Abstract

The importance of systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP), on the incidence of coronary heart disease (CHD) and stroke are known. However, the importance of blood pressure (BP)-age shifts regarding the stroke incidence is not clearly known. The BP changes with the advancement of age from the predominance of DBP in the young to the predominance of SBP in the old. This change is due to the stiffening of the large arteries as a result of the aging process and the replacement of the elastic fibers with collagen fibers. This change results in the loss of compliance and the elastic recoil of these vessels leading to increase in pulse wave velocity, central SBP and widening of pulse pressure leading to an increased incidence of CHD and strokes. It has been demonstrated epidemiologically that the SBP rises linearly with age, whereas the DBP rises up to the age of 45-50 years, and then begins to decline after the age of 60 years leading to a progressive widening of PP. Several studies have shown an inverse relationship between DBP and CHD, whereas no such relationship has been demonstrated for stroke. However, a recent study showed an inverse relationship with DBP and stroke when it dropped below 71 mmHg in subjects 50 years of age or older. In contrast, there was a positive association between BP and stroke when both SBP and DBP were \( \geq 71 \) mmHg. These findings suggest that in treating systolic hypertension in the elderly to reduce stroke risk, attention should be paid on the potential harm of low DBP and the widening of PP regarding CHD and stroke. The implications of BP shifts with age and the potential risks of low DBP regarding the risk of stroke will be discussed in this concise review.
Diastolic The large arteries in young persons possess two func-

AND SYSTOLIC HYPERTENSION

PATHOPHYSIOLOGY OF ARTERIOSCLEROSIS

in a recent study with respect to stroke incidence. This concept was tested age the relative importance of SBP begins to exceed DBP variable, this could have offered a clearer picture at which has been suggested, that if age was used as a continuous association with the risk of cardiovascular disease in correlation with various age subgroups to determine its significance from the early years where the focus was on treating the diastolic BP (DBP), because SBP was considered normal development of the aging process. Even the reports of the Joint National Committees on the detection, evaluation, and treatment of high blood pressure did not emphasize the treatment of SBP till their 5th report in 1993[4]. Recently it has been suggested that in treating hypertension, the age of the subject should be considered since DBP is the predominant BP of the young and SBP is the predominant BP of the older person. The DBP increases from childhood till the age of 50 years and then begins to decline after the age of 60 years, whereas SBP rises continuously from adulthood to the old age. The significance of SBP change with age was first pointed out by the Framingham Heart Study[5]. Previous studies used the BP in correlation with various age subgroups to determine its association with the risk of cardiovascular disease[6-8]. It has been suggested, that if age was used as a continuous variable, this could have offered a clearer picture at which age the relative importance of SBP begins to exceed DBP with respect to stroke incidence. This concept was tested in a recent study[9].

Figure 1 In a young person the elastic aorta expands during systole and absorbs part of the stroke volume. A. This figure depicts the function of the central aorta of a younger person during systole and diastole. During systole, the elastic aorta with each cardiac stroke volume (top filled arrow) is dilated and functions as a reservoir. As a result, not all stroke volume (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 and a decrease in diastolic blood pressure, a decrease in diastolic blood pressure, and a widening of PP. Adapted with permission from Franklin et al[10].

monitoring. In addition, the emphasis on treating hypertension has now been shifted to systolic BP (SBP), since SBP is the most prevalent BP in older age[11], and some authors have gone into the extreme, stating that “systolic blood pressure is all that matters”[12]. This is a significant change from the earlier reports where the focus was on treating the diastolic BP (DBP), because SBP was considered normal development of the aging process. Even the reports of the Joint National Committees on the detection, evaluation, and treatment of high blood pressure did not emphasize the treatment of SBP till their 5th report in 1993[4]. Recently it has been suggested that in treating hypertension, the age of the subject should be considered since DBP is the predominant BP of the young and SBP is the predominant BP of the older person. The DBP increases from childhood till the age of 50 years and then begins to decline after the age of 60 years, whereas SBP rises continuously from adulthood to the old age. The significance of SBP change with age was first pointed out by the Framingham Heart Study[5]. Previous studies used the BP in correlation with various age subgroups to determine its association with the risk of cardiovascular disease[6-8]. It has been suggested, that if age was used as a continuous variable, this could have offered a clearer picture at which age the relative importance of SBP begins to exceed DBP with respect to stroke incidence. This concept was tested in a recent study[9].

