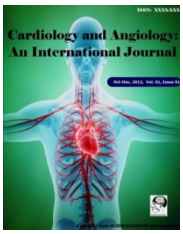

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Age Related Hemodynamic Blood Pressure Changes for Cardiovascular Disease and Stroke: A Mini-review

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Authors' contributions

Both authors contributed equally in the preparation of the manuscript.

Mini-review

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ABSTRACT

The blood pressure (BP) changes with the advancement of age from the predominant diastolic BP (DBP) in the young to the predominant systolic BP (SBP) in the older person. This shift is due to the stiffening of the large arteries as a result of the ageing process and the replacement of the elastic fibers with collagen fibers resulting in the loss of compliance and the elastic recoil of these vessels. The end result is augmentation in pulse wave velocity (PWV) and widening of pulse pressure (PP). The SBP rises linearly with the advancement of age whereas, the DBP rises up to the age 50 years and begins to decline after the age of 60 years leading to a progressive increase in PP. These hemodynamic changes of BP are frequently associated with an increased incidence in cardiovascular disease (CVD) and strokes. Several studies have shown an inverse relationship between DBP and CVD, whereas no such a relationship has been demonstrated for stroke. However, recently, an inverse relationship has been reported between DBP and stroke for subjects 50 years of age or older. The implications of BP changes with age as they are related to CVD and strokes will be discussed in this mini review. It appears from these recent findings that in treating the hypertension in the elderly to reduce CVD and stroke, care should be taken not to allow the DBP to drop below 55-80 mmHg, since below this DBP level the incidence of CVD and strokes increase.

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1. INTRODUCTION

Several epidemiologic studies have shown that the blood pressure (BP) changes with the advancement of age from the predominance of diastolic BP (DBP) in the young person to the predominance of systolic BP (SBP) in the older person. In addition our perception in treating the hypertension has shifted lately from focusing on treating the DBP, in treating the SBP. Also, the significance of office BP has been challenged recently as not being representative of a person's actual BP due to the introduction of new entities like white coat hypertension (WCH) and masked hypertension (MH), discovered with the use of ambulatory BP measurement (ABPM). These two BP entities have opposite meanings, where WCH is the condition with elevated BP in the doctor's office or clinic and normal BP outside the doctor's office measured either by ABPM or with a home BP monitor [1]. In contrast, MH is the condition with normal BP at the doctor's office and elevated BP outside the doctor's office measured by the same means [2]. The shift of focus from the treatment of DBP to the treatment of the SBP is due to the ageing of the population and the fact that the SBP is the predominant BP in this population [3]. Some authors have even gone to the extreme stating that "SBP is all that matters" [4]. This is a significant departure from the early years when the focus was on the treatment of DBP, since the SBP was considered a normal consequence of the ageing process. Even the reports of the National Committees on the Detection, Evaluation, and Treatment of High BP (JNCs) did not emphasize the treatment of SBP until their 5th report in 1993 [5]. Recently, it has been suggested that treating the hypertension, the age of the subject should be considered since the DBP is the predominant BP in the young and the SBP is the predominant BP in the older person. The DBP rises from childhood till the age of 50 years and then begins to decline after the age of 60 years, whereas the SBP rises linearly from adulthood to the old age. The significance of BP change with age was first pointed out by the Framingham study investigators [6]. Previous studies used the changes in BP in correlation with various age subgroups to determine its association with the risk of CVD and stroke [7-9]. It has been speculated that if age was used as a continuous variable, this could have given a clearer picture at which age the SBP begins to exceed the DBP with respect to stroke incidence. This concept was tested in two recent studies [10,11]. The significance of the findings from these studies regarding the relationship of BP changes with age regarding the incidence of CVD and stroke together with collateral literature will be discussed in this concise review.

