either through use of a home blood pressure monitor or an ambulatory blood pressure monitor worn for a 24-h period.[40] There is much controversy on the utility of visit-to-visit in-clinic blood pressure variability, night-time or daytime blood pressure, morning rise in blood pressure, and ambulatory variability in blood pressure in clinical assessment of risk and decision making in treating patients.[41] With a greater number of blood pressure devices uploading patient data to internet-held databases, and with the increase in consumer-based blood pressure devices, the aggregation of data for individual patients suggests that a blood pressure profile, rather than a single blood pressure, is becoming increasingly available to the clinician. How to use that data in clinical assessment and treatment will require research-based consensus.

Continuous quantification of blood pressure

Continuous measurement of blood pressure, in terms of visualization of the continuous pressure pulse waveform, is usually only in the realm of research and has not found its way into clinical applications. In critical care scenarios such as anesthesia monitoring and intensive care, a near-continuous blood pressure will be provided in the form of systolic and diastolic pressure analyzed from an arterial line, updated pulse-by-pulse or at frequent intervals.

The only method for continuous blood pressure quantification is using an invasive approach. Servo-nulling of finger blood volume through changes in a pressure in a cuff around the finger has been investigated as a non-invasive approach to continuous blood pressure monitoring.[42] It has been demonstrated to be relatively accurate in tracking changes in blood pressure, with an average offset from intra-arterial blood pressure of between 5 and 10 mmHg,[43] but with significant between-individual variability.[44] While useful in specifically designed research studies, the technique has not found value in critical care

monitoring due to limitations in accuracy.[45] The technique has found value in autonomic function testing, where quantification of acute blood pressure changes provides valuable information but does not warrant the risks and discomfort associated with an invasive blood pressure line.[46]

Blood pressure estimation without a cuff

Oscillometric brachial cuff measurement is used to quantify blood pressure in the ambulatory scenario (when moving about) and during sleep. However, the technique has limitations in this setting being that: The participant still needs to be relatively still during the measurement; the measurement is intermittent (once over 15–30 min), not continuous; measurement during the night disturbs sleep resulting in a blood pressure measurement that may not be representative of nocturnal blood pressure; the wearing of the cuff and device throughout a 24-h period is uncomfortable.

These limitations could be addressed by estimation of blood pressure without a cuff. At present, devices designed to measure blood pressure without a cuff use either characteristics of an uncalibrated pressure waveform, or the pulse transit time to estimate blood pressure. As blood pressure increases, the arterial pressure waveform shape will change[47] and the arteries will become stiffer, decreasing pulse transit time across a fixed distance.[48] Such devices rely on a defined relationship between the measured parameter and blood pressure to estimate blood pressure. It has been established that this relationship differs between individuals and a fixed parameter-pressure relationship across the population is unlikely.[49,50] For example, it is known that the relationship between pulse transit time and blood pressure has greater sensitivity for normotensive individuals than hypertensive individuals.[51,52] The parameters used to quantify blood pressure without a cuff are even further removed from blood pressure than the non-invasive cuff-based approaches. It is therefore unlikely that the accuracy will be an improvement upon cuff-based devices.

Often the site of measurement of cuffless blood pressure devices is not the brachial artery. It must be considered whether the local vascular changes that are being interrogated are representative of blood pressure changes in the brachial artery, if it is the brachial artery blood pressure reference values that are to be estimated.

It should also be considered that if only one parameter is being measured (e.g., a single waveform feature or the pulse transit time) and both systolic and diastolic blood pressure are reported, how two parameters are estimated from one parameter. While there is some correlation between systolic and diastolic pressure, one cannot be predicted from the other. It follows that cuffless blood pressure devices reporting both systolic and diastolic pressure suffer from variability in accuracy or require further correlative inputs to predict both systolic and diastolic pressure with some accuracy.

The Food and Drug Administration (FDA) recently approved medical style devices marketed directly to the consumer (Apple Watch and AliveCor KardiaBand atrial fibrillation detection) as "*de novo*," that is, not requiring equivalence to medical devices not marketed to consumers. In theory, this also opens the pathway for cuffless blood pressure devices marketed direct to consumers with differing criteria around accuracy to that of medical devices. This is important in considering the utility of consumer cuffless blood pressure in health decision making both on an individual level and at a population level using aggregated data. Separate to the FDA, the Institute of Electrical and Electronics Engineers have developed a standard for validation of cuffless blood pressure devices.[53] The International Organization for Standardization is currently preparing a standard as well.[54]

Improvements in estimating true blood pressure

The seminal advances of Scipione Riva Rocci made by introducing a brachial cuff with peripheral palpation, and of Nikolai Korotkoff by auscultation of sounds associated with changes in arterial blood flow due to cuff pressure, have been the lynchpin of non-invasive measurement of blood pressure. It was known from the very beginning that these techniques rely on the integrity of all components of the system to obtain a reliable estimate of arterial blood pressure by measuring cuff pressure. It is important to understand, the errors are not due to the actual measurement of pressure, that is, the manometric value of cuff pressure. This can be measured with high accuracy, the most accurate being the height of a column of fluid open to the atmosphere, as it is totally devoid of any process of transduction. The problem is the fiducial relationship of cuff pressure with arterial pressure. Indeed, the very first improvement that was required to the Riva Rocci sphygmomanometer was to change the size of the cuff – the original cuff was not wide enough for uniform collapse of the brachial artery under the cuff.

Although the basis of sphygmomanometry has not changed, there have been gradual improvements in cuff and internal bladder design so as to accommodate variable anatomy of the upper arm, use of microphones or flow sensing techniques, or even to visualize the Korotkoff sounds[55] to obtain fiducial points in the brachial cuff pressure that correspond to systolic and diastolic pressure. Improvements in the oscillometric technique have included optimizing parameters for curve fitting to the oscillogram to obtain reliable coefficients for models estimating systolic and diastolic pressure.[56]

Notwithstanding the many functional improvements made to the conventional brachial cuff measurement of blood pressure, the cuff pressure values generally tend to underestimate true intra-arterial systolic pressure. It is unlikely that any non-invasive technique will be able to obtain the true value of intra-arterial pressure with all measurements. However, it should be possible to design methodologies that will reduce the variability of the estimation so that true changes can be reliably estimated with achievable tolerances that are accepted by standards and regulatory agencies. Although, intermittent measurements of cuff-based methodologies have produced all the data on blood pressure for physiopathological associations of high blood

pressure and cardiovascular risk, the future challenges are to obtain reliable continuous blood pressure measurements so as to quantify risk not only on blood pressure values, but on the entire beat-to-beat profile during daily living.

Conclusions

It is undeniable that non-invasive quantification of blood pressure of the brachial artery has utility in risk prediction and hypertension management despite the inherent inaccuracies in the method compared to invasively measured blood pressure, and that brachial artery pressure may not be the precise pressure seen by the heart, kidney, and brain. Detailed guidelines exist around the validation of cuff-based blood pressure devices, and how to take measurements to obtain a seated resting value of blood pressure. More fundamental issues such as regular traceable calibration of devices, including in the laboratories performing validation studies, could be better addressed. Estimation of blood pressure without a cuff promises large gains in presenting a person's blood pressure profile, rather than the broad method of stating a person has a single average blood pressure at rest. However, given that cuffless estimation of blood pressure relies on correlative parameters, accuracy of both clinical and consumer market devices should be carefully considered in employing these devices in clinical decision making and in research studies relying on aggregated data.

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Review Article

Cerebral Microvascular Dysfunction and Clinical Considerations of Systemic Arterial Hypertension

Jenny Kim[1], Rowena Mobbs[2], Antonio Di Ieva[3]

[1]Department of Clinical Medicine, James Cook University, College of Medicine and Surgery, Mackay 4740, QLD, Australia, [2]Department of Clinical Medicine, Specialist Clinician Neurologist, Macquarie University Hospital, Sydney 2109, NSW, Australia, [3]Department of Clinical Medicine, Faculty of Medicine, Health and Human Sciences, Macquarie University and Macquarie Neurosurgery, Sydney 2109, NSW, Australia

Abstract

Hypertension is one of the most commonly diagnosed conditions in the general population. In 2017, the American College of Cardiology and American Heart Association lowered the threshold for hypertension diagnosis from 140 mmHg to 130 mmHg for systolic blood pressures. These new guidelines have brought into question the true prevalence of hypertension and overall risk of hypertensive complications. While the cardiovascular effects of hypertension have been a long-held concern, there is a growing awareness for the need to understand the extracardiac concerns of hypertension. Specifically, the brain and nervous system are vulnerable extracardiac targets of hypertensive damage. Hypertension is a well-known risk factor for ischemic and more so hemorrhagic stroke as well as cerebral small vessel disease (cSVD) including vascular dementia. However, hypertension may also have association to less-known neurological presentations which themselves may also pose risk for stroke and cSVD. This includes obstructive sleep apnea, posterior reversible encephalopathy syndrome, and neurogenic hypertension. We aim to present an overview of the contemporary literature in regard to hypertension and clinical consideration as it applies to the cerebrovascular system.

Key words: Arterial hypertension, cerebrovascular, hypertension, neurology, neurosurgery

Introduction

For decades, arterial hypertension has been a well-established health burden, notably for cardiovascular complications such as ischemic heart disease (IHD). Known as the silent killer, extracardiac complications of hypertension have become a primary concern for preventative healthcare.[1] Ischemic and hemorrhagic stroke are archetypal examples that combined, have risen from fifth (1990) to third (2017) on the list of most prevalent causes of early death globally, after IHD and neonatal disorders.[2]

The global prevalence of hypertension has been predicted to rise from 972 million in 2000 to 1.56 billion by year 2025.[3] Current rates are already at an estimated 1.13 billion (2015).[4] In 2017, the American College of Cardiology and American Heart Association lowered systolic pressure thresholds that define hypertension, from 140 mmHg to 130 mmHg [Table 1].[5] This was in response to a randomized clinical trial data demonstrating that lower cardiovascular events and mortality rates are associated with a systolic pressure target of <120 mmHg.[6] These new diagnostic thresholds have been inconsistently implemented across clinical practice and research, making current prevalence predictions inaccurate and subsequent extracardiac consequences underestimated.[7]

However, there is a growing body of research and clinical knowledge of hypertension-associated pathophysiology and clinical outcomes. In addition, traditional borders segregating the roles and functions unique to each clinical specialty are becoming multidisciplinary. Thus, there is a growing need to have an up-to-date knowledge base of hypertension-associated pathologies as it relates to their specialty. In the context of neurology, this knowledge refers to the impact of hypertension

Address for correspondence:
Antonio Di Ieva, Suite 201, Level 2, 2 Technology Place, Macquarie University, NSW, 2109, Sydney, Australia.
E-mail: antonio.dileva@mq.edu.au

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Table 1: American Heart Association classification of BP in adults[5]

BP category	Unrevised BP thresholds (mmHg)		2017 revised BP thresholds (mmHg)	
	Systolic	Diastolic	Systolic	Diastolic
Normal	<130	<85	<120	<80
High normal	130–139	85–89	120–129	<80
Hypertension stage 1	140–159	90–99	130–139	80–89
Hypertension stage 2	160–179	100–109	≥140	≥90
Hypertensive crisis	>180	>110	>180	>120

BP: Blood pressure

to neurological presentations less known than cerebral small vessel disease (cSVD) and stroke.

This aim of this review is to provide an overview of the clinical impact of systemic arterial hypertension to microvascular brain pathophysiology by: (1) Outlining the pathophysiology of hypertension as it relates to clinical neurology, (2) summarizing the contemporary concerns and findings of arterial hypertension as it relates to the microvascular pathophysiology of neurological and neurosurgical presentations, and to (3) describe potential clinical recommendations and future direction for clinicians.

Literature Review Process

A literature review was conducted on Medline (Ovid) database on February 3, 2020, using the search terms, respective synonyms and MeSH headings: Neurology OR Neurosurgery AND hypertension AND microvascular. Full search criteria can be accessed in Appendix 1. Additional articles were identified perusing reference lists of included articles.

A total of 281 studies were found. For a broad scope, all non-animal English articles and reviews that examined arterial hypertension-associated pathology in neurological pathologies in the past 10 years (2011–2020) were included in this review.

For the limits of our aim, articles discussing hypertension only in association with cSVD or stroke were excluded. Application of the new hypertension thresholds in obstetric presentations is yet to be implemented, and thus peri-partum presentations including pre-eclampsia were excluded from the study. Due to differences in pathology and management, articles in pediatric settings were excluded. Articles discussing venous hypertension were excluded. Conference abstracts, case reports, non-English, animal, and opinion papers were excluded from the study.

Duplicates were removed and 275 articles screened. A total of 29 articles were chosen for review.

Cerebrovascular Autoregulation

The brain is a highly homeostatic dependent, and therefore vulnerable, organ, reliant on exquisite, autoregulatory control of cerebral perfusion, as measured by cerebral perfusion pressure (CPP):[8]

$$\text{CPP (i.e., MAP–ICP)} = \text{CBF} \times \text{CVR}$$

Autoregulation of CPP is a homeostatic process which involves real-time changes in cerebral vascular resistance (CVR) in a pattern inverse to the rate of cerebral blood flow (CBF). As such, it ensures that when the mean arterial pressure (MAP) of the systemic circulation increases, CVR inversely increases. Therefore, a constant CBF sufficient to the cerebral metabolic demands must be maintained despite wider systemic flow variation.

Up to 75% of initial CPP elevations is believed to be relieved by vasodilatory control of large cerebral arteries;[9] in effect, preventing the pulsatile arterial pressure from reaching small pial arteries and arterioles and penetrating arterioles, and thereby preserving the downstream microvasculature. The exact process and control of cerebral autoregulation are not completely understood. However, recent literature has emphasized it to be a more complex interplay between neurogenic, myogenic, as well as intrinsic microvascular metabolic and endothelial mediators.[10] This autoregulation can be visualized as a triphasic curve; the limits of effective autoregulation are within CPP of 50 and 150 mmHg in a supine normotensive patient.[9] However, in chronic hypertension, autoregulation sees a rightward shift (i.e., increasing the set point of regulated pressure range).[9] This shift is thought to be neuroprotective by chronic resistance against high blood pressure (BP) -induced damage to the downstream microcirculation. While the etiology is unconfirmed, it has been hypothesized as a blunting of baroreceptors in response to ongoing tangential arterial wall stress.[11]

Acute cerebral microvascular dysregulation

When the average systemic arterial pressures (i.e., MAP) causes CPP to surpass 150 mmHg, autoregulation is lost. Cerebrovascular resistance is fatigued and pial arteries and arterioles and penetrating arterioles receive unregulated pulsatile systemic flow. Specifically, MAP above 200 mmHg has been shown to cause irreversible cerebral damage.[12] The vasogenic theory instructs unregulated hyperperfusion to create an increased capillary hydrostatic pressure, subsequent capillary rupture, and breakdown of the blood–brain barrier. Secondary injury cascades involve intrinsic pro-inflammatory markers, mass effect, and downstream ischemia causing white matter damage. The outcome of ischemic injury is also anatomically variable; a richer sympathetic innervation to the anterior cerebral circulation (ACC) as opposed to the posterior cerebral circulation. This provides ACC more protection against slight BP elevations by increasing the upper limit of the cerebral autoregulation.[13]

Chronic cSVD and remodeling

cSVD is a collective term for pathological changes in the microvascular architecture; small arteries, arterioles, capillary beds, and small veins.[14] Usually asymptomatic, chronic hypertension causes microatheromatous structural changes to increase risk of acute presentations of ischemic stroke and intracerebral hemorrhage (ICH) as well as chronic cognitive decline. Chronic benign hypertension induces hyaline arteriolosclerosis, the thickening of the vessel wall due to replacement of intramural smooth muscle with fibrin and hyaline plasma materials (lipohyalinosis). In acute malignant hypertension, hyperplastic arteriolosclerosis occurs whereby a rapid resistance is attempted against sudden increase in intraluminal pressure through concentric "onion-skin" hyperplasia of intramural smooth muscle. Rarefaction, vascular pseudo-calcification and microaneurysm (<0.9 mm diameter) development in basal ganglia, thalamus, and pons are less recognized changes in response to poorly regulated BP.[15] Due to the inability to grossly visualize microvascular changes, secondary detection through magnetic resonance imaging (MRI) visual markers have been a commonly substituted tool. These markers include white matter hyperintensities (WMH, leukoaraiosis), lacunes, cerebral microbleeds, cerebral atrophy, and increased perivascular spaces.[14] Often, the early stages of cSVD are asymptomatic and may therefore be neglected. However, such illustrative changes provide an opportunity to discuss vascular processes and to educate patients with regard to modifiable risk factors. However, these are only predicative markers of chronic small vessel disease and are not diagnostic markers.

Posterior Reversible Encephalopathy Syndrome (PRES) and Microvascular Dysregulation

PRES is a rare phenomenon, characterized by an acute or subacute onset of global cerebral manifestations (i.e., seizures, visual disturbances, and nausea/vomiting).[16] Clinically, PRES forms a growing differential among neurological presentations, but is poorly understood.

