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Review Article

Ageing Process and Stiffening of Arteries Shown by Increased Pulse Wave Velocity

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Abstract

Aging is the most profound risk factor for many non-communicable diseases and in itself confers a greater risk for cardiovascular disease than the traditional risk factors such as lipid levels, smoking, diabetes, hypertension and sedentary lifestyle. Arterial stiffening and hypertension are aging-related disorders. The best way of measuring arterial stiffness is determination of carotid to femoral PWV, and this is recommended in the American Heart Association (AHA), as well as in the European expert consensus document. PWV measuring provides us to noninvasively assess arterial stiffness and real age of the arteries and thus the risk of cardiovascular events. PWV is a crucial vascular and hemodynamic parameter that is used to assess the stiffness of aorta as a large vessel. Aging in synergy with traditional and non-traditional risk factor for atherosclerosis led to an accelerated increase in vascular stiffness. The premature aging is result of accelerated vascular aging (stiffening and PWV increase) and the prevalence of hypertension is more than doubled in the elderly than in the young population. The presence of diabetes and prediabets is associated with increased PWV and synergistically effects vascular stiffness expressed by diabetes and hypertension, too. With the aid of Doppler ultrasonography, we can estimate the arterial stiffness. Any increase of arterial stiffness above 9 m/s, which is not correlated with chronologic age, can suggest and direct us to investigate additional comorbidities such a diabetes, hypertension or chronic renal disease that increase arterial stiffness and hence cardiovascular mortality.

ABBREVIATIONS

CV: Cardiovascular; BMD: Bone Mineral Density; PWV: Pulse Wave Velocity; FN: Femoral Neck; AI: Augmentation Index; AHA: American Heart Association; BMI: Body Mass Index; ROC: Receiver Operating Characteristic; CHP: Chronic Hemodialysis Patients; CRP: C - Reactive Protein

INTRODUCTION

Aging is time-dependent physiological functional decline that affects most living organisms, which is underpinned by alterations within molecular pathways, and is the most profound risk factor for many non-communicable diseases [1]. The vascular ageing has consistently been found to be related closely to the chronological age as Thomas Sydenham said, "A man is as old as his arteries" [2]. It means that chronological age may be different from biological age. Some biological testing which measure lung capacity, heart rate variability, memory, reaction time, visual and hearing reaction speed, lipid levels, smoking, and diabetes can evaluate biological aging more closely. Ageing in itself confers a greater risk for cardiovascular disease than the traditional risk factors such as lipid levels, smoking, diabetes, hypertension and sedentary lifestyle [3]. Chronological age is not an optimal indicator for the aging progress. Because there is no golden index for aging, researches have established various statistical models based on biological age, cognitive age [4], work ability index [5], physical fitness age, perceived age and frailty index [6], combining physical, physiological and biochemical parameters using statistical and mathematical methods. Among these, biological age can be used to track the trajectory of damage over time [7].

The aim of this review article is to show the factors that influence the aging and stiffening of the blood vessels, to show our own experiences in PWV and arterial stiffness measurement and compare those findings with the scientific knowledge of other studies.

Cardiovascular aging

Cardiovascular (CV) aging is an important factor that determines vascular stiffness. Arterial stiffening is an independent predictor of cardiovascular (CV) outcomes such as myocardial infarction, cognitive decline in aging, stroke, and kidney diseases [8]. Both, arterial stiffening and hypertension are aging-related disorders [9]. Many studies indicated that arterial stiffness, hypertension and related CV disease such as stroke and myocardial infarction are more prevalent in the elderly than in the young population [10].

The reality is that aging is not responsible for the stiffening of your vessels and your body. The aging process will intensify as the body and vessels becomes stiffer. "Aging does not cause stiffness: Stiffness causes aging" (Jon Burras). Yes, it is also true that advancement of old age increases the arterial rigidity; it means that arterial walls stiffen with age. The most consistent changes are luminal enlargement with wall thickening (remodeling) and a reduction of mechanical-elastic properties (stiffening) at the level of large elastic arteries, namely arteriosclerosis [11]. Arteriosclerosis refers to reduced arterial compliance due to increased fibrosis, loss of elasticity, and vessel wall calcification affecting the media of large and middle-sized arteries, with consecutive increase of pulse wave velocity (PWV) as measure of arterial stiffness [12]. The main distinction between arteriosclerosis and atherosclerosis is that arteriosclerosis results with stiffening and hardening of the artery walls, but atherosclerosis results with narrowing of artery diameter because of plaque build-up. Alternatively, we express ourselves by the language of physics, arteriosclerosis means increased rigidity (stiffness) of the arteries with PWV rise, but atherosclerosis means a reduced arterial diameter with reduced blood flow.