PATHOPHYSIOLOGY OF ARTERIOSCLEROSIS AND SYSTOLIC HYPERTENSION

The large arteries in young persons possess two functions, one to act as conduits transferring the blood to vital organs and tissues, and the other 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[13]. However, as the person ages these functions of the large arteries are modified by arteriosclerosis, which is a consequence of the aging of blood vessels. The primary cause of arteriosclerosis is the fragmentations of the elastic lamellae which become thinned, frayed, and are replaced with collagen tissue. The fracturing of the elastic fibers is the result of the fatiguing effect produced by the cycling stress of the pulsatile blood flow. In a young person the elastic aorta expands during systole and absorbs part of the stroke volume[13]. During diastole it recoils back and sends the retained blood volume distally, thus converting the intermittent blood flow into a continuous steady flow (Figure 1A). In an elderly person, the elasticity and compliance of the aorta is lost[13] and most of the stroke volume is transmitted distally during systole with practically no blood flow during diastole (Figure 1B). The direct result of this function is an increase in SBP, a decrease in DBP, and a widening of pulse pressure (PP). This process is accelerated in the presence of hypertension. These latter changes in the older person lead to acceleration of the pulse wave velocity, which is the main diagnostic characteristic of arteriosclerosis. In addition, the morphology of the pulse wave changes (Figure 2). 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 small muscular arteries and arterioles. 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 faster and reaches the central aorta at the end of systole thus augmenting the central aortic SBP, which increases the pressure load on the left ventricle and leads to the development of left ventricular hypertrophy. In addition, the increased central SBP is associated with a higher incidence of cardiovascular disease (CVD) and stroke complications[13].

TREATMENT OF SBP: THE AGE FACTOR

The brain is protected against stroke through wide fluctuations of BP by the autoregulation of cerebral circulation. Cerebral autoregulation (CA) is the intrinsic capacity of the cerebral vessels to maintain constant cerebral blood flow (CBF) for the metabolic needs of the brain[14]. The CBF is also regulated, besides BP, by the arterial CO2 level of the brain as well. The CA consists of two components, the static and the dynamic component. The static CA regulates CBF during gradual and progressive increases in BP[15], whereas the dynamic CA regulates the CBF during rapid changes in BP[16]. It has been demonstrated that the CBF remains constant through wide changes in mean arterial pressure (MAP) ranging from 60 to 150 mmHg (Figure 3) or from 40 to 125 mmHg from
Older Subject

PWW 12 m/s

Younger Subject

PWW 8 m/s

Figure 2 This figure depicts the configuration of the arterial waveforms in the younger person (left) and the older person (right). The arterial waveforms are composite waves (top heavy line), composed of a forward traveling wave (dashed line) and a backward traveling reflective wave (dotted line). The vertical line represents the closure of the aortic valve. The top solid line indicates the peak systolic blood pressure (SBP) in the younger person (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 diastolic blood pressure and improving the coronary circulation. In the older person (right), the reflected wave returns to the aortic root late in systole, thus augmenting the SBP and increasing the left ventricular outflow pressure leading to left ventricular hypertrophy. Due to the arterial stiffness in the older person, the pulse wave velocity is increased (12 m/s) compared to the younger person (8 m/s). Adapted with permission from Franklin et al[10].

Figure 3 This figure depicts the cerebral blood flow autoregulation and the range of perfusion pressure. An autoregulatory plateau is seen between 60 to 150 mmHg of mean arterial pressure (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 mmHg (lower limit) and > 150 mmHg (upper limit). Adapted with permission from Lucas et al[13].

tice having overestimated the impact of age on the importance of SBP and DBP for stroke risk. In this study, 68 551 subjects 19 years to 78 years old from several European countries free of CVD and not taking antihypertensive drugs at entry of study, were followed for 13.2 years. The subjects were divided in 4 age groups, 19-39 years, 40-49 years, 50-59 years, and 60-78 years. When the SBP and DBP were considered separately, both pressures ≥ 71 mmHg were significantly associated with a higher stroke risk across the 4 age groups (P < 0.0001). In contrast, when the SBP and DBP were considered together, the SBP became no significant in the 19-39 year olds, and the DBP became no significant for stroke risk in the 50-59 and 60-78 year olds. However, for DBP < 71 mmHg there was an inverse relationship between DBP and stroke incidence, which became significant in the 60-78 year olds. Regarding the association of MAP and stroke risk, this was strongest in the younger ages, since MAP represents mostly the DBP, and it declined with advancing age, becoming no significant after the age of 69 years for men and the age of 73 years for women. In addition, there was a significant association between PP and stroke risk, which was independent of age and remained significant after multivariate adjustments. In this study the BP was measured at the doctor's office and might have missed subjects with WCH, or MH. However, the significance of WCH as a cardiovascular risk is debatable, because the pressure load on the heart is minimal, since WCH is elevated only during the visit at the doctor's office, and medical treatment is not associated with further lowering BP and may lead to hypotension[8]. On the contrary, MH is associated with increased cardiovascular complications, since the pressure load on the heart is prolonged. Its discovery is difficult, since the hypertension is diagnosed by office BP measurement and the BP in MH is normal at the doctor’s office. Therefore, its discovery is difficult and is, usually, identified by home BP measurements or by ABPM. Treatment of MH is absolutely necessary[3].