1.1 Pathophysiology of Arteriosclerosis and Systolic Hypertension

The large arteries in young persons possess two functions, a) to act as conduits transferring blood to vital organs and tissues, and b) to act as cushions to smooth out the pulsatile blood flow produced by the intermittent contractions of the heart into a continuous and steady blood flow [12]. However, as the person ages these functions of the large arteries are modified by the onset of arteriosclerosis, which is a consequence of the ageing of blood vessels. The primary cause of arteriosclerosis is the fragmentation of the elastic lamellae which become thinned, frayed, and are replaced with collagen tissue. This fragmentation of the elastic fibers is the result of the fatiguing effect produced over the years by the cycling stress of the pulsatile blood flow. In a young person [13], the elastic aorta expands during systole and absorbs part of the stroke volume (SV). During diastole the aorta recoils back and sends the retained SV distally, thus converting the intermittent blood flow into a continuous and steady blood flow (Fig. 1A). In an elderly person, the elasticity and

compliance of the aorta is lost [13] and most of the SV is transmitted distally during systole with practically no blood flow during diastole (Fig. 1B). The direct result of this function is an increase in SBP, a decrease in DBP and a widening of pulse pressure (PP). These latter changes lead to acceleration of pulse wave velocity (PWV), which is a diagnostic characteristic of arteriosclerosis. In addition, the morphology of the pressure wave also, changes (Fig. 2).

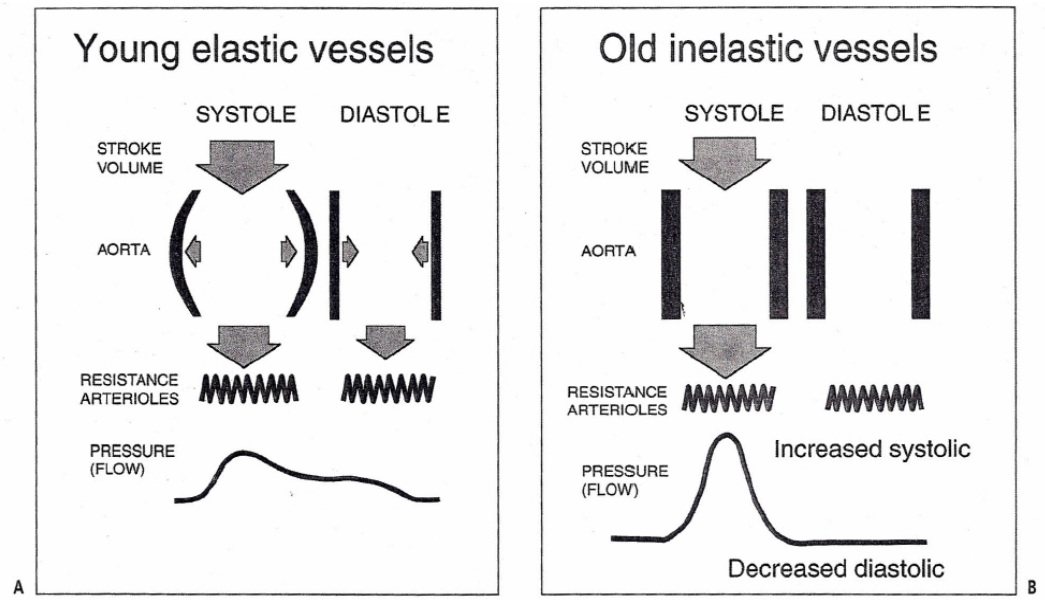

Fig. 1. A. The function of the central aorta in a younger person is depicted. During systole, the elastic aorta is dilated with each cardiac SV and functions as a reservoir (top filled arrow). As a result, not all SV is transmitted distally. During diastole, the elastic recoil of the aorta expels the remnant original SV to distal arteries and arterioles. This function results in a smooth contour of the arterial pulse wave (PW) and a narrow PP (bottom). B. In an older person, the aorta has lost most of its elasticity with a reduction of its reservoir capacity, which results in the expulsion of almost the entire SV to the distal arteries with practically no diastolic blood flow (top filled arrow). The result is a distortion of the arterial PW (bottom), an increase in SBP, a decrease in DBP, and a widening of PP