PRES manifestations are commonly brought about within a matter of hours by a known trigger, most commonly an acute rise in BP. Occurring in up to 80% of presentations, systolic BP has been recorded to peak up to 170–190 mmHg.[17] As such, PRES has been commonly witnessed in groups with pre-existing risk of hypertension including; Guillain–Barre syndrome, illicit drug use, pre-eclampsia, and autoimmune/immunodeficient presentations. With no set diagnostic criteria, a clinicoradiological diagnosis through typical MRI findings of symmetrical cortical and/or subcortical edema in parieto-occipital regions that may "reverse" and disappear within a matter of weeks to months post onset.[18]

The pathophysiology underlying PRES is controversial and has been held attributable to the vasogenic theory.[17] The endovascular damage caused by pre-existing conditions in risk groups possibly lowering the thresholds for auto dysregulation and subsequent syndrome development. However, this theory is difficult to reconcile hypertensive PRES presentations. Furthermore, contemporary literature has shown atypical presentations of grey matter change and non-posterior circulation patterns including the temporal lobes, central deep white matter, basal ganglia, as well as anterior watershed areas.[19] In one retrospective study, 64.2% of patients presented with frontal white matter changes rather than posterior circulatory regions.[20]

Contemporary studies have also made efforts to conceptualize the possible pathophysiology for this prevalence within the medical oncology and transplant subspecialties.[21-24] The immunomodulation and pharmacological metabolic cascades in chemotherapy, in addition to fluid overload, have shown to provide possible theories to these anatomical patterns.[19] This includes the potent vasoconstriction and vasospasm or direct endothelial damage due to pro-inflammatory cytokines from specific pharmacology (e.g., cyclosporin), direct endothelial damage by pro-inflammatory mediators in patients with chemotherapy as well as increased endothelial permeability, and microthrombotic damage due to vascular endothelial growth factors, and T cell activation in organ transplant patients.[19,21-23] Overall, the contemporary theories postulate PRES as a primarily intrinsic endothelial dysfunction, whereas the reversible MRI markers are indicative of reversible endothelial damage rather than hypertensive ischemic damage. While this may explain the cause for PRES presentations in normotensive patients, further research is required to confirm these theories.

The absence of consensus diagnostic criteria has limited the literature to provide empirical data for the appropriate management of PRES. In addition to supportive management, contemporary literature has shown the rapid removal of a trigger to be associated with faster recovery and complications.[17] As such, the use of IV or sublingual anti-hypertensives in the acute setting has been proven effective.[25] While corticosteroids have been reported to precipitate as well as treat PRES, a retrospective study showed no significant association with vasogenic edema.[26] However, its therapeutic impact still requires further evidence.[17]

Sleep Disorders and cSVD

The literature has shown sleep disordered breathing disorders (SDBD) and sleep related movement disorders (SRMD) to have a bidirectional relationship with stroke and cardiovascular mortality/morbidity, whereby sleep disorders are risk factors for cardiovascular disease (CVD).[27,28] This has been generally attributed to diurnal hypoxia-mediated autonomic and hemodynamic responses. However, recent literature has shown obstructive sleep apnea (OSA) to be an independent association to development of SCVD changes.

SDBDs

SDBD is an umbrella term for sleep-associated breathing disorders including obstructive (OSA), central or mixed sleep apnea and/or sleep-associated hypoventilation. OSA is most

prevalent among SBDB subtypes, affecting up to 34% males aged 30–70 years and 17.4% of women aged 30–70 years.[29] Contemporary literature has also demonstrated that moderate-to-severe OSA is independently associated with microvascular changes, using MRI markers of cerebral ischemia.

Two recent meta-analyses have showcased no significant association with OSA and IHD (i.e., myocardial infarction and angina).[27,30] In addition, included literature in our review has not shown any significant link between atrial fibrillation and stroke among OSA patients. These findings may indicate the pathophysiological impact of OSA on cerebral microvasculature to be independent of embolic or IHD pathophysiology. Furthermore, Butt *et al*. showcased patients with moderate-to-severe OSA to have significant brachial artery hyperactivity, independent of a pre-existing arterial BP.[31] This supports the belief that there may be a localized endothelial dysfunction mediated by OSA, independent to systemic BP, rather than an exacerbation of BP. This is in line with previous hypotheses that chronic cerebral microvasculature changes such as capillary rarefaction may be present in OSA patients, as such changes have been recorded in forearm of OSA patients.[32] In addition, there is insufficient knowledge of the impact of hypertensive management and its impact on the microvascular changes from OSA independently. Nevertheless, the qualitative impact of pre-existing hypertension to the degree of microvascular change has yet to be determined and requires further investigation.

SRMDs

Similarly, there is empirical evidence to support periodic limb movements (PLM) as an independent risk factor to CVD, independent of its known cerebrovascular covariation. Boulos *et al*. has shown an increase in PLM (≥5/h) to be significantly associated with increased WMH burden for first minor stroke or TIA presentations.[33] An association significant when age, apnea/hypopnea, and cerebrovascular risk factors (including hypertension) are controlled.

PLM has a common association of up to 15% of restless leg syndrome (RLS) cases.[34] Furthermore, an association with long-standing RLS to WMH burden is recognized. In a prospective study, Ferri *et al*. showcased long-standing RLS (>10 year duration) to have an independent association to asymptomatic and thus subclinical cSVD.[35] Another prospective study executed by Gupta *et al*. found that pre-stroke RLS to only be a predictor for subcortical as opposed to cortical strokes (22.83% vs. 2.74%, $P < 0.001$).[36] Ferri *et al*. did not assess MWH burden within cortical regions and only within subcortical, deep nuclear regions including pons and thus cannot confirm Gupta's findings.[35] Boulos *et al*. showed there to be no significant association between diagnosed RLS and WMH burden ($P = 0.046$).[33] However, the close epidemiological association between PLM and RLS is of note.[33,34]

Overall, the pathophysiology behind PLM CVD risk is theoretical and under-investigated. Contemporary literature suggests the pathophysiology behind PLM CVD risk is multifactorial. However, the main attribution has been deemed as the nocturnal sympathetic hyperactivity causes a high variation in heart rate, vasomotor and thus, arterial BP. Triggering a cascade of mechanical endothelial stress congruent to the mechanisms of cSVD as mentioned above. Ferri *et al*. also postulated this cerebral hemodynamic instability to produce transient intracerebral hypoxia-mediated damage.[35] The hypercoagulable and oxidative stress which may contribute to the rise of pro-inflammatory biomarkers including CRP and Lp-PLA2 to have significant levels in PLM patients.[37,38]

While Boulos *et al*. identified a qualitative assessment for trends of WMH burden, the specific trends of WMH burden to intracerebral location was not investigated.[33] They theorize PLM to have an unrecognized cerebral network which may allow WMH aggregation along these pathways. In turn, WMH themselves may make interconnected pathways that may increase PLM vulnerability to ischemic insult and thus increase risk of CVD. This theory is congruent with Gupta *et al*.'s findings, whereby among the 35 patients with pre-stroke RLS, 8 presented strictly unilateral, and 16 patients had asymmetrical RLS involvement.[36] All 24 patients showing symptom predominance on the motor aspect associated (contralateral) to the stroke affected cerebral hemisphere. Further prospective studies are required to confirm the nocturnal BP changes and determine if transient cerebral hypoxia episodes are confirmed. As well as confirm whether anatomical location of WMH is associated with PLM location.

Neurosurgical Considerations of Hypertension

Peri-operative complications

The contemporary literature has showcased growing concern for hypertension as a significant variable to peri-operative complications and subsequent surgical prognosis. Perioperative hypertension is characterized as a 20% or greater increase of the patient's BP baseline from that of their pre-operative BP.[39] In addition to surgical stress associated Renin-Angiotensin-Aldosterone System (RAAS) and sympathetic nervous system activation and intraoperative fluid overload, sympathetic stimulation from surgical handling of the deep white matter as well as metabolic stress from cerebral activation.[40]

A literature review in 2011 stated the presence of isolated or combined pre-, intra-, and/or post-operative hypertension to increase intra- and post-operative ICH and hematoma formation at and remote from the operating site.[41] Perioperative bleeding, especially at pressures of more than 160/90 mmHg, has been associated with microvascular damage subsequent to the acute hypertensive damage.[41] In addition, surgical disruption of the BBB at the surgical site causes uncompensated vasogenic edema and subsequent secondary injury cascades. The surgical considerations toward preventing and reducing these hemorrhagic complications are still in question. Soghomonyan *et al*. stated up to 50.8% of survey responders aim to reduce such complications by performing permissive hypotension for cerebral aneurysm clipping.[42] In addition, the literature

has recommended slow weaning from anesthesia to effectively suppress surgical stress-induced hypertension and bleeding tendency.[41] In contrast, other studies have stated concern for intraoperative hypotension among pre-existing hypertensive patients due to anesthesia-induced vasodilation in an already constricted blood volume, causing ischemic microvascular damage. Overall, empirical data to support the best perioperative management of hypertension are poor and cannot be appropriately evaluated until further investigation.

Hypertension undoubtedly creates deleterious acute and chronic consequences on the cerebrovascular architecture. Lifestyle and pharmacological management have been successful endeavors by medicine. However, up to 35.3% of current hypertensive presentations are diagnosed as resistant hypertension, whereas BP is perceived and/or confirmed as unresponsive to diuretic-containing triple drug combination.[43] Up to 50% of such presentations have been likely attributed to an undiagnosed neurogenic etiology rather than a true pharmacological resistance.[44]

The brain-heart axis requires complex multi-level processing. The brainstem contains the nucleus of solitary tract, a cardiovascular center which processes mechano- and chemo-peripheral baroreceptor and vagal inputs to deliver parasympathetic control to vascular tone, heart contractility, and rate.[45,46] A similar process is seen in the rostral ventrolateral medulla (RVLM) to deliver sympathetic output.[45,46] While the left RVLM has an additional function for receiving input from the baroreceptors of the left atrium. First hypothesized in the 1970s by Jannetta *et al*., the vascular compression of the RVLM and adjacent root entry zone (REZ) of the glossopharyngeal (CNIX) and vagal (CNX) nerves to be a neurogenic etiology of hypertension.[47] The pulsatile compression by adjacent vasculature activate residing RVLM sympathoexcitatory C1 neurons creating transient episodes of sympathetic and RAAS metabolic cascades, resulting in microvascular endothelial inflammation and remodeling.[48]

Studies have shown success in the use of microvascular decompression (MVD) as a therapeutic treatment of the above hypothesis. Lu *et al*. identified a significant mean BP reduction when the left trigeminal nerve, RVLM, and REZ were decompressed (experimental group) as compared to trigeminal nerve decompression alone (control group).[49] The experimental group found up to 83.3% of the experimental group to have an improvement or resolution of their hypertension ($P\Delta SBP < 0.001$; $P\Delta DBP < 0.001$), with an overall significant decrease in the mean SBP and DBP.[49] While only the control group saw no significant improvement in BP ($P\Delta SBP = 0.131$; $P\Delta BDP = 0.078$).[49] These trends were confirmed by Sindou *et al*. who prospectively determined a 79.2% effective rate among its 48 patient pool with combined RVLM and REZ decompression.[50] No cases of elevated or rebound BP post-operative were reported. Except for transient vertigo, no post-operative complications were reported.

However, the indication for MVD for resistant hypertension remains controversial. The hypothesized pathophysiology would foresee further antihypertensive effect upon left-sided decompression. Studies show inconsistencies as to the location of the decompression itself. Lu *et al*. showed the successful antihypertensive effect of concomitant left RVLM and REZ decompression at least 6 months postoperatively.[49] Legrady showcased no significant difference in the location of left-sided decompression (i.e., RVLM or REZ).[48] However, this study used a 1 week post-operative follow-up, which may be too short a time frame, considering a maximum anti-hypertensive effect has been shown at 1 year.[48,49] If we consider the duration of post-operative assessment as a variant for result validity, results by Sindou *et al*. would deem most valid. With a mean follow-up of 7 years (2–16 years), the side of decompression (of REZ and RVLM) was ipsilateral to concomitant facial nerve spasm.[50] These results showcased left- and right-sided decompression to have no significant difference in efficacy.[50] The efficacy of the right-sided decompression may be accountable by Lu *et al*.'s theory where an associated cranial nerve symptom (e.g., trigeminal neuralgia or facial spasm) may enhance anxiety-induced sympathetic activation.[49] Nevertheless, the results of the contemporary study are inconsistent and more prospective studies with long-term follow-up are required.

All three studies consistently suggest MVD to only be indicated in patients presenting with resistant hypertension that has MRI confirmed NVC at REZ and/or RVLM. Nevertheless, detection of an elongated arterial loop on MRI is only a presumptive diagnosis. The neurogenic nature of the MRI finding cannot be confirmed. While internationally recognized as a modality for hypertensive treatment, there remains no unified criterion for diagnosing neurogenic hypertension and thus the patient selection for MVD.

Greater research into long-term prognostic outcomes, cost-efficacy, and patient selection is likely to be of benefit; however, the literature on these factors is sparse. MVD was indicated for primary cranial nerve disorders including hemifacial spasm and trigeminal neuralgia rather than for resistant hypertension. As such, the etiology and identification of resistant hypertension as well as post-operative reduction in hypertension were not pursued. Until all such factors are investigated and evaluated, the benefit of therapeutic surgery for hypertension will remain uncertain.

Discussion

Overall, contemporary research has shown its growing efforts to investigate the direct association of hypertension and neurological outcomes. By providing a broad overview of multiple neural pathologies, we can see the negative effects of hypertension as it influences multiple pre-existing acute and chronic neurological and neurosurgical concerns.

Specifically, on a microvasculature level, the association of hypertension to neurological pathologies seems to be based upon overriding compensatory adaptations made within the intrinsic endothelial rather than systemic vascular environment.

However, there is an overarching lack of detailed knowledge to support this pathophysiological basis. With many associations and trends being theorized by the literature, we can also see that the subsequent efficacy of management is put into question.

In addition, none of the contemporary studies had appropriately evaluated hypertension as per the new hypertension thresholds. Instead the trends and associations of hypertension was under the definition of a BP greater than or equal to 140/90 mmHg. Thus, the findings of contemporary literature cannot be guaranteed applicable to all hypertensive patients, as these trends are yet to be confirmed prevalent in BP values between 130–140 mmHg and 80–90 mmHg, systolic and diastolic, respectively.

Conclusion and Future Perspectives

There is growing contemporary evidence that supports hypertension as an important risk factor and etiology to multiple neurological pathologies. Nevertheless, we have been able to see several gaps in the literature. This has made it difficult to determine the true impact of BP optimization to each neural pathology. Future research should reinvestigate the contemporary concerns of hypertension as mentioned above, but in the context of the new hypertensive thresholds. This will reconfirm contemporary concerns and thus determine a true qualitative value of hypertension to each neuropathology. Research must be executed through more in-depth analysis, for example, examining if associations of hypertensive severity to microvascular damage and autoregulatory loss.

We believe it is also crucial for respective clinicians to advocate and implicate hypertension prevention and intervention into their subspecialty practice. Thus, we believe it is important for clinicians involved in neurological care (e.g., neurologists, neurosurgeons, neuroradiologists, and neuropsychologists) to recognize the gravity of hypertension to the morbidity and mortality of their patients. Specialty clinicians must begin to change their perceived role in patient management from treatment and symptom reduction to complication prevention and on-going optimization of BP. We also suggest researchers and clinicians to begin to identify current clinician knowledge, perception, and concerns regarding hypertension. This will allow barriers, limitations, and potential solutions to the integration of hypertension care to be identified. In hopes to create an appropriate standardized guidelines of the role of each specialist to the management of hypertension.

This review is to provide a broad umbrella of up-to-date knowledge and recommendations for patients, health professionals, health service providers, and researchers in the context of rapidly developing vascular knowledge. Furthermore, the knowledge we present is focused on the unidirectional direct impact of arterial hypertension toward neural complications. We iterate that the relationship of arterial hypertension and neurological/neurosurgical conditions is increasingly understood to be bi-directional. Future research should explore the complex and unique impact of neurological/neurosurgical conditions to arterial hypertension.

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Appendix

Appendix 1: Medline (OVID) search criteria

S1	Intracranial hypertension/or hypertension.mp. or essential hypertension/or hypertension/or hypertension, malignant/or hypertension. mp
S2	(hypertension or "arterial hypertension" or "hypertension in neurosurgery" or "hypertension in neurology").m_titl.
S3	1 or 2
S4	(neurology or neurosurgery or "neurological surgery" or "surgical neurology" or cerebrovascular).m_titl.
S5	Cerebrovascular.mp. or cerebrovascular trauma/or cerebrovascular disorders/
S6	neurosurgery.mp. or Neurosurgery/
S7	neurology.mp. or Neurology/
S8	4 or 5 or 6 or 7
S9	Cerebral small vessel diseases/or "small vessel disease".mp.
S10	(microvascular or "small vessel disease" or "cerebral small vessel disease" or microneurosurgery or microaneurysm or "microvascular brain damage" or microaneurysm).mp.
S11	(PRES or "posterior reversible encephalopathy syndrome" or "hypertensive encephalopathy" or "hypertensive crisis" or "hemorrhagic stroke" or "hemorrhagic stroke" or AVM or "arteriovenous malformation").mp.
S12	9 or 10
S13	11 or 12
S14	3 and 8 and 13
S15	Limit 14 to (English language and humans and yr="2011-2020")

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Review Article

Hypertension and the Eye

Stuart L. Graham, Angela Schulz

Department of Clinical Medicine, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney 2109, Australia

Abstract

The retina provides an opportunity for *in vivo* visualization of the microvasculature. In systemic hypertension, the retina shows characteristic progressive changes which have been termed hypertensive retinopathy. The extent of these changes correlates with increased risk of systemic cardiovascular disorders. In addition, hypertension itself is a risk factor for several ocular disorders including retinal artery and vein occlusion, anterior ischemic optic neuropathy, and microvascular oculomotor nerve palsies. Glaucoma has been associated with both hypertension and hypotension, with the implication that over-treatment of blood pressure may be detrimental to glaucomatous optic neuropathy. The retinal arteries and veins can be imaged and their diameters estimated to provide an index that may be used as a marker for systemic vascular change. Dynamic changes in vessel diameter can be recorded with video-imaging with the aim of assessing arterial stiffness, while optical coherence tomography angiography (OCT-A) provides a new non-invasive technique to assess the microvascular density. Here, we review links between retinopathy and both systemic and ocular disease, and some of the techniques for assessing retinal vessels.