The medial degeneration as principal structural change with aging, unstoppably leads to progressive stiffening of the large elastic arteries. The increased calcium content of arterial wall (usually due osteoporosis) after the fifties, may also contribute to the loss of arterial distensibility i.e. a rise of arterial stiffness. In the last prospective study, we found high degree of correlation between bone mineral density (BMD) and arterial stiffness which suggests that the process of atherosclerosis has many common pathophysiological and epidemiological factors with the process of osteoporosis [13,14]. Excessive bone resorption during a dynamic state in osteoporosis causes rapid accrual and removal of calcium and phosphorus from the bone. In our previous, prospective study with 36-month follow-up, 558 patients (226 male and 332 female) from general population was underwent noninvasive dual energy x-ray absorptiometry and PWV measurement [13]. Unpublished results from this study [13] showed the dependence of arterial rigidity on bone density (Figure 1).

There is an inverse correlation between these two variables [Pulse Wave Velocity (PWV) and BMD of femoral neck (FN)]. By increasing of bone density, the arterial stiffness decreases. The stiffness is expressed by PWV.

The coefficient of determination R^2 (0.1856) showed that 18.56% of the total variability was explained with the linear relation between PWV and BMD FN or that 18.56% from PWV changes were dependent on BMD FN. Only 18.56% of the changes in aortic stiffness were the result of osteoporosis (BMD FN) value changes, and the remaining from the total variability between them were not explained (81.44% of aortic stiffness expressed by PWV were dependent on other factors, which were not covered with the this linear regression model.

Noninvasive measurements of arterial stiffness

Several noninvasive techniques have been developed to estimate arterial stiffness. These include simple calculation of pulse pressure (systolic minus diastolic blood pressure) [15], regression equation that evaluates the relative changes in diastolic pressure regressed onto the systolic pressure over 24 h [16], and aortic pressure wave reflection expressed as magnitude of increase in the systolic pressure diagram (augmentation index) [17]. Augmentation index (AI) is higher when measured over the carotid than radial artery, and it is positively related to diastolic blood pressure. AI is not reliable surrogate marker for increased aortic stiffness [18]. Applanation tonometry methods for measuring of PWV using commercial devices *Sphygmocor® 2000* (AtCor Medical, Sydney, Australia), *Complior* SP® (*Artech* Medical, Pantin, France), and *VaSera®* VS-1000 (Fukuda) showed significant ($P<0.05$) differences in measured traveled distance. Differences in PWV obtained by compared commercial devices resulted primarily from using various methods for measuring traveled distance [19]. The best way of arterial stiffness measuring is determination of PWV, and this is recommended in the American Heart Association (AHA), as well as in the European expert consensus document [20]. Other methods such for PWV measuring such as brachial-ankle PWV and the cardio-ankle vascular index also provide excellent estimation of arterial stiffness and cardiovascular disease prediction, but the use of these techniques are limited when compared with carotid-femoral PWV.

Pulse wave velocity estimation

We provided sequential recording of carotid and femoral artery signals by color Doppler ultrasonography (Toshiba SSA-340A, Toshiba Medical System Corporation, Tokyo, Japan). The signals were acquired transcutaneously at the base of the neck for left common carotid artery and in the left groin for common femoral artery. The distance from this arterial site was indicated by "D". We detect the delay ΔT or difference in arrival time of the flow wave at these arteries. The time delay of the signals was compared with the reference point of the "R" wave of the synchronized electrocardiography. Anthropometric measure was made to find distance between this two sampling sites, the distance "D" measured as straight line between that two points on the body surface. Dividing the distance "D" by time delay ΔT we got carotid-femoral PWV, exactly $PWV\left(\frac{m}{s}\right)=\frac{D(\mathrm{m})}{\Delta T(\mathrm{s})}$. This method for carotid to femoral estimation of PWV was been previously described, reported and validated in many studies [21]. The transit time or time delay (ΔT) is the time of travel for the onset of the Doppler wave (carotid or femoral) over a known distance and it was estimated by "foot to foot" method. The foot