Adapted with permission from Franklin [13]

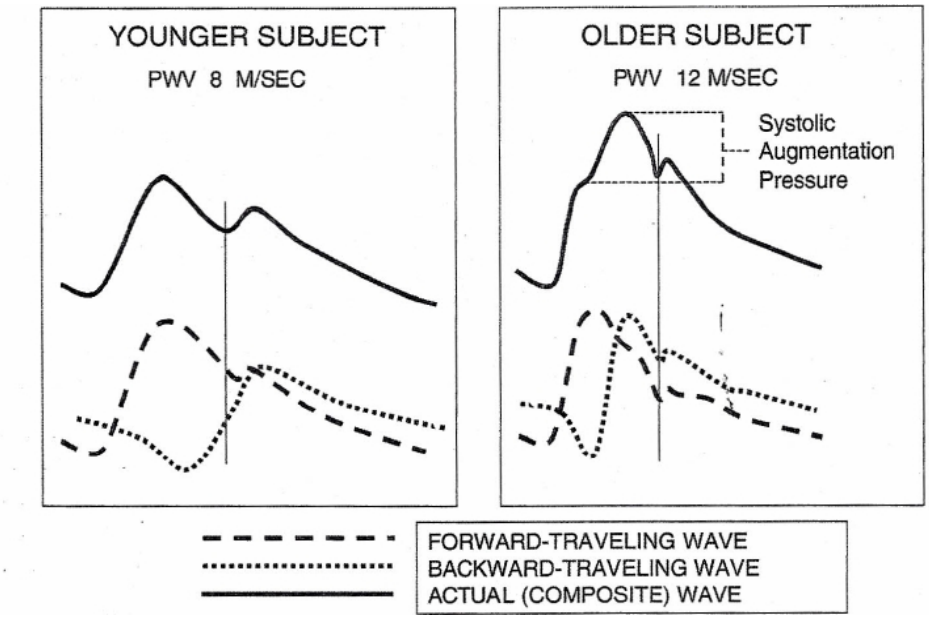

Fig. 2. This figure depicts the configuration of the arterial waveforms in the younger (left) and older person (right). The arterial waveforms are composite waves (top heavy line), and are composed of a forward wave (dashed line) and a backward reflective wave (dotted line). The vertical line represents the closure of the aortic valve. The top solid line indicates the peak SBP in the younger (left) and the older person (right) together with the augmentation pressure. The reflected wave in the younger person (left) returns to the aortic root early in diastole augmenting the DBP, which helps the perfusion of the coronary arteries, whereas in the older person (right) it returns to the aortic root late in systole augmenting the SBP, which increases the left ventricular outflow pressure. Due to the arterial stiffness, the PWV is increased in the older person (12 m/sec) compared with the younger person (8 m/sec)

Adapted with permission from Franklin [13]

The pressure wave is a composite of the incident (forward) wave generated by the contraction of the heart and the reflected (backward) wave generated by the resistance of small vessels. In young persons, the reflected wave travels slower and reaches the central aorta in early diastole leading to augmentation of the DBP, which is useful for the perfusion of coronary arteries. In older persons, the reflected wave travels a lot faster and reaches the central aorta in late systole leading to augmentation of the central SBP causing an increase in the pressure load of the left ventricle and the development of left ventricular hypertrophy (LVH). The increased central aortic SBP is also associated with a higher incidence of CVD and strokes [14]. Also,the pulsatile stress produced by the intermittent action of the heart has been shown recently to increase the media layer of the small muscular arteries thus, decreasing their lumen and leading to further acceleration of PWV in older persons [15]. Pathophysiologically, the pressures in the large arteries (aorta, carotids) are more relevant than the peripheral (brachial) pressures for the pathogenesis of CVD and strokes. It is the central aortic SBP that the left ventricle encounters during systole (afterload) and not the DBP, which is mostly responsible for the perfusion of coronary arteries [16].