Key words: Glaucoma, hypertension, intra-ocular pressure, retinal imaging, retinal perfusion, retinopathy

Hypertensive Retinopathy

The retina provides a unique opportunity to assess the systemic circulation *in vivo* and has long been recognized as an important site for identifying systemic vascular changes in disorders such as hypertension and diabetes. The progressive changes in the vessels occurring in hypertension are readily visible and the accompanying hemorrhages, exudates and infarcts have been described as early as 1939 in a grading system for hypertensive retinopathy by Keith-Wagener-Baker (the KWB system).[1] More recently this has been simplified to a 3-step grading system by Mitchell and Wong,[2] which has been suggested to be easier to apply in practice [Table 1].[3,4]

The pathophysiology of sustained hypertension involves initially a vasoconstriction of the retinal arteries, followed by progressive thickening of the elastic lamina and hyaline degeneration.[5] This may be recognized on fundoscopy as focal narrowing of vessels, arteriovenous crossing changes (referred to as "nipping or nicking") where the hardened artery compresses the vein as it crosses with a shared adventitia, and a progressive change in the vessel wall reflectivity termed copper wiring and silver wiring. With sustained hypertension, small hemorrhages, focal areas of infarction ("cotton-wool spots" – so-called because of their white appearance), as well as lipid exudates from break-down of the blood retinal barrier occur. Lipids can form a visible "macular star" pattern. These changes occur in the inner retinal circulation which is derived from the central retinal artery. The choroid, which is the deeper vascular layer of the eye directly beneath the retina supplying the photoreceptors, derives its circulation from the long and short posterior ciliary arteries, which branch from the ophthalmic artery. In severe hypertension, choroidal changes can also occur,[6,7] including choroidal infarcts (represented as Elschnig's spots – seen as pale, yellow lesions) and pigmentation lines along the larger choroidal vessels (termed Siegrist streaks). Severe hypertension can also lead to optic disc swelling through raised intracranial pressure and optic disc ischemia – termed hypertensive optic neuropathy, and this stage has been termed "malignant hypertension." The risk of stroke and systemic organ damage is high at this stage, as discussed below.

Address for correspondence:
Stuart L. Graham, Department of Clinical Medicine, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney 2109, Australia. E-mail: stuart.graham@mq.edu.au

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Table 1: Classification of hypertensive retinopahy

A. Keith-Wagener-Baker classification of hypertensive retinopathy[1]	
Grade	Signs
1	Generalized arterial narrowing
2	Focal narrowing and arteriovenous nipping
3	As above plus hemorrhages, exudates, and cotton wool spots
4	As above plus optic disc swelling
B. Mitchell-Wong classification of hypertensive retinopathy[2]	
Grade	Signs
Mild	Generalized or focal narrowing, arteriovenous nipping, copper/silver wiring
Moderate	Hemorrhages, exudates, and cotton wool spots
Malignant	As above plus optic disc swelling

While the classification of the severity of the hypertensive retinopathy provides a guide as to the severity of the likely systemic manifestations, hypertension itself is also linked to several pathological disorders within the eye, most of which are vision threatening. Therefore, recognition of hypertensive changes and the initiation or upregulation of treatment are useful for both managing the general cardiovascular health of the patient and preventing ophthalmic complications. Figure 1 shows a case of hypertensive retinopathy.

Retinopathy and Systemic Risk

The presence of hypertensive retinopathy has been linked to increased risk of cardiovascular disease including stroke, congestive heart failure, and incident coronary artery disease.[8-10] Moderate retinopathy was associated with up to 4-fold risk of stroke,[9] while retinal microvascular changes indicated a higher risk of cerebral atrophy.[11] The relationship of retinopathy with coronary artery disease is less clear, but several studies support an association[8,10] which is not unexpected given the known association between hypertension and cardiovascular mortality. Early retinopathy signs may be more valuable in younger populations (<55 years) with an association demonstrated with target organ damage that was not shown in the older cohort of the study.[3] This may be because retinopathy signs become attenuated in the elderly.

Hypertensive retinopathy has been associated with target organ damage such as renal impairment and left ventricular hypertrophy.[12,13] Retinal microvascular changes have also been associated with cognitive decline, brain white matter lesions, and possibly prevalence of dementia. However, epidemiological studies pertaining to dementia have had variable conclusions, complicated by different definitions, sample cohorts, and the inclusion of both diabetic and hypertensive retinopathy in the analysis. For example, the Cardiovascular Health Study found that retinopathy was associated with dementia only in subjects with hypertension or without diabetes.[14] The Rotterdam Study reported an association of retinopathy and prevalent dementia in the whole population with no difference between presence or absence of hypertension and diabetes.[15] The AGES-Reykjavik Study suggested that retinopathy was associated with vascular dementia but not with all-cause dementia or Alzheimer's Disease.[16] Therefore, while it is reasonable to conclude that retinopathy reflects systemic vascular disease which may be associated with increased risk of dementia, at present it cannot be concluded that the microvascular signs are predictive or diagnostic for the disease process.

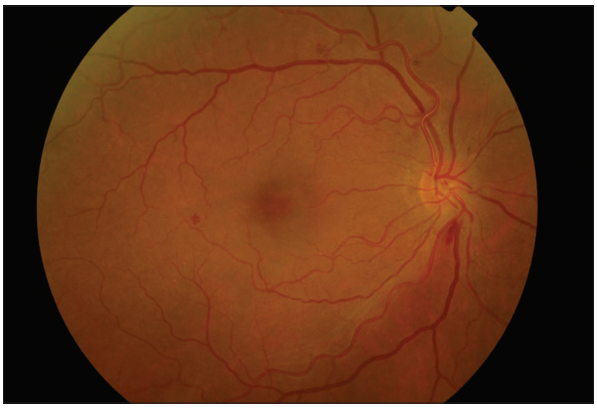

Figure 1: Fundus photo from patient with moderate hypertensive retinopathy showing arteriovenous crossing changes (nipping) particularly evident at the inferior optic disc region (white arrows), with scattered hemorrhages (black arrowheads). Image courtesy Dr. Amy Pai

Hypertension and Ophthalmic Disorders

Central and branch retinal vein occlusions

A widely recognized and common association with hypertension is the development of retinal vein occlusions, including central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO).[17-19] In BRVO, the arteriovenous crossing changes provide a site for compression and focal vascular damage due to the shared adventitial sheath. These can be large quadrantic occlusions or may only involve smaller branches. CRVO affecting the main trunk of the central retinal vein at the optic nerve head produces more profound visual loss, is more likely to produce macular edema, and can produce more widespread ischemia. Many BRVOs and CRVOs will resolve spontaneously and remain non-ischemic, but both can be associated with significant ischemia increasing the risk of neovascularization, with secondary retinal and vitreous hemorrhage, and eventual neovascular glaucoma. Ischemic CRVO is the most problematic and often requires pan-retinal photocoagulation and intravitreal anti-vascular endothelial growth factor (VEGF) injections. While clinical trial evidence is lacking for anti-hypertensive therapy providing an improved prognosis, to reduce the risk of occurrence in the fellow eye, it is recommended that subjects have a full cardiovascular work-up as several other systemic risk

factors have been associated with vein occlusions, including hyperviscosity.[17]

Central and Branch Retinal Artery Occlusions

Central retinal artery occlusion (CRAO) is increased in subjects with hypertension,[20] and it is associated with a high risk of subsequent systemic events, including stroke and acute myocardial infarction.[21] A CRAO requires referral for immediate vascular work-up, and as these subjects often have co-existent silent ischemic infarcts[18] which can be detected on brain MRI. There is a high incidence of ipsilateral carotid artery disease.[22] Embolic disease from various causes and vasculitis such as giant cell arteritis can also produce a CRAO. The subject experiences sudden, painless loss of vision and the prognosis is usually poor, although some patients can be salvaged with rapid lowering of intraocular pressure and ocular massage. CRAO may be preceded by episodes of transient visual loss (amaurosis fugax). The classic clinical finding is the "cherry red spot" at the macula representing the preserved choroidal circulation, while the retinal circulation is markedly reduced or absent, with associated retinal edema. Patients with a cilio-retinal artery may preserve some central vision. There is an increased risk of neovascularization in CRAO, so patients need to be monitored for this, although the risk seems to be less than for ischemic CRVO.

Branch retinal artery occlusions (BRAO) are very frequently associated with emboli. The prognosis for BRAO is better than CRAO in that most will not have significant vison loss unless the residual scotoma is in the paracentral region. However, these subjects also have a higher risk of stroke and mortality due to their risk of embolic disease,[23] they should undergo carotid and cardiac assessment.

Anterior Ischemic Optic Neuropathy (AION)

Non-AION is a frequent cause of sudden vision loss in people older than 50 years of age. The exact mechanism is not known but it is associated with systemic hypertension[24] and is more prevalent in anatomically small crowded discs[25] ("the disc at risk"), where disc swelling secondary to ischemia leads to infarction of a sector of the optic nerve head, often involving the lower or upper half of the optic disc, producing altitudinal visual field loss. There are no effective treatments for the condition[26] but it does seem to be self-limiting. Patients with at-risk discs should be advised to monitor their blood pressure and other cardiovascular risk factors carefully.

Retinal Macroaneurysm

Retinal arterial macroaneurysm is a saccular dilation of a larger retinal arteriole usually within the first three bifurcations.[27] It is associated with systemic hypertension in 60–75% of cases.[27,28] It is often self-limiting with spontaneous thrombosis and resolution of the aneurysm, but it can be associated with sudden intra-retinal and pre-retinal hemorrhage, exudation, and associated macular edema. The edema may be chronic in up to a third of cases.

Glaucoma

Glaucoma represents of a group of disorders that are characterized by progressive retinal ganglion cell loss with excavation (cupping) of the nerve head, producing visual field loss and eventual blindness. The two main sub-types are primary open angle glaucoma (POAG) which is a slow chronic disease, and angle closure glaucoma (ACG) which is associated with sudden onset and extremely high intraocular pressure (IOP). The common causative factor in both is raised IOP, but a large proportion of POAG patients never manifest IOP outside the normal range (often termed normal tension glaucoma – NTG), and many patients progress despite IOP lowering. It was, therefore, proposed that vascular factors may play a role in glaucomatous damage.[29,30] It appears likely that both hypertension and hypotension may be implicated.[31] Hypertension can cause long term damage to vessels and impaired autoregulation. Hypertension has been linked to glaucoma prevalence and to raised IOP,[32,33] although some studies have found contradictory results.[34] On the other hand, hypotension can lead to reduced ocular perfusion pressure (the difference between IOP and mean blood pressure) which could adversely affect the optic nerve.[35] In fact, reduced ocular perfusion pressure has now been accepted by the World Glaucoma Society as a risk factor in their Consensus document on ocular blood flow.[36] A major problem with many of the studies is they use blood pressure as a continuous variable, whereas there may be different phenotypes of glaucoma manifesting different pathophysiological processes at either end of the blood pressure scale. It has also been reported that systolic blood pressure variability is a more important parameter in POAG.[37]

Several major clinical studies have looked at vascular risk factors in the development of glaucoma. The Early Manifest Glaucoma Treatment Study found lower systolic perfusion pressure, lower systolic BP, and cardiovascular disease as predictors of progression.[38] The Barbados Eye Study found that low systolic BP and low ocular perfusion pressure doubled the risk of OAG incidence.[39] The Egna-Neumarkt Eye Study found an association between hypertension and glaucoma but also that lower diastolic BP increased risk. There was no relation to other systemic vascular disease.[40] The Rotterdam Study determined lower diastolic BP a risk factor, especially in treated hypertension,[41] but its most recent report did not find any clear link with progression.[42] The Singapore Epidemiology of Eye Diseases Study found that low systolic ocular perfusion pressure was associated with POAG and this association was in part secondary to low systolic blood pressure and high IOP.[43].

The Los Angeles Latino Eye Study[44] reported hypertension increased risk ratio (systolic 2.0 and diastolic 2.5) while

hypotension did also (lLow diastolic BP 1.6, low systolic perfusion pressure 2.9, and low diastolic perfusion pressure 2.0). They produced a U-shaped curve for glaucoma prevalence based on BP with the lowest point at normotensive levels. A similar curve was produced by Zhao *et al*. in their meta-analysis of glaucoma and BP[33] and recently confirmed for both systolic and diastolic BP in the National Health and Nutrition Survey study.[45]

There is a recognized normal diurnal curve of BP, with a 10% reduction at night considered physiological, usually around 2.00–4.00 am.[46,47] In the mid 1990's, studies by Graham[48] and Hayreh[49] using ambulatory BP monitoring (ABPM) suggested that subjects with greater nocturnal dips were more likely to have glaucoma and more likely to show visual field progression.[50] This raised implications for anti-hypertensive therapy, as certain anti-hypertensive agents may have a profound effect on nocturnal blood pressure and exacerbate the fall in BP. Since IOP is known to elevate at night in the supine position the combination would lead to reduced ocular perfusion pressure at night. Many studies[51] have associated large dips in blood pressure with both POAG and normal tension glaucoma.[52-54] Bowe *et al*. conducted a meta-analysis[55] of all studies reporting on 24 h ABPM in glaucoma and found a consensus of progressive glaucoma in those with larger nocturnal dips of blood pressure. The odds ratio for deteriorating visual fields over 2 years with nocturnal dips of >10% in systolic or diastolic BP was 3.32 (1.84–6.00) and 2.09 (1.20–3.64), respectively.

While there is no dispute that treating hypertension is important, there may be potential adverse consequences in glaucoma from over-treating BP. The Systolic Blood Pressure Intervention Trial (SPRINT) found that a systolic target of <120 mmHg was more protective of cardiovascular complications than the conservative target of 140 mmHg.[56] However, in aiming for this there may be less margin for error, potentially pushing down the perfusion pressure in the eye to levels that could be detrimental in certain individuals, such as those with poor autoregulatory capacity. Notably, there were more episodes of hypotension and syncope in the lower target group. The more recent guidelines for hypertension therapy use stricter cutoffs; the 2017 American College of Cardiology recommending a target of <130/80 for most hypertensive patients.[57] Given the potential for nocturnal hypotension particularly when medications are taken at night,[58] we recommend checking ABPM in glaucoma patients aiming for this stricter BP therapeutic target and in patients with progressive glaucoma despite reasonable IOP control. These recommendations have also been suggested by Leeman and Kestelyn.[59]

Association with Diabetic Retinopathy

The retinal changes occurring in diabetic retinopathy, which like hypertensive disease also include hemorrhages, exudates, and cotton wool spots, may be exacerbated by the presence of systemic hypertension, likely through enhanced damage to retinal capillary endothelial cells and impaired autoregulation.[60] In several early studies, hypertension was demonstrated as an independent risk factor[61-63] for progression of retinopathy. In the Beaver Dam Study, higher systolic blood pressure was also associated with increased diabetic macular edema. The UK prospective Diabetes Study[63] proposed that patients with tighter BP control, defined as <150/85 mmHg, showed a 34% reduction in diabetic retinopathy progression and were less likely to need laser photocoagulation for their retinopathy. However, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study,[64] which specified even tighter BP control, did not show any additional benefit on progression of diabetic retinopathy. Laboratory studies demonstrate hypertension may enhance VEGF release[65,66] which is a stimulus for neovascularization – a feature of proliferative retinopathy. However, a recent Cochrane review[67] concluded that while there was evidence of blood pressure control reducing the 5 years incidence of diabetic retinopathy, there was less evidence to support treatment of hypertension specifically as a means of minimizing progression and macular edema.

Of note, both hypertension and diabetes are also risk factors for microvascular cranial nerve palsies, particularly 3rd and 6th cranial nerves supplying innervation to extraocular muscles.[68]

Vascular Imaging and Grading Techniques

Retinal imaging techniques allow for the detection and monitoring of hypertension associated ocular vascular changes. Traditional fundus photography and more recent advances in imaging technologies such as dynamic vessel analyzer, optical coherence tomography, and optical coherence tomography angiography have allowed for quantitative analysis of retinal structural and vascular changes in response to hypertension.