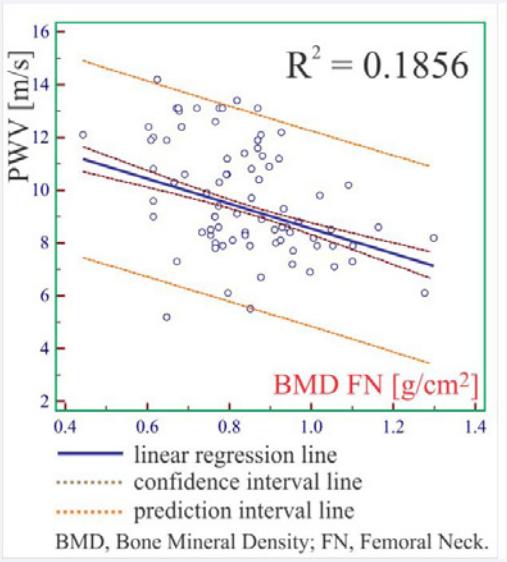

Figure 1 Linear regression analysis and scatter plot of PWV and BMD FN.

of the wave is defined at the end of diastole, where the rise of the waveform begins. The basic principle of PWV estimation by time diversity of propagation of both Doppler signals (Figure 2).

In this way, by measuring the PWV it is possible to noninvasively assess arterial stiffness and real age of the arteries and thus the risk of CV events. PWV as a crucial vascular and hemodynamic parameter is a physiological phenomenon that is used to assess the stiffness of aorta as a large vessel. This parameter assessed by noninvasive Doppler ultrasound measurements, measures the speed of pressure wave propagation, not the displacement of the blood. The PWV speed (6 to 12 m/s) is always greater than the actual velocity of the blood flow (5 m/s). The faster speed of pulse wave, more pronounced reduction capability of an artery to expand and contract in response to blood pressure changes.

Arteriosclerosis refers to reduced arterial compliance due to increased fibrosis, loss of elasticity and vessel wall calcification. The consequence of reduced compliance/distensibility is an increased propagation velocity of the pressure along the arterial tree, called PWV [22,23]. This value of stiffness rise with aging.

Pulse wave velocity and aging

Unpublished results from our previous and extended study [13], showed the dependence of arterial rigidity on aging. We see a strong positive correlation between PWV and aging. By increasing of age, the arterial stiffness increases, too. The stiffness was expressed by PWV (Figure 3).

The coefficient of determination R^2 (0.6963) showed that 69.63% of the total variability was explained with the linear relation between PWV and age or that 69.63% from PWV changes was dependent on age. A great value percentage of 69.63% of the changes in aortic stiffness were result of aging process value changes, and the remaining from the total variability between them were not explained (30.37 % of aortic stiffness were dependent on other factors, which were not covered with this linear regression model). The influence of aging on the arterial stiffness is so pronounced in many multiple regression analyzes; the age is excluded from this statistical model in order to avoid the phenomenon of multicollinearity.

In previous study [13], by multiple regression analysis, we showed predictable values of independent variables [predictors: age, body mass index (BMI), BMD of femoral neck, hypertension, diabetes and smoking] on the dependent variable PWV. We found by β^{st} (regression coefficient) of 0.1393, standard error of β^{st} (0.00421), t = 33.075 and p-value<0.0001 that age has more predictable value than other independent variables (femoral neck and hypertension) We extended this study from 558 to 743 participants and we estimated the cut-off point for age as predictor for CV mortality. The cut-off point was assessed by receiver operating characteristic (ROC) curve analysis. The summary image of two ROC curves for age and PWV as a prognostic marker for CV event is shown in Figure 4.

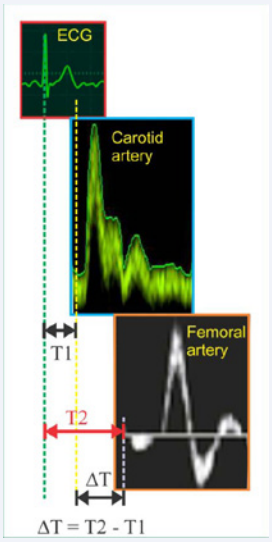

Figure 2 Principle of PWV estimation: time diversity of electrocardiographic and carotid-femoral Doppler signal. ΔT: time diversity; T1: carotid artery signal time delay; T2: femoral artery signal time delay.