1.2 Pulse Pressure Amplification and Cardiovascular Disease Risk

The shape of pressure wave changes as it travels down the aorta resulting in augmentation of the peripheral SBP and PP as the distance from the heart increases, in contrast to DBP and mean arterial pressure (MAP), which change very little for the same distance from the heart. The merging of the forward and reflected pressure waves result in augmentation in SBP and PP but not a change in the DBP thus, leading to the widening of PP [17]. The degree of augmentation of SBP is higher in older persons than the younger persons and can be calculated from the difference between the first and second systolic peaks of the central aortic SBP (Fig. 2). From the augmentation of pressure (AP) and PP, the augmentation index (AIx) can be calculated as AIx = AP/PP. Clinical evidence from the Strong Heart Study has indicated that the peripheral PP is associated with a higher incidence of cardiovascular mortality, which was independent of LVH and the systolic dysfunction of the heart in the absence of overt coronary artery disease [18]. In addition, the 5 year follow-up of these patients showed that the non-invasibly measured central PP was a better predictor of incident CVD than the brachial PP, since the former is a better representative of left ventricular pressure load. Also, a meta-analysis of studies in older persons showed that the PP was more strongly related to increased cardiovascular complications than MAP [19]. Moreover, an increased AIx has been shown to be, independently, associated with a higher risk of short-and-long-term cardiovascular events in patients undergoing percutaneous coronary interventions [20].

1.3 Changes of Blood Pressure with Age and Their Relationship to Stroke and CVD

The brain and the heart are protected against stroke and myocardial infarction through wide fluctuations of BP due to the autoregulation of cerebral and coronary artery circulation. Cerebral autoregulation (CA) is the intrinsic capacity of the cerebral vessels to maintain a constant cerebral blood flow (CBF) for the metabolic needs of the brain [21]. The CBF is also regulated, besides BP, by the arterial CO2 level of the brain as well. The CBF consists of two components, the static and the dynamic component. The static CA regulates the CBF during gradual and progressive increases in BP [22], whereas the dynamic CA regulates the CBF during rapid changes in BP [22]. It has been demonstrated that the CBF remains constant through wide changes in MAP ranging from 60 to 150 mmHg (Fig. 3) or from 40 to 125 mmHg by transcranial Doppler [23]. From these studies it appears that the CBF is not seriously affected even with very low DBP, and this could explain the lack of a J curve effect for stroke incidence with low DBP in contrast to the heart which is susceptible to J curve effect with low DBP, since DBP is responsible for coronary artery perfusion [24]. However, a recent study has shown that there might be a J curve effect for stroke risk with a DBP < 71 mmHg in older persons [10]. In this study, 68,551 subjects 19 to 78 years old from several European countries free of CVD and not taking antihypertensive drugs at study entry, were followed for 13.2 years. The subjects were divided into 4 age groups, 19-39, 40-49, 50-59, and 60-78. The data showed that when the SBP and DBP were analyzed separately, both pressures were associated with a high stroke risk if they were ≥ 71 mmHg across all age groups (*P < 0.001)*. In contrast, when the SBP and DBP were considered together, the SBP became not significant in the 19-39 year olds, whereas the DBP became significant for stroke risk in the 60-78 year olds if dropped < 71 mmHg. Regarding the association of MAP with stroke risk, this was stronger in the younger age groups and declined progressively with advancing age becoming not significant after the age of 69 years for men and the age of 73 years in women. In addition, there was a significant association between PP and stroke risk,

which was independent of age and remained significant after multivariate adjustments. Similarly, in the study by Safar et al [11], in 4,293 hypertensive patients with or without the metabolic syndrome followed for 9 years (DESIR Study), the DBP was the strongest predictor for CVD in subjects < 50 years old, whereas the SBP was the strongest predictor for CVD in subject's ≥ 60 years old. After adjustments, there were no major differences in the findings in patients with or without the metabolic syndrome regarding the effects of age on BP changes. Besides the BP, the increased PP has also been demonstrated to be an important factor for CVD by these and other studies [17-20].