Analysis of retinal vascular changes relies on indices derived from either static or dynamic imaging. Static indices, such as central retinal artery equivalent (CRAE), central retinal vein equivalent, and the arteriovenous ratio (AVR), utilize analysis of fundus images to indicate retinal vascular caliber. Using the Parr-Hubbard formula, CRAE and CRVE can be calculated using artery and vein diameters in an annulus 0.5–1 disc diameter from the rim of the optic disc. The CRAE has been shown to be significantly narrower in hypertensive patients compared to non-hypertensive controls.[69-72] The link between hypertension and CRVE is less clear with some studies reporting venular dilation in hypertensive patients,[73] whilst other studies have reported that venular caliber is reduced in hypertensive patients compared to non-hypertensive controls,[74] or has no association.[72]

Adaptive optics

Adaptive optics have enhanced the potential resolution of standard fundus imaging to allow for qualitative and quantitative assessment of retinal microvasculature utilizing opto-electronic technology.[75] Using this technology, it has been possible to more accurately determine the wall to lumen

ratio of retinal arteries in hypertensive patients and to establish that hypertension correlates with an increase in the wall to lumen ratio[75,76] compared to non-hypertensive subjects. Furthermore, Rosenbaum *et al.*[76] reported that short-term use of antihypertensives in hypertensive patients resulted in a decrease in the retinal arterial wall to lumen ratio which was attributed to an increase in arteriolar internal diameter as there was no change to wall thickness.

Optical coherence tomography (OCT) and OCT-angiography

OCT is a non-invasive retinal imaging technique that provides high resolution cross-sectional images of the retina and is now widely used to document retinal and optic nerve pathology in vivo. OCT utilizes infra-red light to penetrate the retina and the backscattered light is used to produce high resolution images of the retinal layers and microstructure. Using spectral domain OCT, evidence of retinal thinning has been reported in patients with hypertension.[77-79] The average thickness of the central macula, peripapillary retinal nerve fiber layer, and ganglion cell/inner plexiform layer was significantly reduced in patients with chronic hypertension both with and without clinical signs of retinopathy.[77,78] These changes are believed to be due to the chronic ischemia resulting from retinal microvascular changes that occur in hypertension.

OCT-angiography (OCTA) is a newer technique that allows for non-invasive visualization of the retinal vasculature without the need for contrast dye. This technique uses motion detected during the OCT scan capture to produce high resolution images of the retinal and choroidal vasculature. Further analysis of the OCTA images allows for quantification of vessel density, perfusion density, and the size of the foveal avascular zone. Studies utilizing OCTA have reported that hypertension results in a significant decrease in retinal vessel density particularly in the deep vascular plexus, decreased perfusion density, and a significant increase in the foveal avascular zone.[78-80] These results suggest that OCT and OCTA could prove to be useful tools for non-invasive monitoring of hypertension induced vascular changes. In glaucoma defects in the inner capillary network are identified in areas of nerve fiber damage [Figure 2]. Longitudinal studies may determine whether this capillary vascular dropout precedes nerve fiber and retinal ganglion cell loss (implying a potential causative role in damage) or in parallel secondary to reduced demand.

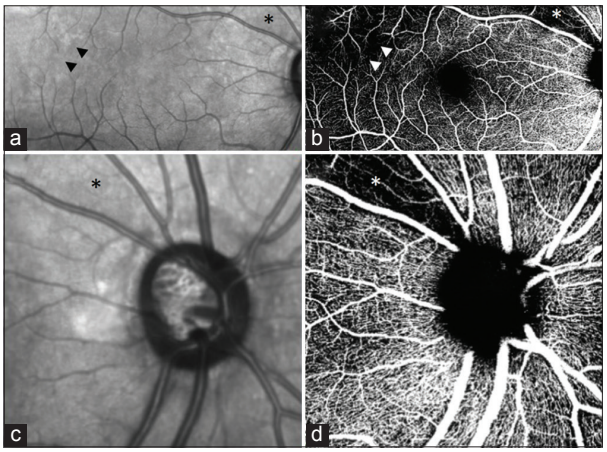

Figure 2: Infrared image (a and c) and optical coherence tomography angiography (OCT-A) images (b and d) of the retina centered on the macula (a and b) and higher resolution of the optic nerve head (c and d) from a patient with glaucoma. Regions affected by vascular dropout highlighted in superotemporal nerve fiber distribution (asterisks, arrowheads) seen in (b) and (d) which correspond to structural loss of retinal fibers in a similar distribution

Dynamic Vascular Recording

The Dynamic Vessel Analyzer (DVA; Imedos Systems UG, Jena, Germany) software allows for analysis of dynamic changes in the diameter of retinal vessels from video. The eye tracking software helps to maintain a steady image of the retinal vessels at the optic nerve head to allow for detailed analysis of arterial and venous pulse amplitude – Figure 3 showing a frame from DVA video recording with vessels labeled and corresponding trace. With this technique the vascular dilation response to light stimulus

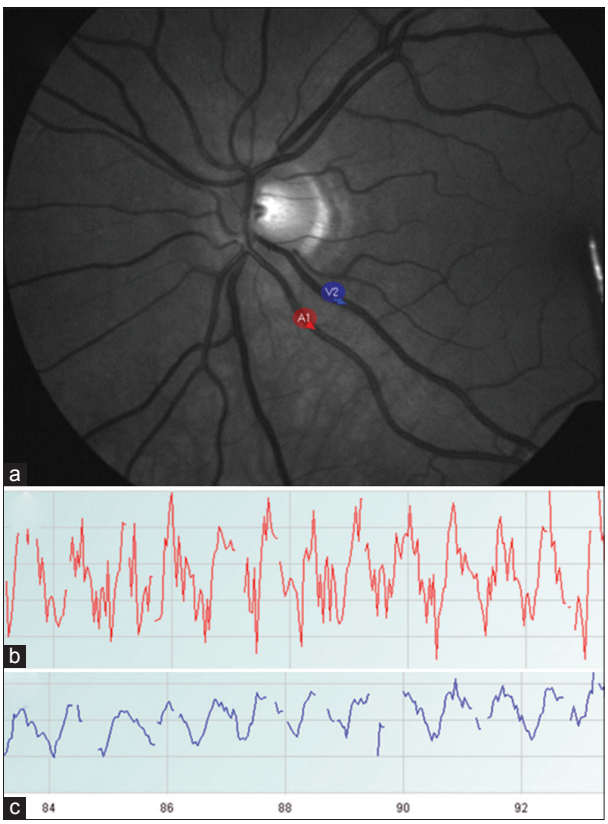

Figure 3: Optic-disc centered fundus photo (a) with arterial (b) and venous (c) pulsation waveforms recorded with the Dynamic Vessel Analyzer (DVA). Retinal artery (A1) and vein (V2) are labeled on the live fundus image (a) and a 100 s recording captured. Analysis of the recording generates pulsation waveforms for arteries (b) and veins (c)

can be measured, and arterial and venous pulse amplitudes estimated. Using DVA analysis of video, Tong *et al*. reported and association between increased apnea-hypopnea index and attenuated retinal vascular pulsatility in addition to decreased CRAE and AVR.[81]

Potential for measuring retinal pulse wave velocity

Pulse wave velocity (PWV) indicates the speed with which the pulse wave travels along an artery. There is a well-established association between PWV in larger arteries and arterial stiffness; the stiffer the artery, the faster the pulse wave. A variety of techniques have been used to attempt to determine retinal pulse wave velocity in humans with values ranging from 0.4 mm/s to 600 mm/s.[82-85] Initial studies aimed at determining retinal PWV used fluorescein angiography,[86] while more recent studies utilized the DVA,[82,83] swept source OCT,[84] and spectral domain OCT.[85] Although these studies vary greatly in the reported retinal PWV values, each of the techniques detected an increased velocity in older or hypertensive subjects compared young or normotensive control subjects. Using the DVA, Rezaeian *et al*. demonstrated that retinal PWV correlated with carotid-femoral PWV in elderly patients suggesting that remodeling of the retinal microvasculature mimics that observed in larger vessels.[87] Such findings warrant further studies to determine if retinal PWV can be used for determining arterial stiffness *in vivo* and if it could be utilized for screening or monitoring of systemic cardiovascular changes.

Summary

Hypertension induces characteristic retinal vascular changes which can be visualized and measured non-invasively. These changes correlate with systemic vascular disease and risk. Hypertension can also be associated with several vison threatening ocular disorders and so should be identified and managed in consultation between the ophthalmologist and the treating physician. In glaucoma both hypertension and hypotension may be risk factors, the latter from over-treatment with anti-hypertensives.

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Review Article

Physical Activity Can Reduce Hypertension and the Long-term Benefits May Contribute toward a Lower Risk of Cognitive Decline and Dementia

S. J. Fuller[1], T. Shah[1,2,3], P. Chatterjee[1,2], C. B. Dias[1], H. Hillebrandt[1], H. R. Sohrabi[3,4], Ralph N. Martins[1,2,3,5,6,7]

[1]Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University, North Ryde, NSW, Australia, [2]School of Medical Health and Sciences, Edith Cowan University, Joondalup, WA, Australia, [3]Australian Alzheimer's Research Foundation, Nedlands, WA, Australia, [4]College of Science, Health, Engineering and Education Murdoch University, Murdoch, WA, Australia, [5]KaRa Institute of Neurological Disease, Sydney, Macquarie Park, Australia, [6]School of Psychiatry and Clinical Neurosciences, University of Western Australia, Crawley, WA, Australia, [7]The Cooperative Research Centre for Mental Health, Carlton South, Australia

Abstract

Epidemiological studies have consistently shown that chronic mid-life hypertension is linked to an increased risk of cognitive decline and dementia, especially vascular dementia and Alzheimer's disease. However, clinical trials of pharmacological or exercise-based anti-hypertensive treatments have not always noted reductions in cognitive decline in treated patients. The many pharmacological modes of treatments available, the short-term nature of many studies, and the range in participant ages are some of the reasons clinical trials may not have consistently shown an influence on cognition. Furthermore, hypertension studies have led to the understanding that arterial stiffness is a better indicator of cognition than blood pressure (BP), possibly reflecting inadequacies in BP measurement methods. Exercise interventions have been successful in reducing hypertension, and recent studies have highlighted improvements in certain aspects of cognition. In addition, both aerobic and resistance training exercises are proving to be beneficial. With the aim of reducing the risk of cognitive decline and dementia, multi-domain lifestyle changes encompassing regular exercise, dietary improvements, and cognitive training are being investigated in long-term clinical trials, with encouraging results. In this review, we discuss hypertension, links between hypertension and cognitive decline, as well as clinical trials of hypertension which have investigated exercise and pharmacological treatments and their potential effects on cognition. We also highlight recent multi-domain interventions aimed at reducing the risk of cognitive decline.

Key words: Blood pressure, brain, cognition, Dementia, exercise, lifestyle, mild cognitive impairment, oxidative stress

Introduction

There is currently no cure for Alzheimer's disease (AD) or most other forms of age-related dementia, despite several decades of research. Therefore, especially in the case of AD, the focus has moved to modifiable risk factors. Hypertension, during mid-life has been associated with an increased risk of later cognitive decline and dementia, mainly vascular dementia and now also AD.[1] This review discusses how hypertension is measured, current pharmacological treatments, exercise as a treatment, and the potential of such treatments in reducing dementia risk. Furthermore, the advantages of multidomain, lifestyle-based preventative measures to reduce dementia risk are highlighted.

What is Hypertension?

Until recently, hypertension was defined as a chronic blood pressure (BP) equal to or greater than 140/90 mm Hg. High BP can lead to serious health problems such as stroke, kidney disease, heart attack, or heart failure.[2] However, the guidelines concerning treatment options, which depend on associated risk factors, age, and the presence of comorbid conditions, have made this definition inadequate.[3] Most analyses concerning hypertension and treatment options investigate the risk of major cardiovascular events or death in the next 5 years; yet for many, there are clearly risks of being in what was considered the high normal range (130/85–139/89 mm Hg), as most people who

Address for correspondence:
Ralph N. Martins, Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences,, Macquarie University, North Ryde, NSW, Australia. E-mail: ralph.martins@mq.edu.au

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have heart attacks or strokes do not quite meet this original definition of hypertension. In 2018, the American College of Cardiology and the American Heart Association Task Force on Clinical Practice Guidelines redefined hypertension to a lower BP threshold, of 130/80 mm Hg.[4]

In addition to the cardiac risks and potential of kidney damage, hypertension has been known for many years to be linked to cognitive decline, and this added risk provides yet another reason for people to maintain their BP in the normal range, either by pharmacological or non-pharmacological means.[5,6] Furthermore, as described below, the strongest links to age-related cognitive decline (manifesting from the sixth to ninth decade) have been to hypertension in middle-age (in the fourth to fifth decade),[7-9] thus well outside the 5-year time frame of most studies, partly explaining why this association has been hard to establish.

Measuring BP

The standard method used to measure BP is on the brachial artery.[10] Recent research concerning potential physiological nuances of the multiple components of BP, such as systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP), mean BP, and central BP have led to doubts about the accuracy and relevance of brachial artery BP. This is of concern as most clinical trials of BP-reducing drugs have used the brachial artery as their means of determining drug effectiveness. Using the brachial artery does not reliably represent central aortic pressure, which is the pressure against which the heart pumps blood.[11] Although the DBP decrease has been shown to be minimal from central to peripheral vessels (<2 mm Hg), the drop in brachial artery BP can be as much as 12 mm Hg and the PP can drop up to 14 mm Hg.[12,13] These differences are important, as cardiovascular mortality can be more strongly related to aortic compared to brachial BP.[12,13] Studies have found that a wide variation in the brachial-aortic SBP difference occurs between patients with similar brachial SBP, finding that 64% of people with normal brachial BP have central SBP at the hypertension class 1 level.[14] Just as importantly, anti-hypertensive drugs can exert differential effects on brachial and central pressure.[13] Thus, the use of the brachial artery for monitoring effects of hypertension on central organs may be sub-optimal on many levels. To complicate this further, reviews of long-term BP measurement have concluded that BP variability, from day to day, or week to week, influences cardiovascular events and cardiovascular mortality risk.[15] A recent study has similarly shown that a large BP variation over a period of years is associated with an increased long-term risk of dementia.[16] This adds to the evidence that maintaining a healthy BP from middle-age onward is critical to long-term health.

Pharmacological Treatments for Hypertension

There are several classes of anti-hypertension treatments, including angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), beta-blockers, diuretics, neprilysin inhibitors, and other agents. Due to different modes of action, each class has a different effect on central BP. For example, ACEIs, ARBs, CCBs, and nitrates appear to have greater beneficial effects on central SBP and PP than beta-blockers, despite their similar effects on brachial BP.[17] Therefore, for a similar drop in (brachial) BP, the different anti-hypertension treatments can have different outcomes in clinical trials, for example, concerning cardiovascular mortality. They also have different effects on other aspects of metabolism, in fact the Losartan Intervention for Endpoint Reduction in Hypertension, Anglo-Scandinavian Cardiac Outcomes Trial, and Conduit Artery Function Evaluation trials demonstrated that beta-blockers had adverse effects on metabolism, which increased the risk of diabetes type II, including impaired glycemic control, lower high density lipoprotein-cholesterol, and higher triglycerides.[18-20]

Exercise as a Treatment for Hypertension

According to the statistics in the United States, nearly 50% of Americans have high BP, using the redefined hypertension definition, and normotensive people at age 55 have a 90% risk developing hypertension during their lifetime.[21,22] Such statistics, which may be indicative of levels in many western countries, underscore the need to promote preventative measures to reduce such prevalence of what is the most common and costly, yet preventable, risk factor for cardiovascular disease.[23] Although a systematic review in 2008 did not find consistent conclusive evidence of improvements in BP following exercise,[24] more recent studies have added considerable evidence to show such benefits.[22] In 2018, the American College of Cardiology and American Heart Association Task Force on Clinical Practice Guidelines redefined hypertension to a lower BP threshold, of 130 mm Hg for SBP and 80 mm Hg for DBP.[4] The previous Joint National Committee 7 threshold consisted of 140 mm Hg for SBP and 90 mm Hg for DBP. It has been stated that almost all of the new cases of hypertension (using the new definition of 130/80 mm Hg) should be able to reduce their BP without medication, and instead use lifestyle modifications such as exercise.[4] The updated review on the use of physical activity in the prevention and treatment of hypertension concluded that there was strong evidence that physical activity could reduce BP amongst all adults tested (hypertensive, pre-hypertensive, and normotensive). Those subjects with hypertension showed the largest gains (largest drop in BP), followed by those defined as pre-hypertensive.[22] Other studies have since indicated that the quoted drops in BP should translate to significantly reduced levels of cardiovascular disease and stroke.[25,26]

Previously, aerobic and dynamic resistance exercise training had been shown to be beneficial by providing a small but clinically significant reduction in BP, with the greater evidence concerning aerobic exercise. The more recent review reported moderate evidence of similar reductions of hypertension with

either aerobic exercise or dynamic resistance exercise training (or a combination of the two).[22] It was also shown that other forms of physical activity are beneficial in lowering BP; however, the evidence is currently limited. With such a positive outcome expected, it is unsurprising that exercise is being encouraged and investigated further as a preventative measure for reducing cognitive decline, as hypertension itself, as well as cardiovascular disease and stroke have all been linked to forms of dementia, including AD.[7,27-29]

Hypertension and Cognitive Decline

Many studies and extensive reviews of observational studies have concluded that cognitive decline and dementia are linked to hypertension, particularly mid-life hypertension.[1,30,31] In the 6th and 7th decade, hypertension has been linked to poorer overall cognitive function as well as decline.[1,32,33] The level of hypertension also appears to be important. For example, in a clinical trial, keeping BP under tight control at 120/80 mm Hg was found to reduce incidence of dementia, compared to just keeping BP under systolic levels of 140 mm Hg.[34] The strongest links, however, as mentioned earlier, seem to be in people who have had hypertension for a long time, or who have had the longest period of time between the initial diagnosis of hypertension, and the later development of cognitive problems.[8,35,36]

Not all studies agree, however, as studies of the very elderly have shown that (untreated) high BP is associated with reductions in cognitive decline.[37,38] It has been suggested that age-related changes in the vascular system might explain the different response in the very elderly. Since the strongest relationships between hypertension and cognitive decline appear to be related to duration of hypertension, especially if hypertension started in midlife, this suggests long-term vascular damage may be involved.[8,35,36] If this is the case, a strong relationship between hypertension (newly) diagnosed in the very elderly, and cognitive decline, would be unlikely.