DISCUSSION

New evidence suggests that there is an age factor on the importance of SBP and DBP regarding the incidence of fatal and nonfatal strokes[10]. In this study, participants with SBP and DBP ≥ 71 mmHg, had a higher risk for stroke until the age of 62 years, after which, only the SBP remained significant. In addition to age, there was also a sex effect between the MAP and stroke risk up to the age of 69 years for men and 73 years for women. Similar findings in shifts of BP with age have been reported from the Framingham study for coronary heart disease (CHD), but not stroke[18]. In the study by Vishram et al[10], in persons < 50 years of age, the DBP was the strongest predictor for stroke risk, whereas in persons ≥ 60 years of age the SBP was the strongest predictor. In persons 50-59 years of age, both pressures were equally important. Another significant finding of this study was the J curve effect of DBP with stroke risk for participants with a DBP < 71 mmHg. In this group there was an increase in stroke risk and this became significant after the age of 73 years for men and 73 years for women.
of 60 years. Such an association is not commonly seen with strokes in contrast to CHD[7,19-23], although it has been reported by some investigators[24]. This is important when treating elevated SBP in the elderly. Kannel et al[25] showed that the incidence of cardiovascular events increased with a decrease in DBP < 80 mmHg, when the SBP remained ≥ 140 mmHg. Similarly Fagard et al[26] suggest that the antihypertensive treatment in subjects with systolic hypertension should be stopped when the DBP reaches the level of 55 mmHg to prevent further widening of PP and the higher risk for cardiovascular complications. In the study by Kannel et al[25], the 10-year risk ratio of cardiovascular events for men and women was 1.22 (95%CI: 0.97-1.50) with PP 46-55 mmHg, and 1.66 (95%CI: 1.32-2.07) with PP 55.5-136 mmHg. The significance of PP as a stroke risk in elderly subjects has been demonstrated besides Vishram et al[27], by other investigators as well[16,20-26]. The higher cardiovascular risk with wide PP has been attributed to the increased pulsatile burden on the heart and blood vessels produced by the wide PP[27]. In this report from the Framingham study, the age and sex of 4993 participants were tracked for 28 years and demonstrated that the SBP and PP became higher with older age, and were higher in older women compared to men of similar age[25]. In a large meta-analysis of older subjects with systolic hypertension it was shown that the PP was more important in inducing cardiovascular complications than the MAP[28]. Given that both PP and chronological age are positively associated with cardiovascular risk and strokes, PP may be regarded as an index of arterial aging. This could suggest that the biology of aging differs between men and women, and has 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 the vitality of organ systems[29]. In addition, an inverse association was 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[26]. With respect to age-BP interrelationship regarding the risk of stroke, it appears that both SBP and DBP are important up to the age of 50 years after which, the significance of SBP supersedes that of DBP. In addition, in treating the SBP in older persons attention should be paid to the level of DBP not to be lower than 71 mmHg, although this finding was observed in a small number of subjects. Based on other studies, the risk of cardiovascular events increased when the DBP dropped to 55 mmHg[30], or to 80 mmHg, if the SBP was ≥ 140 mmHg[25]. The current National and International guidelines recommend reducing BP to < 130/80 mmHg in high risk subjects regardless of age[20,30]. However, some investigators suggest that the SBP and DBP not to be lower than 130-139 mmHg and 80-90 mmHg, respectively[31], whereas others propose to test the safety of SBP in the range of 130-150 mmHg[21]. Regarding drug selection for the treatment of hypertension in the elderly, drugs that block the rennin-angiotensin-aldosterone system (RAAS) and calcium channel blockers (CCB) either alone or in combination are preferable as first line treatment, since these drugs have been shown to be more effective in lowering the central SBP and PP than b-blockers (atenolol) and thiazide diuretics[32]. Also, a recent Japanese study 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 disease[33]. Old fourth b-blockers like atenolol are not as effective in lowering central aortic SBP and preventing strokes[34]. However, it would be useful, if the BP besides the doctor’s office, is also measured by ABPM to diagnose the presence of WCH, where antihypertensive treatment is, usually, not necessary[35], and especially to diagnose MH, where treatment is necessary, since MH is associated with increased cardiovascular complications and death[35].

In summary, this concise review has demonstrated that the SBP increases linearly with the advancement of age and becomes the dominant factor for stroke risk after the age of 60 years. In contrast, the DBP is more dominant in younger persons and its rise with age levels off at the age of 50 years and begins to decline after the age of 60 years. In addition, new evidence suggests a J-curve effect for stroke risk with DBP < 71 mmHg or lower and the importance of wide PP as a risk factor for cardiovascular events. Finally, in treating the SBP in the elderly, drugs that block the RAAS in combination with CCBs is the best regimen in lowering the SBP. However, care should be taken not to lower the DBP below 55 mmHg, because the risk for stroke and cardiovascular complications increases significantly.

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