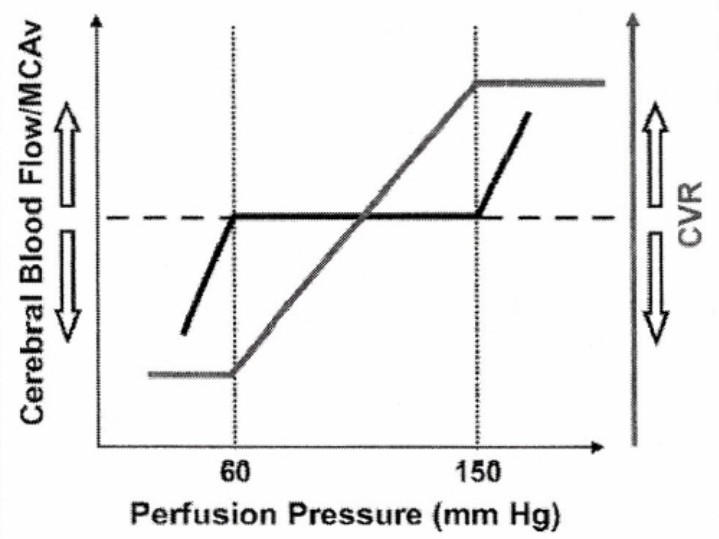

Fig. 3. This figure depicts the CBF autoregulation and the range of perfusion pressures. An autoregulatory plateau is seen between 60 to 150 mmHg of MAP. This autoregulatory plateau is maintained through changes in cerebral vascular resistance (CVR). Once the limits of autoregulation are reached, CVR cannot correct for further changes in pressure as demonstrated by the MAP limits of < 60 (lower limit) and > 150 mmHg (upper limit)

Adapted with permission from Lucas et al. [21]

2. DISCUSSION

New evidence now suggests that there is an association between age and BP regarding cardiovascular and stroke risk. In subjects ≤ 50 years old, the DBP remains a dominant factor for CVD and stroke risk, whereas in subjects ≥ 60 years of age, the SBP is the dominant risk factor [10,11]. In addition to BP there is also a sex effect with the MAP becoming not significant for stroke risk in men after the age of 69 and in women after the age of 73 years, since the MAP represents the DBP. Similar findings have also been reported by other investigators [11,25]. An important new finding is the inverse relationship between DBP and stroke risk in older persons. In subjects ≥ 60 years, there was an increased risk for stroke when the DBP dropped below 71 mmHg. Such an association is not commonly seen with strokes in contrast to CVD which depends on the DBP for coronary artery perfusion, and where the J curve effect has been demonstrated by several studies [24,26-30]. This finding has important clinical significance when treating elevated SBP in the elderly. Kannel et al [32] have shown that the incidence of CVD risk increased with a