The variety of anti-hypertensive treatments and their modes of action are likely to influence their effectiveness in reducing dementia risk. One retrospective study compared rates of AD diagnosis in over 1.3 million users of six different anti-hypertensive drug treatments, with the users aged 65 years or older. It was found that treatments targeting the renin-angiotensin system (RAS), particularly ARBs, were slightly more protective against onset of AD than non-RAS treatments.[39]

A review by Hughes and Sink[40] summarizes the current knowledge concerning the links between cognitive decline and hypertension to a few main points: (1) Longitudinal studies have shown mid-life high BP is linked to increased incidence of cognitive decline and dementia later in life, (2) this association is not as clear from cross-sectional studies of hypertension and cognition in the elderly, (3) randomized controlled trials of anti-hypertensive treatments have not shown clear-cut benefits concerning cognition, (4) studies at midlife have indicated the duration of hypertension and its associated arteriosclerosis (thickening and stiffening of the arteries) are linked to cognitive decline, and (5) greater Abeta (Aβ) amyloid deposition and cerebrovascular disease, pathologies seen in AD, and dementia, are reported to occur in hypertensive older adults.[40,41] It has been known for some time in fact, that both Aβ amyloid deposition (a hallmark feature of AD brains) levels and the number of neurofibrillary tangles (another hallmark pathology of AD) are greater in patients with high BP,[42] as well as atherosclerosis.[40,43] Furthermore, in post-mortem studies of people with normal age-related neuropathology as well as people with non-complicated AD pathology, those who had been on anti-hypertensive medications were found to have less plaques and neurofibrillary tangles than those who had not received treatment for hypertension, though not less than those who had not had hypertension.[44]

Hypertension, Cognition, and Pathological Mechanisms

Hypertension has been shown to affect brain structure – recent advances in neuroimaging methods have led to the findings that high BP, particularly in mid-life, is linked to cerebral atrophy, white matter microstructural damage, and cerebral small vessel disease.[5,45,46] This is believed to be the result of endothelial dysfunction and/or vessel wall remodeling.[5] The higher BP leads to hypertrophic remodeling of the vascular media and smooth muscle cells, leading to reduction in lumen diameter, which in turn leads to increased vascular resistance and vessel wall stiffening. This eventually leads to reduced numbers of downstream capillaries, and in the brain, which needs continuous perfusion; this can lead to hypoperfusion at times when BP is reduced.[47,48] Lower blood flow (oligemia) can lead to oxidative stress, acidosis, reduced oxygen delivery, and unmet glucose demands, which have all been shown to reduce neuronal function.[47-50] In addition, a recent review concluded that chronic inflammation (a known risk factor for AD) triggers oxidative-nitrosative stress, which over a long period of time damages fatty acids, proteins, DNA, and mitochondrial function.[50] Over time, this leads to dysfunctional energy metabolism, endothelial dysfunction, and blood brain barrier disruption, which in turn leads to decreased cerebral perfusion and chronic glucose hypometabolism.[50] Most of these changes have also been linked to increased production of Aβ peptides, Aβ amyloid deposition, activation of the receptor for advanced glycation end (RAGE) products, and increased tau phosphorylation – all pathologies found in AD.[51-54]

Hypertension is often seen in association with other conditions common from middle age onward such diabetes type II. In people with both conditions, SBP increases linearly with age, whereas DBP declines curvilinearly from as early as 45 years of age, together suggesting the development of increased arterial stiffness. Subjects with both conditions have additive effects on arterial stiffness, and some studies have suggested this is

linked to increased risk of dementia.[55] Reviews of clinical trials, epidemiological data, and other studies support this concept as they have concluded that arterial stiffness is a sensitive predictor of cognitive impairment,[5,56] in fact it has been found that increased arterial stiffness is more useful in predicting cognitive decline in healthy subjects, than BP itself.[57] In support of a link with AD in particular, a recent study of subjects with mild cognitive impairment (MCI) and dementia revealed associations between higher levels of certain forms of arterial stiffness (as measured by pulse wave velocity) and lower brain volume in areas highly affected in AD, higher brain Aβ amyloid deposition levels as determined by florbetapir-PET scans, and higher white matter hyperintensity.[58] The associations were strongest in individuals with MCI. Interestingly, it has also been shown that education attainment appears to moderate the effects of central artery ageing (including higher aortic stiffness and central BP) on cognitive performance in middle-aged and older adults.[59] This is similar to higher education and occupation levels being linked to cognitive reserve, protecting against development of dementia.[60]

Studies have also investigated the relationship between hypertension and sleep disturbances.[61-63] Sleep apnea and sleep deficiency are known as symptoms of several neurodegenerative diseases, including AD, yet a causative role is emerging, and sleep impairments are now considered as risk factors for dementia.[64] For example, recent studies have found higher levels of biomarkers (such as homocysteine, clusterin, acute-phase proteins, Aβ, and inflammatory cytokines) of both AD and vascular dementia in people with obstructive sleep apnea.[65,66] In one recent study of an older population considered at risk of dementia, reduced cortical thickness was found to be linked to oxygen desaturation; though conversely, increased hippocampal and amygdala volumes were associated with sleep disturbances,[67] with the authors concluding that further sleep studies in such dementia high risk groups are required. Inadequate sleep has also been associated with oxidative stress and homocysteine levels,[68] both of which are risk factors for cognitive decline and AD. Such findings are relevant here as sleep apnea is strongly associated with hypertension, and further studies into the pathophysiological mechanisms linking hypertension, sleep disturbances, and dementia are needed. Sleep apnea is also readily treatable, providing an avenue to delay dementia onset.

Hypertension Treatments and Cognitive Decline

As hypertension has shown significant links with later cognitive decline, it would be expected that treatments to control BP would reduce incidence of dementia, however, as mentioned above, studies of hypertension treatments have not shown clear-cut conclusions concerning this potential treatment effect. One reason often mentioned that may explain this apparent discrepancy is that cognitive measures have almost always been a secondary measure, not a primary outcome of a trial, and studies of hypertension treatments are rarely of the longitudinal type required to determine any effect on risk of cognitive decline or dementia, many years later.[69,70] The differences between the effects of the classes of antihypertensive treatments also make comparisons of such treatments difficult. Furthermore, treatments for hypertension are now rarely prescribed alone; for example, lipid-lowering statins are often given together with antihypertensive treatments, which further limits the interpretation of the beneficial effects of anti-hypertensives in preventing or delaying cognitive decline.

Nevertheless, there is considerable evidence that hypertension is linked to later cognitive damage, as recent systematic reviews of both longitudinal and cross-sectional studies show that antihypertensive drugs, particularly CCB and RAS blockers, may be beneficial in preventing cognitive decline and dementia.[40,69-71] However, these studies conclude that there is still a need for more clinical trials where the primary aim is to discover whether anti-hypertensive treatments can reduce the risk of cognitive decline and dementia.[40,69-71]

Exercise and Dementia

A Cochrane systematic review in 2008 concluded that aerobic exercise improved aspects of cognitive function in healthy older adults, particularly in the areas of cognitive speed, delayed memory functions, auditory and visual attention, as well as motor function. Cardiovascular fitness also improved with the exercise, and although it would seem likely this was responsible for the improved cognition, there was no clear evidence that this was the case, and as such, it was considered that any exercise might achieve the same changes.[72] The variety of exercise interventions, the types of neurological disorders being tested, the different cognitive tests carried out, and the relatively short time span of most of these studies have all limited the progress in this research to some extent.[73] A more recent Cochrane review of 12 clinical trials (8–26 weeks long) also found little evidence of cognitive benefit in healthy older adults over 55, even if cardiorespiratory fitness improved.[74] Again, the range of study formats may have limited the chance of significant overall findings and in most (if not all) cases, cognitive changes were secondary outcome measures.

In non-hypertensive populations, some studies and meta-analyses have indicated that acute exercise improves executive function, for example speed of processing,[75-77] and may also improve memory.[75,76] More recently, moderate to vigorous exercise was found to produce significant benefits to executive function and memory,[78] and acute aerobic exercise was found to improve certain cognitive functions in both hypertensive and non-hypertensive middle-aged adults.[79] Another recent study has shown that resistance exercise in subjects with MCI can protect AD-vulnerable regions of the hippocampus from degeneration.[80] In the study of acute aerobic exercise above,[79] it was noted that many of the hypertensive subjects were on anti-hypertension medications, which are likely to have attenuated differences between the groups, with varying degrees of

influence, due to the different types of anti-hypertensive drugs being taken.

Hypertension is common from middle age onward, and aerobic exercise is highly recommended as a method to reduce BP.[81] As mentioned earlier, there is mounting evidence of strong links between long-term high BP and associated artery damage and stiffening, and the development of dementia later in life,[30,31,40,82] yet there is a paucity of data demonstrating a direct effect of exercise on cognitive function and/or decline later in life, in subjects with hypertension. The length of clinical trials needed to provide conclusive evidence may be prohibitively long. Nevertheless, the considerable knowledge of links between hypertension and later cognitive decline has led healthcare professionals to promote aerobic exercise to reduce BP, with the aim of maintaining cognitive health.[83,84] A recent international consortium across 15 countries in 5 continents, the Cohort Studies of Memory in an International Consortium collaboration cohort study, found that vigorous physical activity was associated with better cognitive performance,[85] along with higher levels of education. The same study highlighted how other individual modifiable risk factors can influence study results, as declines in at least one cognitive outcome were shown to be associated with current smoking status, diabetes, and history of stroke.

Multi-factorial Lifestyle Changes

We have discussed evidence of positive cognitive outcomes following aerobic exercises and resistance training in aged cohorts, and it is likely that these benefits result at least partly from a reduction in hypertension. Healthy ageing, longevity, and a reduced risk of dementia have also been linked to diet – another modifiable lifestyle component. The traditional Mediterranean diet (MeDi) and Okinawan diet have both been associated with longevity.[86-88] More recently, aspects of the MeDi and the Dietary Approaches to Stop Hypertension (DASH) diet have been combined to form the MIND diet, with the specific aim to promote brain health. The MeDi, Okinawan diet, DASH, and MIND diets all emphasize the intake of a variety of fruits and vegetables, fish, whole grains, and healthy fats, while having a low intake of saturated fat, processed foods, added sugar, and little or no red meat or processed meats. Epidemiological studies and more recent clinical studies have provided evidence that the MeDi and MIND diets can reduce aspects of cognitive decline.[89-91]

Until quite recently, most preventive interventions have been tested in small groups, with studies focusing on only one lifestyle factor. Many of these studies have yielded negative or modest results. The etiology of AD dementia is considered to be multifactorial and multidomain interventions that simultaneously target several risk factors and mechanisms might be the strategy for optimal preventive effects, as discussed in a recent review.[92] With the Lancet Commission recently indicating that up to one third of AD and related dementias may be delayed or prevented with reductions in modifiable risk factors, the optimization of lifestyle modifications to reduce such risk factors is urgently needed.[93]

In the last 10 years, several ambitious multidomain lifestyle intervention studies to prevent cognitive decline have yielded encouraging results. Some studies combined regular exercise and healthier diets, for example, the Washington Heights-Inwood and Columbia Aging Project and Exercise and NutritionaL Interventions for coGnitive and Cardiovascular HealTh Enhancement (ENLIGHTEN) trial, with the combined lifestyle changes showing greater benefits than the individual components.[94,95] ENLIGHTEN investigated the benefits of aerobic exercise, the DASH diet, or a combination of both, in a cohort of sedentary people aged 55 or over, with vascular cognitive impairment though no dementia. Interestingly, the DASH diet groups in the study, and not the exercise-only group, showed reduced dependence on anti-hypertensive treatments as a result of the intervention.[96] Conversely, improved aerobic fitness and lower sodium intake were associated with improved executive functioning in this study.[96] Other studies have investigated physical exercise in combination with brain training exercises. For example, a study using a cohort of healthy older adults which tested physical activity (a combined walking and resistance training program), a computerized brain training program (through Posit Science) and a combination of both, discovered that the combination improved cognition and cerebral glucose metabolism.[97] A more recent pilot clinical trial which tested an interactive physical and cognitive exercise program (iPACESTMv2.0) reported significant improvements in executive function[98] and that the improvements were associated with changes in levels of the salivary metabolic biomarkers cortisol and insulin-like growth factor-1.

The multi-domain Alzheimer preventative trial (known as MAPT) investigated the effect of physical activity counseling (Advice to engage in 150 min of moderately intensive physical activity per week), nutrition counseling, cognitive training, and preventative consultations in a cohort of adults aged 70 or over, with subjective memory complaints. Participants also received either an omega-3-polyunsaturated fatty acid supplement or placebo.[99] Only those participants in the intervention group who were also taking the supplements demonstrated significant improvements, in the Mini-Mental State Examination (cognitive impairment questionnaire) scores. The ENCORE (Exercise and Nutritional Interventions for Cardiovascular Health) study investigated the effect of aerobic exercise, following the DASH diet and the combination of the two on BP and metabolic outcomes in an overweight middle-aged cohort. The DASH diet resulted in lower BP, and the addition of exercise and weight loss resulted in even greater BP reductions.[100] The combined treatment also improved the secondary outcome measures of executive functioning, learning, and memory.[101]

The ambitious Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability[102] trial combined regular aerobic exercise, aspects of the MeDi and DASH diets,

a computerized brain training program, and regular health monitoring.[103,104] In their cohort of adults aged 60–77, with cardiovascular risk factors and some evidence of neurocognitive weakness based on the CERAD test battery, this study provided evidence of neurocognition improvements resulting from the 2-year intervention. Cardiorespiratory fitness was found to associate most strongly with the observed neurocognitive improvements in executive function and processing speed (but not memory).[105] This study has initiated a world-wide FINGERS collaborative network of trials, to replicate the study in many countries with the aim of validating the results in different populations and cultures.[102] Studies are already underway or being planned in the USA (US-POINTER), Australia (AU-ARROW), Singapore (known as SINGER), China (MIND-CHINA), and other countries (for further information see http://wwfingers.com).

The aforementioned multimodal intervention studies, mostly ongoing or completed in the last 10 years, have demonstrated that changes to multiple aspects of lifestyle are providing health improvements in various domains, delivering benefits to the cardiovascular system, metabolism, and cognitive health. The promotion of such lifestyle changes, particularly to middle-aged and older adults, would be a valuable preventative strategy to both improves the quality of life of ageing populations and to reduce the burden on public health departments, hospitals and carers.

Conclusions

Hypertension is a major risk factor for many chronic diseases and serious health events. It affects more than 40% of adults worldwide and is associated with stroke, myocardial infarction, heart failure, and other cardiovascular diseases. It has also been shown to cause functional and structural damage to the brain, which increases the risk of cognitive impairment and dementia. Vascular structural changes, endothelial dysfunction, and sympathetic overstimulation have been described as the major contributing factors to the pathophysiology of hypertension.[106,107] Exercise has been shown to be an effective component of nonpharmacological interventions for BP control. The type and frequency of exercise that may be needed to be effective in BP management are currently being investigated, both to understand the physiology behind the improvements, as well as to find the most effective individual exercise "prescriptions." More recently, clinical trials of multidomain lifestyle interventions that include for example exercise, diet modification, brain training exercises, medical counseling, and encouragement of social engagement, are showing considerable promise, both in the preservation of certain cognitive function domains, as well as in the improvement of cardiovascular, and metabolic risk factors. The benefits of such trials will be far-reaching, by providing a pathway for improving the quality of life for the ageing population as well as reducing public health costs.

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Review Article

Cardiorenal Protective Effects of Renal Denervation in Chronic Kidney Disease

Sheran Li, Cara M. Hildreth, Jacqueline K. Phillips

Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University, 2109, NSW, Australia

Abstract

Hypertension and cardiovascular disease contribute to increased morbidity and mortality in patients with chronic kidney disease (CKD). As an interventional antihypertensive treatment, renal denervation appears to offer benefits beyond a simple blood pressure reduction. This review article will discuss the available experimental and clinical evidence on the application of renal denervation in CKD. Specifically, experimental studies suggest that renal denervation could reduce blood pressure in some but not all forms of CKD and that there is a differential contribution of the renal afferent nerves to high blood pressure in different conditions. A few clinical studies have documented a blood pressure reduction following renal denervation in CKD patients, but none of these studies are randomized, sham-controlled trials, potentially undermining the strength of this evidence. Experimental and clinical studies show that renal denervation is not only safe for CKD patients, but may offer renoprotective effects, such as attenuation in proteinuria, glomerular, and tubular-interstitial damage and slowing down decline in kidney function, but these benefits again await further substantiation in controlled trials. There is also preliminary evidence suggesting renal denervation might improve cardiac hypertrophy and autonomic function as assessed by heart rate variability, systolic blood pressure variability, and baroreflex sensitivity, in both animal models and patients with CKD. Despite therefore significant progress in the application and understanding of the mechanisms underlying renal denervation as a therapeutic procedure, ongoing work is required to confirm whether or not proposed cardiorenal benefits are associated with a reduction in the comorbidity of cardiovascular disease in CKD populations.

Key words: Blood pressure, cardiovascular disease, chronic kidney disease, kidney function, renal denervation

Introduction

Chronic kidney disease (CKD) is a well-recognized public health problem, prevalent in approximately 10–15% of the general population worldwide.[1] Notwithstanding the risk of progression to end-stage renal failure (ESRD), CKD also brings with it an increased risk of cardiac and cerebrovascular disease due in part to the high incidence of hypertension in CKD. Indeed cardiovascular death is the most common cause of mortality in CKD patients[1] Resistant hypertension is a key feature in CKD patients[2] and is thought to be driven by multiple and interrelated factors. Evidence from experimental models suggests that the autonomic nervous system plays an important role in the development of hypertension and cardiovascular complications associated with CKD, with evidence for both increased sympathetic efferent drive to the kidney[3] and increased afferent signaling from the kidney to the central nervous system[4] [Figure 1].

Catheter-based renal denervation is emerging as a potential antihypertensive strategy for resistant hypertension. The underlying rational is based on a number of concepts arising from clinical and experimental studies:

1. Non-selective surgical sympathectomy, a procedure that removes the thoracic and lumbar ganglia, markedly reduced hypertension when it was in use prior to the advent of effective antihypertensive drugs,[5] and though it was not without adverse effects, for example, profound hypotension, supported the premise that hypertension is associated with sympathetic overactivity.

Address for correspondence:
Jacqueline K. Phillips, Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University, 2109, NSW, Australia. E-mail: Jacqueline.phillips@mq.edu.au

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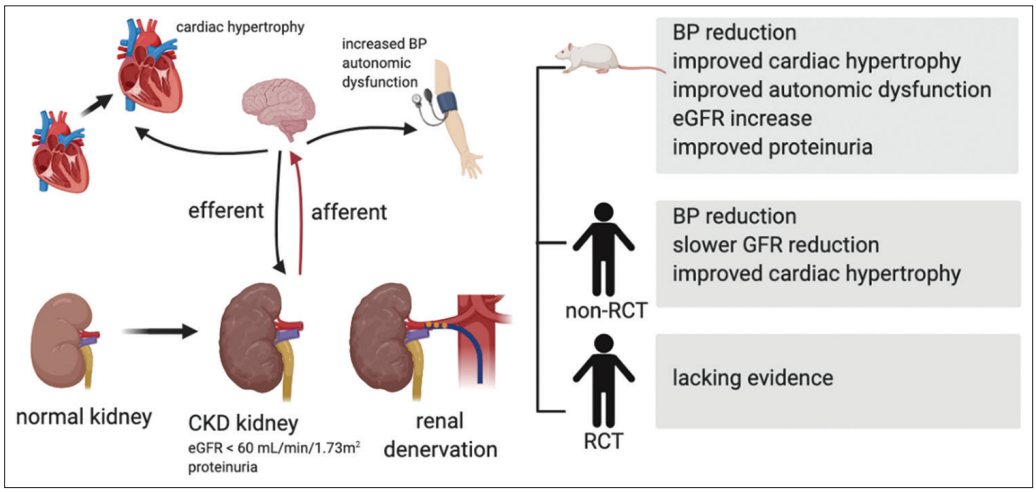

Figure 1: Summary figure illustrating CKD association with increased renal afferent (sensory) and efferent (sympathetic) nerve activity, their proposed contributions to the complications of CKD, and the available experimental and clinical evidence of the benefits of renal denervation. CKD, chronic kidney disease, BP, blood pressure; eGFR, estimated glomerular filtration rate; RCT, randomized clinical trial. Figure created with BioRender.com

2. Chemical renal denervation can prevent the development, delay onset or attenuate the degree of hypertension in experimental animal models of hypertension,[3,6] and renal sympathetic activity, as determined by renal noradrenaline spillover, is elevated in patients with essential hypertension compared with normotensive controls,[7] with these two points collectively supporting increased sympathetic drive to the kidney as a key driver of hypertension.
3. The renal nerve bundle, which consists of both renal afferent sensory and efferent sympathetic nerves, is readily accessible to radiofrequency energy emitted through a catheter in the renal artery lumen making a surgical approach feasible on a wide scale.[8]
4. The technical development of interventional angioplasty for treatment of conditions such as acute myocardial infarction facilitated the development of devices suitable for renal denervation.[9]

Under these circumstances, the first-generation radiofrequency-generating catheter, which could be advanced into the renal artery to ablate renal nerves, was developed by Ardian and later put in a clinical trial under the executive of Medtronic.[8] Subsequent proof-of-concept studies demonstrated that renal denervation may have beneficial effects that reach beyond a simple reduction in blood pressure and for patients with CKD could have significant clinical impact providing both cardiovascular and renoprotective effects.[10,11] Of note is that in CKD patients, evidence of sympathetic overactivity alongside increased afferent signaling derived from the native injured kidneys[12] would suggest they are ideal candidates for the procedure. This review will summarize the current evidence for the potential cardiorenal protective effects of renal denervation in CKD [Figure 1].

Effect of Renal Denervation on Blood Pressure

Evidence from animal models

Renal denervation has been used in a variety of animal models of hypertension as an experimental approach to reduce blood pressure, with stripping of the renal nerves and periaxonal application of phenol to the renal artery, which removes both renal afferents and efferents, being shown to reduce blood pressure in models of two-kidney-one clip hypertension,[13] 5/6 renal ablation,[14] and polycystic kidney disease.[3] More recently, catheter-based renal denervation has been shown to reduce blood pressure in the fetal uninephrectomized sheep CKD model.[15] While there are studies in certain animal models where renal denervation has not had an impact on blood pressure, for instance, in the Ang II-salt model and deoxycorticosterone acetate (DOCA)-salt model induced with lower than typical doses of Ang II or DOCA, respectively,[16] these studies, and specifically their application to models of CKD, provide a strong foundation for the use of renal denervation in CKD patients.

In the clinical setting, however, it remains unclear whether the effect is mediated by removal of sympathetic nerves or sensory nerves or a combination of both. This applies equally to the use of renal denervation to treat hypertension arising from other causes. To answer this question, researchers have sought to selectively ablate the renal afferent sensory nerves by either dorsal rhizotomy[6] or periaxonal application of capsaicin.[4] Available evidence suggests that afferent renal denervation can attenuate hypertension in the 5/6 renal ablation model of CKD[6,12] and in the subtotally nephrectomized spontaneous hypertensive rat (SHR).[17] Sensory denervation of the kidney has also been shown to reduce blood pressure in the DOCA salt model,[4] but notably, not in the AngII-induced hypertension

model.[16] These results suggest two things: Firstly, that the renal afferents may make a differential contribution to hypertension in different disease states and importantly, not all forms of CKD may be responsive to renal denervation.

Evidence from the clinic

The initial clinical trials undertaken to determine the efficacy and safety of catheter-based renal denervation in patients focused on patients with essential hypertension, excluding patients with moderate to severe CKD.[18] Following the initial promising results, a pilot study examining 15 patients with moderate to severe CKD found that renal denervation caused a marked blood pressure reduction at 1, 3, 6, and 12 months of follow-up without deterioration of renal function.[19] Subsequent single-center and multi-center prospective studies have shown a similar blood pressure lowering effect of renal denervation in CKD patients.[20,21] Moreover, a significant blood pressure reduction within 6 months of follow-up after denervation was also observed in ESRD patients.[22] Of note, however, is that a lack of central or 24-h ambulatory blood pressure reduction following renal denervation in CKD and/or ESRD patients has also been reported.[23] Importantly, none of these clinical studies were randomized sham-controlled trials, potentially undermining the strength of evidence. As such, whether or not renal denervation can truly produce a meaningful and sustainable blood pressure lowering effect in CKD cohorts needs further investigation.

Renoprotective Effect of Renal Denervation

In addition to a blood pressure lowering effect, beneficial effects of renal denervation on kidney damage in CKD have been reported. In the 5/6 renal ablation model, both total and afferent renal denervation are reported to increase glomerular filtration rate (GFR), lower proteinuria, and ameliorate the development of glomerular and tubular-interstitial damage.[24] Similar findings are described in the uninephrectomized Dalt-salt sensitive model.[25] Interestingly, the attenuation of renal damage paralleled a reduction in blood pressure in the 5/6 renal ablation but not uninephrectomized Dalt-salt sensitive model of CKD, suggesting that renal denervation can provide renal protection independent of any effect on blood pressure.

In humans, observational studies suggest that renal denervation can slow or even halt the decline rate of estimated GFR (eGFR) in patients with CKD.[11,20] For instance, in a study consisting of 46 CKD patients, eGFR showed an annual decline of 3.5 mL/min/1.73m^2 for the 60 months before renal denervation but was stable during the 24 months after renal denervation.[11] The most recent study examining the impact of renal denervation on long-term renal function, published as part of the Global SYMPLICITY Registry, showed that over a 3 year period, there were no statistically significant differences in the decline in renal function between patients with and without chronic kidney disease.[21] Although these studies show promising benefits and indicate that there are no long-term safety concerns associated with renal function after renal denervation, further large-scale multicenter randomized clinical trials are warranted to substantiate the observed renoprotective effects.

Cardioprotective Effect of Renal Denervation

Cardiovascular disease is the leading cause of morbidity and mortality in CKD patients, and patients present with cardiac hypertrophy and fibrosis, arrhythmias[26] and abnormalities in autonomic function, namely sympathetic overdrive, parasympathetic insufficiency, and reduced baroreflex sensitivity (BRS).[27] Data available from both experimental and clinical studies suggest that renal denervation has cardioprotective effects and that this is also evident in CKD studies [Figure 1].

Improvements in cardiac hypertrophy and fibrosis have been reported after renal denervation in the SHR model[28] and in the fetal uninephrectomized sheep CKD model.[15] Renal denervation, however, failed to prevent the development of cardiac hypertrophy in the DOCA salt hypertension model.[29] In clinical studies, the beneficial effect of renal denervation on cardiac hypertrophy and fibrosis, reflected by reduced left ventricle mass, increased ventricular ejection fraction or decreased collagen turnover, have also been reported in patients with resistant hypertension[30,31] and importantly, those with CKD.[10] Similar to the renoprotective effects, the observed cardioprotective effects are associated with a lowering in blood pressure in some patients[30] but independent of such effect in others.[31]

Heart rate variability (HRV), systolic blood pressure variability (SBPV), and BRS have been measured in both experimental and clinical studies as indirect measures of autonomic activity and yielded inconclusive findings. In patients with resistant hypertension, an increase in all frequency components of HRV and reduction in low/high frequency ratio at 1 and 6 months post-denervation were present, suggesting a restoration of cardiac sympathovagal balance.[32] However, a lack of impact on HRV has also been reported in patients with resistant hypertension.[33] With regard to SBPV, reduced LF SBPV has been described after renal denervation in the SHR, indicating a reduced sympathetic control of blood pressure.[34] In human studies, the impact of renal denervation on cardiac sympathetic activity has been assessed through the uptake and washout of I^{123} metaiodobenzylguanidine (MIBG), which is actively transported into sympathetic nerve terminals by the noradrenaline transporter. Using this method, Donazzan *et al*.[35] showed reduced cardiac sympathetic nerve activity 9 months after renal denervation in resistant hypertension patients. In contrast, van Brussel *et al*.[36] showed no impact on the cardiac sympathetic activity was observed at 6 weeks post-denervation using the same measure. The discrepancy between these studies could be caused by variable factors including the efficacy of the denervation procedure, differing baseline cardiac sympathetic tone and small sample size. To the best of our knowledge, there

have been no clinical studies examining the impact of renal denervation on these parameters in CKD patients.

A variable impact of renal denervation on baroreflex control has similarly been reported in animal models of hypertension and CKD. Renal denervation did not cause any significant changes in heart rate baroreflex curve parameters assessed by infusion of phenylephrine and sodium nitroprusside compared with sham controls in a sheep heart failure model,[37] while renal denervation of the clipped kidney in two-kidney-one-clip rats improved the arterial BRS upon infusion of sodium nitroprusside 10 days post the procedure.[13] Renal denervation did not improve impaired heart rate BRS, but did improve impaired renal sympathetic nerve activity BRS in a cisplatin-induced acute renal injury model rat 1-week post-denervation.[38] An improved heart rate and lumbar sympathetic nerve activity BRS were also reported in SHR 1-week post-denervation.[39] In 5/6 nephrectomy rats, total renal denervation partially recovered baroreflex control of heart rate in response to phenylephrine administration 8 weeks post-denervation.[14] Using spontaneous BRS as their measure, Hart *et al*.[39] showed that total renal denervation caused a significant albeit small increase in cardiac BRS within 24 h of denervation surgery in the SHR. Evidence of the impact of renal denervation on cardiac BRS in humans including CKD patients is sparse. The only evidence is from the work of Hart *et al*.,[39] who observed improved spontaneous BRS in patients with resistant hypertension 6 months post-denervation procedure. Interestingly, this improvement in BRS was not associated with a reduction in blood pressure, suggesting that the beneficial effect is independent of changes in blood pressure. Although Grassi *et al*.[40] documented an improvement in baroreflex control in muscle sympathetic nerve activity in patients with resistant hypertension at both 3 and 6 months after denervation, this was unrelated to the blood pressure reduction induced by the procedure. Whether the improvement in BRS following renal denervation could reduce the comorbidity of cardiovascular disease in CKD populations awaits future investigation.

Conclusion

Hypertension and cardiovascular disease contribute to increased morbidity and mortality in CKD and are contributing factors to the progression to ESRD. While observations from clinical practice in hypertensive and CKD patients and a large body of experimental evidence suggests renal denervation could provide cardiorenal protection in CKD, no large scale randomized sham-controlled trials are available that so far to support these findings. Furthermore, the data suggest that not all forms of CKD may be equally responsive to renal denervation and specific cohort studies are required. Given that patients with CKD are at high risk for cardiovascular events, including heart attack, arrhythmia, and stroke, this is an important area of research that warrants close investigation.

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Review Article

Central Aortic Blood Pressure and Pulse Wave Velocity as Tools in the Hemodynamic Assessment of Hypertension

Isabella Tan[1], Mark Butlin[1], Fatemeh Shirbani[1], James R. Cox[1], Karen Peebles[2], Junli Zuo[1,3,4], Alberto P. Avolio[1]

[1]Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia, [2]Department of Health Professions, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia, [3]Department of Hypertension, Ruijin Hospital North, Shanghai Jiaotong School of Medicine, Shanghai, China, [4]Department of Geriatrics, Ruijin Hospital North, Shanghai Jiaotong School of Medicine, Shanghai, China

Abstract

The effects of age on arteries are associated with stiffening of the artery wall, and this phenomenon is a major determinant of the age-related increase in isolated systolic hypertension. Arterial stiffness affects the speed of the arterial pulse which can be readily measured noninvasively. Alterations in arterial stiffness also affect the relationship between the conventionally measured blood pressure in the brachial artery and the pressure in the central aorta, which characterizes the pressure load on the ejecting ventricle. Central aortic systolic pressure is lower than peripheral systolic pressure and is affected by a range of hemodynamic factors, including heart rate. Devices are now available that can estimate central aortic pressure from the calibrated peripheral pulse waveform. Studies have shown that arterial stiffness, as measured by pulse wave velocity, and central aortic pressure can enhance the characterization of cardiovascular risk beyond the conventional measurement of brachial blood pressure. Although measurements of central aortic pressure and pulse wave velocity have provided a wealth of research and epidemiological data, there has been limited entry of these techniques in the routine clinical setting as well as in guidelines for treatment and management of hypertension. This review will address the current evidence of the use of central aortic pressure and pulse wave velocity for assessment of hypertension as a major cardiovascular risk.

Key words: Blood pressure, vascular stiffness, arterial pressure, hypertension, heart disease risk factors

Introduction

The hemodynamic assessment of hypertension, or "hard pulse disease" as it was once known,[1] has its roots in the late 19th century when Frederick Akbar Mahomed (1849–1884) used the sphygmograph to quantify the "hardness of the pulse."[2] By quantifying the amount of hold-down force necessary to obtain an ideal arterial pulse trace, Mahomed was able to describe both quantitatively, using measured force, and qualitatively, using pulse contour changes, the phenomenon of essential hypertension. However, perhaps due to the technical difficulties and the meticulousness required to operate the sphygmograph, this form of hemodynamic assessment did not gain traction in the medical field. It was not until some 25 years after the introduction of the Riva-Rocci method of using an occlusive cuff, together with the application of Korotkoff sounds, that routine measurement of blood pressure became a part of standard clinical care.[3] Since then, the hemodynamic assessment of hypertension, at least in clinical practice, has been based solely on two discrete numerical values – systolic pressure and diastolic pressure. From the first Build and Blood Pressure study conducted in 1959[4] that produced the first diagnosis threshold for hypertension diagnosis, to subsequent large epidemiological studies, such as the Framingham Heart Study[5] identifying the risks associated with hypertension, research evidence that informs clinical practice has all been based on measurements of brachial systolic and diastolic blood pressure. Furthermore, studies have shown that lowering brachial blood pressure in hypertensive individuals resulted in reduced cardiovascular events[6] and regression of left ventricular hypertrophy (LVH).[7] As such, despite the knowledge that brachial

Address for correspondence:
Dr Isabella Tan, Level 1, 75 Talavera Road, Macquarie University, Sydney, NSW 2109, Australia. E-mail: isabella.tan@mq.edu.au

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blood pressure is not the same as central aortic blood pressure, which represents the real pressure load on the heart, it has been clinically accepted that diagnosis and treatment of hypertension based on brachial blood pressure values would be sufficient. However, as differential effects on the heart of pharmacological antihypertensive treatments come to light despite achieving the same reduction in brachial blood pressure,[8] questions have been raised as to whether assessing central aortic pressure, which can now be readily measured non-invasively, would provide additional benefits in the diagnosis and management of hypertension. In addition, large artery stiffness, the major determinant of central aortic pressure and moderator between central and brachial blood pressure, is an established prognostic factor for hypertension.[9] Research in the past two decades has time and time again shown that large artery stiffness, as assessed by pulse wave velocity, is an independent risk factor for cardiovascular disease and events above and beyond the risk of hypertension itself,[10] yet routine measurement of pulse wave velocity in clinical practice is scarce. Evidently, this intricate relationship between central aortic pressure, large artery stiffness, and hypertension is currently underappreciated in clinical practice. This review will discuss the evidence supporting the use of central aortic pressure and pulse wave velocity in the hemodynamic assessment of hypertension and postulate why the clinical uptake of these measurements may have been slow despite this supporting evidence.