decrease in DBP < 80 mmHg, when the SBP remained > 140 mmHg. Similarly, Fagard et al [31] recommend that in treating the systolic hypertension of older individuals, the treatment should be stopped if the DBP drops < 55 mmHg to prevent further widening of PP. In the study by Kannel et al. [32], the 10 year risk ratio (RR) for cardiovascular events for men and women was 1.22 (95% CI 0.97-1.50) when the PP was 46-55 mmHg, and the RR increased to 1.66 (95% CI 1.32-2.07) when the PP was 56-136 mmHg. The significance of PP as a cardiovascular [13, 17-20] and stoke risk [7,25,33,34) has also been demonstrated. This higher cardiovascular risk has been attributed to the increased pulsatile burden on the heart and blood vessels produced by the wide PP [34]. In this regard, the Framingham study tracked the age and sex of 4,993 participants for 28 years and demonstrated that the SBP and PP increased with age and were higher in older women compared to older men and were associated with a higher cardiovascular risk [34]. Given that both PP and chronological age are positively associated with a high cardiovascular and stroke risk, PP may be regarded as an index of arterial ageing. This could suggest that the biology of the ageing process differs between men and women. It has also, been suggested that the chronological age as determined by calendar time, is distinct from the biologic age, which is a progressive and irreversible process of deterioration of vital organ systems [33]. In addition, an inverse association has been found between PP and telomere length suggesting that the biologic age of persons with wide PP is more advanced than their chronological age would indicate [33]. With respect to the new findings regarding the interrelationships of BP with age regarding treatment of hypertension, both SBP and DBP are important up to the age of 50 years, after which the SBP becomes the dominant factor for cardiovascular and stroke complications. However, when treating the hypertension of older persons, attention should be paid that the level of DBP not be < 71 mmHg [10], or 80-55 mmHg, especially if the SBP remains ≥ 140 mmHg to avoid further widening of PP [11,29,31-34]. Although the risk for CVD and stroke appears to increase with a DBP below these levels, the National and International guidelines regarding treatment of hypertension, still recommend the BP to be < 130/80 mmHg for persons in high cardiovascular risk [35,36]. In contrast to these guidelines, some investigators recommend the SBP and DBP not to be lower than 130-139 and 80-90 mmHg, respectively [11,37]. Additionally, other investigators even propose to test the safety of SBP in the range of 130-150 mmHg [28]. These controversies require clarification from future studies. For the time being, the recommendations of National guidelines for the treatment of hypertension should remain in effect till new evidence becomes available. Regarding drug selection for the treatment of hypertension in older subjects, drugs that block the renin-angiotensin-aldosterone system (RAAS) alone or in combination with calcium channel blockers (CCB) are preferable as first line treatment in these individuals, since these drugs have been effective in lowering the central SBP and PP compared to beta blockers (atenolol) and thiazide diuretics as was demonstrated by the Conduit Artery Function Evaluation (CAFÉ) study [38]. In addition, the older beta blockers like atenolol have been shown to be less effective against stroke prevention [39]. Supporting the superior role of combination of RAAS blockers and CCBs, are the results of a recent Japanese study, which showed that the combination of RAAS blockers with CCBs was more effective in reducing the BP and cardiovascular complications than high dose RAAS blockers in high risk elderly hypertensive patients with or without renal failure [40]. With respect to the current practice of treating hypertension based on office measurements of BP, it would be prudent to, also measure the BP by ABPM before initiating treatment to diagnose the presence of WCH or MH. This is very important because treatment of WCH is, usually, not necessary [1], in contrast to MH where treatment is absolutely necessary, since MH is associated with a high incidence of cardiovascular complications and death [2]. Finally, it should be emphasized that despite of some differences in the action of the various antihypertensive drugs, the

focus should always be on good BP control and to this end, all classes of antihypertensive drugs should be used either alone or in combination.

3. CONCLUSION

This concise review has presented evidence that the SBP increases linearly with the advancement of age and becomes the dominant factor for stroke risk after the age of 60 years. The BP change is due to arteriosclerosis and the stiffening of the large arteries as a consequence of the ageing process and results in the loss of their compliance and elastic recoil. These changes lead to increase in SBP, PP, and PWV, which, in turn increase the risk for CVD and strokes. New evidence suggests that there is a J-curve effect for stroke risk if the DBP < 71 mmHg in older persons. Therefore, care should be taken when treating resistant systolic hypertension in the elderly not to allow the DBP to drop below this level in order to prevent the widening of PP and its adverse effects on CVD and strokes. Regarding the treatment of SBP in the elderly, drugs that block the RAAS either alone or in combination with CCBs should be the first line of treatment, since these drugs are more effective in lowering the central SBP than other drugs. However, the focus should be on good BP control, and in this regard all drug classes should be utilized.

CONSENT

Patient consent was not applicable for this study.

ETHICAL APPROVAL

Ethical approval was not applicable for this study.

COMPETING INTERESTS

The authors have nothing to declare and have no conflicts of interest.

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