The Arterial Pulse, Central Aortic Pressure, and Pulse Wave Velocity

While current hemodynamic assessment of hypertension is mainly based on discrete numerical values of systolic and diastolic pressure, it cannot be forgotten that arterial pressure changes continuously within each cardiac cycle, forming the arterial pulse. As the heart beats, a train of arterial pulses travels from the aorta to the peripheral vessels and the pulse changes shape in the process, becoming narrower in the systolic portion and with systolic pressure increasing as the wave travels further away from the heart. Mahomed was the first to describe pulse contour changes between the central and peripheral arteries using tracings from the sphygmograph.[2] However, changes in the pulse contour were not specifically studied until the work of Kroeker and Wood,[11] in which arterial pulse waveforms were measured simultaneously in a central artery (the arch of the aorta or left subclavian artery) and a peripheral artery (brachial, radial, and femoral artery) using intra-arterial catheters. Kroeker and Wood observed that, while diastolic pressure and mean arterial pressure showed a small progressive decrease as the arterial pulse wave travelled from central to peripheral arteries, systolic pressure in the peripheral arteries was consistently higher than the central artery, with brachial, radial, and femoral systolic pressure at 109%, 112%, and 110% of central systolic pressure, respectively.[11] Later studies showed that this amplification of systolic pressure from the central to peripheral arteries varies greatly both within and between individuals depending on age, gender, height, and heart rate.[12] This phenomenon of systolic pressure amplification can be attributed to the nature of the arterial system, whereby vessels get stiffer further away from the heart. As the arterial pulse wave travels from the compliant central arteries to the stiffer peripheral arteries, the pulse wave is reflected toward the heart, resulting in a summation of a "forward" traveling pulse wave and a reflected "backward" travelling pulse wave. This leads to an augmented systolic pressure in the periphery, as the reflected wave generally meets the forward wave during systole due to the speed at which the arterial pulse wave travels, that is, pulse wave velocity. This pulse wave velocity is dependent on the stiffness of the arterial wall, and, as documented by Kroeker and Wood,[11] increases as the arterial pulse wave travels from the central to peripheral arteries, thus explaining, at least in part, the larger augmentation in systolic pressure in the peripheral arteries compared to central arteries. However, as central arteries stiffen with age, the difference between central and peripheral systolic pressure decreases, resulting in reduced systolic pressure amplification.[13]

Central aortic pressure, as opposed to brachial pressure, represents the true pressure load on the heart, as it is the pressure the heart must work against to expel the ventricular content (stroke volume). One of the main determinants of central aortic pressure is the compliance of the aorta. As blood is ejected intermittently from the heart, the aorta acts as a cushion and stores a portion of stroke volume during systole, which then is released during diastole. This ensures that blood flow reaches peripheral tissues in a continuous fashion with pulsatility minimized. A compliant aorta would store a larger proportion of the stroke volume during systole than would a stiffer aorta. Thus, given the same stroke volume, a stiffer aorta would result in a higher peak pressure during systole and lower pressure during diastole, resulting in an increase in pulse pressure. In addition, due to the reduction of the stroke volume stored during systole this will inherently this increase the in pulsatility which will continue throughout the vasculature. This will lead, leading to increased stress on small vessels that are not designed to accommodate pulsatile flow and ultimately result in end-organ damage, such as in the brain and kidneys.[14] In essence, an increase in large artery stiffness has both upstream effects on the heart (through increase in central aortic pressure) and downstream effects on end-organs (through increased pulsatility transmitted to small vessels). As such, it is not unreasonable to assume that measurement of central aortic pressure and large artery stiffness, the latter by way of pulse wave velocity measurement, can provide additive value in risk stratification beyond the assessment of hypertension with brachial blood pressure alone.

Evidence for the Use of Central Aortic Pressure and Pulse Wave Velocity in the Hemodynamic Assessment of Hypertension

Central Aortic Pressure

Hypertension is conventionally diagnosed using systolic and diastolic pressure values measured by brachial cuff sphygmomanometry. However, although the blood pressure

values present a cardiovascular risk and the condition is essentially asymptomatic, there are important progressive pathological sequalae such as LVH.[15] Hence, assessment of antihypertensive treatment is quantified by the effect of blood pressure lowering on regression of LVH. This was done in a major clinical trial comparing the effect of different pharmacological interventions on reducing brachial blood pressure and regression of LVH. The Losartan Intervention for Endpoint reduction in hypertension study (LIFE)[16] compared an angiotensin receptor blocker, losartan, against a beta blocker, and atenolol. The study showed that although both agents had similar effects in lowering brachial blood pressure after a 4-year follow-up, and both were associated with regression of LVH, losartan produced a greater degree of LVH regression, as assessed by reduction of Cornell voltage-duration product (10%) and Sokolow-Lyon voltage (15%), compared to atenolol (5% and 9%, respectively). Hence, the conclusion was drawn that losartan had beneficial effects beyond lowering blood pressure.

The LIFE study was an important study since it was one of the first studies to show the superiority of one class of antihypertensive agent (angiotensin receptor blocker, losartan) compared to another class (beta-blocker, atenolol). However, as expected, atenolol was associated with a reduction in heart rate (−7.7 bpm for atenolol vs. −1.1 bpm for losartan). This is a significant feature of this trial in interpreting the final results since the amplification of the aortic pulse toward the periphery is intrinsically dependent on heart rate due to the frequency characteristics of the brachial transfer function.[12] Hence, for a similar reduction in pulse pressure measured at the brachial artery, the pulse pressure at the aortic root would be relatively higher in those treated with a beta-blocker. Since the LIFE trial ran for over 4 years, those treated with atenolol would have had a relatively higher central aortic systolic pressure compared to those treated with losartan for a sufficiently long time to affect left ventricular remodeling. Thus, if central aortic pressure were measured in the LIFE study, some of the effect on regression of LVH could have been explained by the difference in central aortic pressure, even though the effect on brachial blood pressure was similar for both agents. The difference in central and peripheral systolic pressure due to heart rate was convincingly demonstrated in a later study (the Conduit Artery Functional Endpoint study) where central aortic pressure was estimated from the radial pulse calibrated to brachial systolic and diastolic pressure and comparisons were made between a calcium channel blocker (amlodipine) and a beta blocker (atenolol).[8]

The above studies provide evidence that central aortic pressure can give additional information compared to conventional brachial blood pressure on the effect of hypertension on end organ damage (LVH) when there are changes in other hemodynamic parameters such as heart rate. In addition, when pharmacological intervention for blood pressure lowering is guided by non-invasive measurement of central aortic pressure, the same reduction in brachial pressure can be achieved with reduced medication with no adverse effect on quality of life and LVH. A similar qualitative conclusion was reached in treatment of heart failure where titration of medication based on the central aortic waveform improved exercise capacity.[17] Interested readers are encouraged to read a more in-depth review of the current evidence on the utility of central aortic pressure in clinical practice.[18]

Pulse Wave Velocity

It has been over two decades since aortic stiffness, as assessed by pulse wave velocity, was first shown to be a marker of cardiovascular risk in patients with essential hypertension,[10] whereby the risk of being in a high cardiovascular mortality risk group was up to a staggering 7 times higher in those whose pulse wave velocity was in the upper quartile.[10] In the years since, increased pulse wave velocity has been firmly established as an independent risk factor for cardiovascular events such as stroke and coronary heart disease, as demonstrated in the Framingham study,[19] as well as cardiovascular and all-cause mortality in both general[20] and diseased populations such as those with hypertension.[21] The role of pulse wave velocity in the diagnosis and management of hypertension was further consolidated when increased pulse wave velocity was recognized as an influencing factor on the prognosis of hypertension by the 2007 Guidelines on the Management of Arterial Hypertension from the European Society of Hypertension (ESH) and European Society of Cardiology (ESC).[9] The most recent guidelines continues to recognize increased aortic stiffness as a factor influencing cardiovascular risk in patients with hypertension.[22] Furthermore, measurement of pulse wave velocity has been added as a recommendation for clinical evaluation of hypertension-mediated organ damage with a Class B recommendation and Level IIb evidence.[22]

The Framingham Heart Study was the first study to show that including pulse wave velocity in risk factor assessment in a general population was additive to standard risk factors such as systolic blood pressure.[19] In a cohort of 2232 participants, predicted cardiovascular risk was calculated based on age, sex, systolic blood pressure, use of antihypertensive medication, cholesterol, smoking, presence of diabetes mellitus, and aortic pulse wave velocity over a period of 8 years. The study showed that higher aortic pulse wave velocity was associated with a 48% increase in the risk of experiencing a first major cardiovascular event. Furthermore, inclusion of aortic pulse wave velocity in the risk assessment model resulted in significant improvement of risk reclassification and risk discrimination. A more recent meta-analysis of 16 studies, with a combined cohort of 17,635 participants, showed that addition of aortic pulse wave velocity in risk assessment improved the 5-year risk prediction of cardiovascular events by 5% in the whole cohort and 14% in the intermediate-risk group.[23] Together, these studies demonstrate that measurement of pulse wave velocity may be beneficial in risk stratification, particularly in individuals who are already at risk of cardiovascular events, such as those with hypertension.

The relationship between blood pressure and arterial stiffness is intrinsically inseparable. The mechanical design

of the arterial wall with its composite lamellae of elastin and collagen is such that an increase in pressure results in the recruitment of more collagen fibers, which is over 1000 times stiffer than elastin.[24] In other words, the artery stiffens with increasing blood pressure. As such, along with age, blood pressure is one of the main determinants of pulse wave velocity. However, this is not a unidirectional relationship. As mentioned earlier, increased arterial stiffness, in particular aortic stiffness, results in an increase in central aortic systolic pressure and a decrease in diastolic pressure, thereby widening pulse pressure. At the same time, elevated blood pressure increases pulsatile stress on the arterial wall, resulting in accelerated degradation of elastin fibers beyond the effects of normal aging[25] and further increasing arterial stiffness.[26] This bidirectional relationship between blood pressure and arterial stiffness raises the question of whether hypertension causes arterial stiffening, or whether arterial stiffening causes hypertension. Studies in both animal models[27] and humans[28] have shown that arterial stiffening can precede the development of hypertension. In the Baltimore Longitudinal Study of Aging, pulse wave velocity was an independent predictor of systolic blood pressure increase over a median follow-up of 4.3 years.[29] Furthermore, in individuals who were normotensive at baseline, pulse wave velocity predicted incident hypertension beyond median follow-up years.[29] In light of the above evidence, it can be seen that the value of pulse wave velocity measurement in the assessment of hypertension lies not only in the improved risk stratification of patients but also in the prediction of the development of hypertension in normotensive individuals.

Measurement of Central Aortic Pressure and Pulse Wave Velocity in Clinical Practice

Measurement of Central Aortic Pressure

In the past, central aortic pressure could only be measured invasively. Numerous commercial devices are now currently available for the non-invasive measurement of central aortic pressure.[18] One method implemented by several devices is the use of a generalized transfer function. The characteristics of the transmission of the pulse waveform from aorta to brachial artery are relatively constant between individuals in the adult population.[30] This permits a generalized transfer function, in essence a low pass filter, to be applied to a peripheral artery waveform to estimate the aortic waveform and thereby central aortic pressure.[31] Utilization of the generalized transfer function method requires the peripheral artery waveform to be calibrated and accuracy of the estimated central aortic pressure is dependent on the calibration method. Other methods for estimation of central aortic pressure have also been developed, such as identification of the late systolic peak in a peripheral arterial waveform.[32] Notwithstanding, all methods are reliant upon acquisition and analysis of a peripheral arterial waveform (pulse wave analysis) and on calibration. Discussion of issues surrounding calibration and subsequent accuracy of measured central aortic pressure is beyond the scope of this review. Commonly, the peripheral arterial waveform is obtained using applanation tonometry at the radial, brachial, or carotid artery and be calibrated to oscillometric brachial systolic and diastolic blood pressure (or mean and diastolic blood pressure). Brachial arterial waveform can also be obtained using a cuff over the arm, which can be integrated into oscillometric blood pressure measurement and is therefore less operator-dependent than tonometry. Studies have shown that central aortic pressure values of acceptable accuracy can be obtained with both tonometry-based[33] and cuff-based devices[34] when conventional brachial cuff pressure measurements are used to calibrate the peripheral waveform. One study[35] showed reduced accuracy with non-invasive brachial pulse waveform calibration compared to invasive pressure calibration. Figure 1 shows an example of a central aortic waveform derived from the cuff-measured brachial waveform using a generalized transfer function in a young and old individual, respectively.

Measurement of Pulse Wave Velocity

Measurement of pulse wave velocity requires the measurement of arterial waveforms from two arterial sites some distance apart. A fiducial point, most commonly the foot of the wave, is used to determine the time delay between the points on the two pulse waves, that is, transit time. Pulse wave velocity is then determined by dividing the arterial path length, measured as a linear distance between the arterial recording sites, by the transit time [Figure 2].

Although pulse wave velocity can be determined across any arterial segment, carotid-femoral pulse wave velocity, which can be measured non-invasively, is considered the gold standard in the assessment of aortic stiffness and is the measure recommended for use in the ESC/ESH Guidelines on the Management of Arterial Hypertension.[22] Determination of carotid-femoral pulse wave velocity involves obtaining arterial pressure waveforms from the carotid and femoral arteries. Carotid and femoral waveforms can be obtained by applanation tonometry, and most commercially available devices for carotid-femoral pulse wave velocity measurement are tonometry-based. Most tonometry-based devices require that the arterial waveforms be obtained sequentially, and an electrocardiogram (ECG) is additionally required. The transit time would then be determined with the R peak of the ECG as a common reference point. There are also devices available that are fully cuff-based, where both carotid and femoral pressure waveforms can be obtained with a cuff around the neck and thigh, respectively, or use a combination of both tonometry and cuff, whereby carotid waveform is obtained by tonometry and femoral waveform is obtained with a cuff around the thigh. Cuff-based devices are simpler to use and require less time than tonometry-based devices, as carotid and femoral waveforms can be obtained simultaneously without the need of an ECG. They also tend to be less dependent on operator experience, therefore, making them more suitable for use in a clinical setting. Other methods

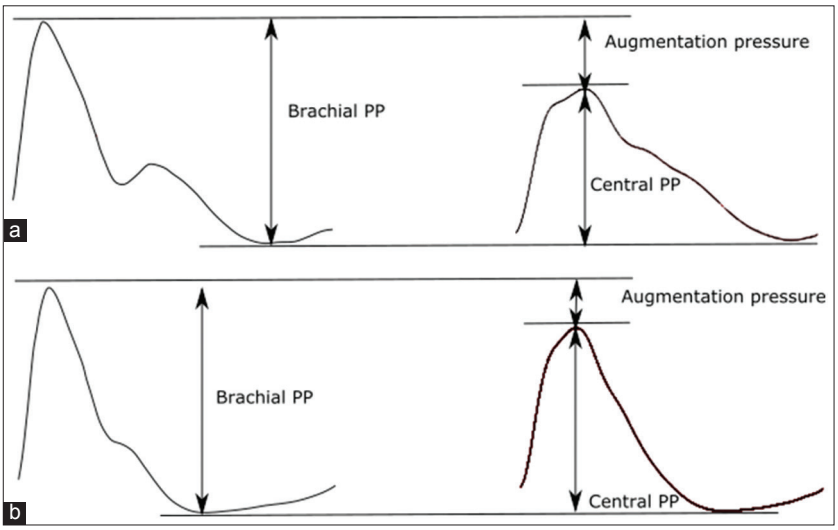

Figure 1: Examples of central aortic waveforms (right) derived from corresponding brachial waveforms (left) from (a) a young individual and (b) an older individual. Notice that in the older individual, the augmentation pressure and hence pressure amplification is reduced compared to the young individual. PP: Pulse pressure

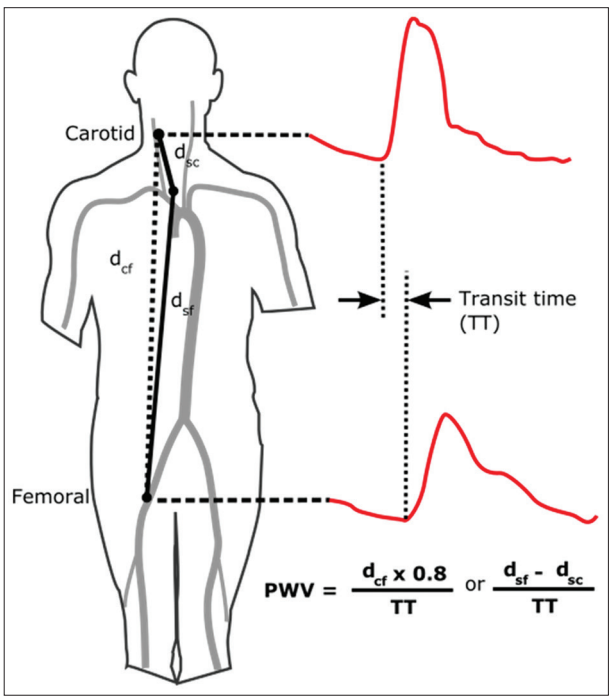

Figure 2: Schematic of carotid-femoral pulse wave velocity (PWV) determination. PWV is determined as arterial path length divided by the time delay between the foot of the pressure waves (transit time, TT), measured at the carotid and femoral artery, respectively. Arterial path length can be determined as direct linear distance from carotid to femoral recording sites (d_{cf}) multiplied by a factor of 0.8, or as the distance between sternal notch and femoral site (d_{sf}) minus the distance between carotid site and sternal notch (d_{sc})

of pulse wave velocity measurement, such as indirect estimation of pulse wave velocity based on pulse wave analysis using a single cuff around the arm,[36] and measurement over a different arterial segment, such as ankle-brachial pulse wave velocity,[37] are also available but beyond the scope of this review. A comprehensive review has recently been published on the measurement of arterial stiffness in humans[38] and interested readers are encouraged to refer to it.

An important aspect to pulse wave velocity measurement is the determination of arterial path length. For carotid-femoral pulse wave velocity, distance between the carotid and femoral recording sites can be determined by measuring distance over the body surface using a tape measure. It is currently recommended that the direct distance between the carotid and femoral recording sites be measured and multiplied by a factor of 0.8.[39] Another commonly used method is the subtraction method, whereby the distance between the carotid measurement site and the sternal notch is subtracted from the distance between the sternal notch and the femoral recording site, which is commonly on the inguinal fold for tonometry measurements or top edge of the thigh cuff for cuff-based measurements. The carotid-to-sternal-notch distance is subtracted to account for the pressure wave travelling in opposite directions from the aorta. Cuff-based devices may require an additional distance measurement from the inguinal fold to the top edge of the thigh cuff.

Impediments to the Use of Central Aortic Pressure and Pulse Wave Velocity in Clinical Practice

Despite the many years of research and established body of evidence on the value of central aortic pressure and pulse wave velocity, clinical uptake of their measurement remains scarce. One of the main reasons could be due to the limited number of randomized controlled trials with either central aortic pressure or pulse wave velocity as the treatment target or outcome

measure. While the body of evidence for the prognostic value of pulse wave velocity in hypertension is strong enough for it to be included in the guidelines, the benefit of using central aortic pressure over brachial blood pressure is still unclear.[22] To-date, there has only been one randomized trial that investigated the value of using central aortic pressure to guide hypertension treatment as compared with brachial blood pressure.[40] The results of this prospective, open-label, and blinded-endpoint trial showed that use of central aortic blood pressure resulted in a significant reduction of medication dosage to achieve the same blood pressure control, but there were no significant differences in left ventricular mass nor aortic stiffness when compared to treatment guided by brachial blood pressure. Recently, a double-blinded randomized controlled trial, the Guiding Hypertension Management Using Different Blood Pressure Monitoring Strategies (GYMNs study),[41] was set up to assess the optimal strategy for guiding hypertension management based on unattended office brachial blood pressure, home blood pressure, and central aortic blood pressure. The results of this trial are yet to be published, but the study will no doubt provide further insights as to whether central aortic blood pressure guided treatment will lead to better outcomes. Another reason for the lack of central aortic pressure measurements in clinical practice could be the lack of established reference values. At present, only Taiwan has published guidelines on the use of central aortic pressure in the management of hypertension, with a recommended cut-off value of 130/90 mmHg for the diagnosis of hypertension and treatment target.[42] A recent consensus statement on the clinical application of using central aortic pressure in the management of hypertension was also published from Taiwan.[43] On the other hand, the European guidelines state that measurement of central aortic pressure may be useful only in some circumstances, such as isolated systolic hypertension in the young with Class C recommendation and Level IIb evidence.[22] Due to the absence of pharmacological treatment to de-stiffen arteries beyond that of blood pressure control, there are currently no randomized controlled trials to-date with pulse wave velocity as a treatment target.

Practicalities of central aortic pressure and pulse wave velocity measurement may also pose a major barrier to the clinical uptake of these measurements. While central aortic pressure can now be readily determined with the use of an oscillometric cuff, measurement of pulse wave velocity still requires the use of applanation tonometry in most devices, which requires a certain level of operator expertise. Pulse wave velocity determination also requires straight distance measurement over the body surface, which can be difficult in some patients. As such, despite being included in the European guidelines as an important prognostic factor of hypertension, the same guidelines also stated that "routine use of (pulse wave velocity) measurement is not practical and is not recommended for routine practice."[22] This has led to the development of estimated pulse wave velocity based on age and mean arterial pressure,[44] which has been shown to provide similar risk prediction to measured pulse wave velocity.[45,46]

Conclusions

Both central aortic pressure and pulse wave velocity are valuable tools in the hemodynamic assessment of hypertension, especially in terms of providing additive value in assessing hypertension-related organ damage and in risk stratification. The body of evidence supporting their use in clinical practice continues to grow, but more randomized controlled trials may be needed, particularly for central aortic pressure, for sufficient improvement of the class of recommendation and level of evidence before widespread clinical uptake. In addition, more automated and operator-independent methods in the measurement of pulse wave velocity would be beneficial to ensure practicality of its use in a fast-paced clinical setting.

Declarations

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Topical Commentary

Should the Treatment of Hypertension be based on Blood Pressure Level Only or on Total Cardiovascular Risk?

Grant Shalaby[1,2], Jasper Lin[1,3]

[1]Department of Clinical Medicine, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia, [2]Department of Cardiology, Napean Hospital, Sydney, Australia, [3]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia

Abstract

The treatment of hypertension is a mainstay of cardiovascular medicine. This was not always the case but was established only 60 years ago with the publication of the Framingham study in 1961. Despite the compelling findings of this landmark study which established the link to coronary heart disease, the medical community was slow to take up blood pressure control to strict targets. The philosophy of care has evolved in the ensuing years, and there is now universal support for this approach. However, an understanding of the goals and targets of hypertensive therapy as related to an individual patient's overall cardiovascular risk is somewhat less clear. This paper provides a review of relevant literature with regard to the question of whether total cardiovascular risk should be taken into consideration when treating the hypertensive patient.

Key words: Blood pressure targets, end-organ damage, cardiovascular risk

Background

Hypertension is an important determinant in the spectrum of cardiovascular disease (CVD), and treating hypertension is a central tenet of modern cardiac care. However, the decision of whether to initiate therapy based on cardiovascular risk factors or absolute blood pressure (BP) measurements is less defined. The Framingham study began the cardiology community's focus on epidemiological risk in the pursuit of the etiology of cardiac disease.[1] Historically, antihypertensive therapy was determined by signs of the development of overt end-organ damage in patients but became modified with accumulation of epidemiological data. Hypertension was established as a causal risk factor, with a significant reduction in BP being correlated with a reduction in hypertensive heart failure in those with CVD.

The Framingham study established cardiovascular prospective population epidemiological research and preventative cardiology. The "risk factor" concept evolved, indicating that multiple interrelated factors promote increased risk of the development of coronary heart disease (CHD).[2] To date, no single essential factor has been identified. Epidemiologists began to conceptualize vascular disease as an outcome of multiple forces, and hypertension is primed among these. This research determined the influence of hypertension on the full clinical spectrum of CVD including sudden death, silent and overt myocardial infarction, heart failure, and clinical and silent strokes.

The study determined population CVD incidence attributable to hypertension at a time when only mortality statistics was available, and most recently, the lifetime risk of developing it and its vascular consequences. The study also provided some valuable insights into mechanisms of hypertension-induced CVD. In the past, initiation of antihypertensive treatment was often delayed until there was evidence of target organ involvement. Framingham study data indicated that this practice was imprudent as 40–50% of hypertensive persons developed overt cardiovascular events before evidence of target organ damage such as proteinuria, cardiomegaly, or electrocardiogram abnormalities. However, patients with CVD appear to also benefit, with reductions in hypertensive heart failure. Within the original Framingham study subgroup of patients who have

Address for correspondence:
Dr. Grant Shalaby, Department of Clinical Medicine, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW 2109, Australia. E-mail: grant.shalaby@mq.edu.au

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hypertension, there was benefit from significant BP reduction and evidence of end-organ damage seems to be an increased risk for cardiovascular complication.

There appears to be a group of patients with accelerated disease that seems to benefit from aggressive antihypertensive treatment. Patients who have had significant cardiovascular risk in the past particularly benefit from intervention for their hypertension. The link between hypertension and coronary artery disease is long established but the link between cerebrovascular disease and hypertension appears more compelling. Several studies such as ALLHAT have shown that significant reduction in BP directly correlates with reduction in cerebrovascular disease end points.[1]

Risk Stratification

Risk stratifying patients according to the hypertensive risk appear to benefit in the management of patients with CVD. Elevated BP is a causal risk factor for CVD. Epidemiological analyses have established the graded and continuous association between higher BP and CVD. In a population-based study of older adults, although all measures of BP were strongly and directly related to the risk of coronary and cerebrovascular events, SBP was the best single predictor of cardiovascular events.[3] Moreover, randomized clinical trials among individuals with hypertension have demonstrated, in aggregate, a reduction in CVD events by 20%, CHD by 17%, stroke by 27%, and heart failure by 28% for every 10 mmHg systolic BP (SBP) lowering with medical therapy.[4] This approximately correlates with a doubling in cerebrovascular and cardiovascular events for every 20 mmHg rise in SBP over 120 mmHg. Therefore, prevention, detection, treatment, and control of elevated BP are an important public health priority and a primary target for CVD prevention. This suggests that stratifying patients according to BP may be beneficial in targeting the treatment of hypertension in patients who should be aggressively managed.

Concerns and Special Populations

There are concerns about the potential harm from aggressive BP management at lower BP.[5] The common adverse effects of antihypertensive therapy can be grouped two ways:

- Effects of the particular drug chosen (e.g., cough associated with ACE inhibitors)
- Effects of BP lowering (often hypotension and syncope).[6]

For example, there are risks in overzealous treatment in hypertensive patients, particularly in the elderly and those with isolated systolic hypertension. These patients often have quite low diastolic BP and with aggressive reduction in mean arterial pressure often lead to an increased risk of falls. Diastolic hypertension is often present in pediatric and obstetric patients although systolic hypertension also is of significance.

Concerns have also been raised about renal safety due to the statistically significant difference in participants without chronic kidney disease experiencing at least 30% reduction in estimated glomerular filtration rate (eGFR) in SPRINT.[7] This measure is not a clinically meaningful outcome in those with eGFR above 60 mL/min/1.73 m^2. For those with chronic kidney disease, there was no significant difference in the composite renal outcomes, but there was insufficient power to determine if there was any effect on long-term dialysis.

Alternatively, a systematic review by Xie *et al*. revealed no significant differences in severe adverse events associated with BP lowering, dizziness, or adverse events leading to discontinuation of more intensive BP lowering therapy. However, there was a small difference in severe hypotension.[8]

Conclusion

There appears to be significant benefit in BP reduction over and above end-organ damage, particularly in patients with cardiovascular risk. The treatment of absolute BP measurements rather than cardiovascular risk alone seems to be of value, particularly given the insidious onset of end-organ damage in many patients, and the lack of symptoms of CVD until significant macro- and microvascular damage has occurred. Patients with cardiovascular risk may warrant BP treatment to more aggressive BP targets. However, there are also limitations to aggressive BP reduction, particularly in certain populations such as the elderly. In view of this, the authors recommend that ongoing vigilance in primary care and physician settings to tight BP control will be associated with better outcomes, although certain populations may require more pragmatic approach. Most patients will require vigilance and careful cardiac risk management including BP monitoring to ensure the avoidance of the long-term sequelae of CVD.

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Topical Commentary

Clinical Utility of Ambulatory Blood Pressure Monitoring to Define Phenotypes of Hypertension

Anastasia S. Mihailidou[1,2]

[1]Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia, [2]Department of Cardiology and Kolling Institute, Royal North Shore Hospital, St. Leonards, Sydney, Australia

Abstract

Blood pressure (BP) is one of the vital markers of health and high BP (hypertension) continues to be major health burden, with high systolic BP the leading preventable risk factor for cardiovascular disease. Early detection and management require accurate measurement of BP, with clinical practice guidelines now universally recommending out-of-clinic ambulatory or home BP monitoring to confirm the diagnosis of hypertension. Ambulatory BP monitoring (ABPM) provides detailed information of the pattern and fluctuations of BP throughout a 24 h period. This brief review provides a summary of several of these different patterns which indicate specific BP phenotypes and how these may guide better prognosis of cardiovascular risk as well as efficacy of treatment of hypertension. Although patient awareness and acceptance are important for reliable AMBP measurements, there are limited reports and the results of a pilot survey assessing patient satisfaction are presented.

Key words: Ambulatory blood pressure, hypertension management, hypertension phenotypes

Introduction

Clinic blood pressure (BP) remains the measurement for initial screening and management of hypertension, although there are recognized limiting factors, including accuracy of the measurement and the "white coat effect." Introduction of automated office BP overcomes these factors,[1] although the importance of out-of-clinic measurement with either home or ambulatory BP monitoring (ABPM) for confirming diagnosis of hypertension is recommended by clinical practice guidelines for Australia,[2] Europe,[3] the America,[4] and Canada.[5] The advantage of ABPM is that it allows multiple measurements of BP over 24 h period without patient intervention, ambulant, and during sleep and reveals variations in circadian BP profile which would have been missed with clinic alone. This brief review provides a summary of several of these different patterns which indicate specific BP phenotypes of hypertension, such as nocturnal hypertension and masked hypertension. Although there is specific guidance for physicians/health professionals for the measurement of ABPM,[6,7] patient satisfaction in wearing the equipment also needs to be considered[8-11] for reliability of the measures but also for engagement in their health and adherence to treatment. While ABPM is increasing in use in Australia, there are no reports on patient satisfaction and the results of a pilot survey are presented.

Nocturnal BP

Ambulatory BP is a stronger predictor of cardiovascular risk than clinic BP[12,13] as well as provides the pattern/profile of BP changes throughout the 24 h period to assess variability, especially during sleep (nocturnal) and early morning. Lack of a decrease in BP of at least 10% during sleep is often referred to as non-dipping[14] and when it rises compared to daytime, it is reverse dipping pattern, which has been shown to be a marker of cardiovascular dysautonomia in Parkinson disease.[15] Adjusting for this dipping and daytime BP, Yang *et al.* (2019)[16] found that higher 24 h and nocturnal BP were associated with greater risk of

Address for correspondence:
Dr. Anastasia S. Mihailidou, Department of Cardiology and Kolling Institute, Royal North Shore Hospital, St Leonards, NSW 2065, Sydney, Australia. E-mail: anastasia.mihailidou@mq.edu.au

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cardiovascular outcomes. Interestingly, variability in nocturnal BP is also an independent predictor of all-cause mortality and cardiovascular events.[17]

Masked Hypertension

The clinical utility of ABPM for diagnosis of hypertension and treatment is particularly evident with identifying masked hypertension which is normal clinic BP with elevated ambulatory or home BP. When there is treatment initiated and BP is elevated away from the clinic but is assumed to be controlled during the clinic visit, it is labeled "masked uncontrolled hypertension (MUCH). Both masked hypertension and MUCH are associated with increased cardiovascular risk almost equivalent to sustained hypertension.[18] A recent meta-analysis[19] found that while the prevalence of masked hypertension was comparable when determined by ABPM (11%) compared to home BP monitoring (13%); ABPM had greater sensitivity to identify patients with masked hypertension/MUCH when both methods were compared in the same patients.

Patient Satisfaction with AMBP

While ABPM is recommended for out-of-clinic BP measurement by clinical practice guidelines, the patent perspective needs to be considered since it is not often assessed but may influence treatment adherence and engagement in their health. Consecutive patients who had ABPM were asked their satisfaction in wearing the monitoring equipment once the 24 h monitoring was completed. The question was "*how did they feel about wearing the monitoring equipment"* and there were three options to select: 1 – "didn't mind;" 2 was "uncomfortable but necessary," and 3 was "disliked and not for repeat." Of the 59 patients asked for this pilot survey, 32/59 (54%) did not mind having the 24 h monitoring, while 26/59 (44%) found it uncomfortable but necessary and only 2/59 (0.11%) could not tolerate. The higher acceptance by patients may have resulted from the communication of the need testing by AMBP and also how BP is measured during monitoring. This pilot study is supported with similar findings by Ernst and Bergus (2014)[8] who found that ABPM was well accepted by patients even though they reported to have disturbed sleep and discomfort.

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