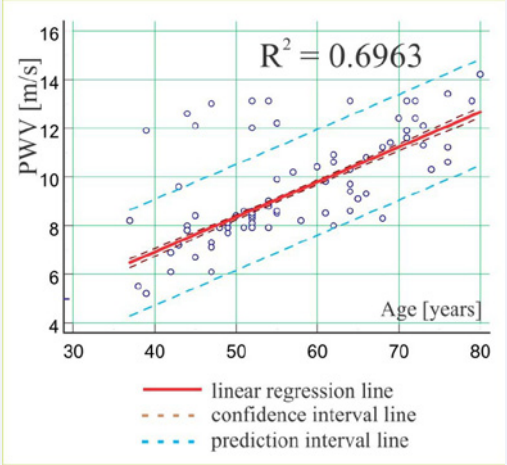

Figure 3 Linear regression analysis and scatter plot of PWV and AGE.

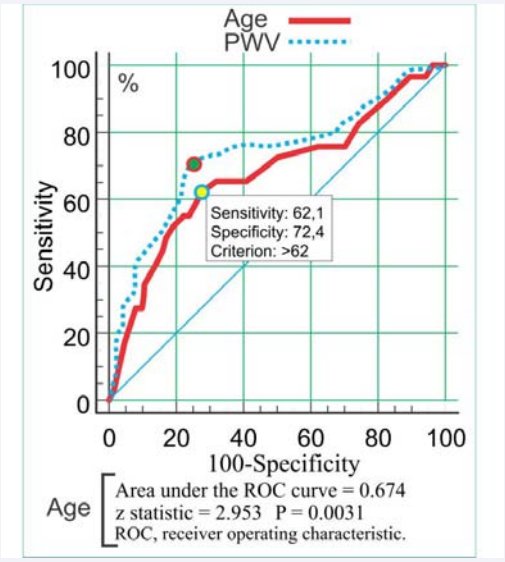

Figure 4 Receiver operating characteristic curves for age and PWV as a prognostic marker for cardiovascular event.

Both ROC curves are shown by different color and line styles (red solid line for age and blue dashed line for PWV). Each point on the ROC curves (PWV or age) represents a sensitivity/specificity pair corresponding to a particular decision threshold (PWA or age: sensitivity = 62.1%, specificity = 72.4%) in detection of cardiovascular event. The criterion for critical age is age greater than 62 years (P = 0.0031). The criterion cut-off value for PWV is 9.15 m/s. Our result is well matched with the results for critical cut-off value of PWV with other studies [24]. The greater sensitivity and specificity for PWV (67.3% and 83.1%) makes this variable more predictive than age.

Accelerated progression of arterial stiffness

In our previous prospective study [25] we estimate control group (60 patients) and 80 patients undergoing hemodialysis with follow-up period of 36 months. PWV progression was recorded in this period and the determinants of this progression were evaluated. We concluded that accelerated arterial aging was more pronounced in the chronic hemodialysis patients (CHP) than in the general population patients. In both groups, independent determinants of the stiffness and PWV progression were traditional risk factors, albumin and C-reactive protein (CRP) levels. Total cholesterol and uremia-related factors were determinants only in CHP. Aging was an indisputable factor, which in synergy with traditional and non-traditional risks factor for atherosclerosis led to an accelerated increase in vascular stiffness. The premature aging named as progeria is result of accelerated vascular aging (stiffening and PWV increase).

The prevalence of arterial stiffening and hypertension increased with age [26]. The prevalence of hypertension is more than doubled in the elderly than in the young population [27]. Initial rise in blood pressure is not independently correlated with the risk of accelerated arterial stiffening, but arterial stiffness predicts an increase in systolic blood pressure. Arterial stiffening reflects gradual fragmentation, loss of elastin fibers and accumulation of stiffer collagen fibers in the media of large arteries, and occurs independently of atherosclerosis. Aging is associated with a decreased ratio of elastin/collagen which is due to, in part, an enhanced degradation of elastin and/or increased accumulation of stiffer collagen. Above-mentioned observations indicate a strong relationship between aortic stiffening and the development of hypertension in human subjects [28,29].

Among older diabetes is correlated with aortic stiffness and prediabetes is associated with higher PWV, too. Cross-sectionally, the magnitude of the effect of diabetes on central stiffness is equivalent to 6 years of arterial aging [30]. While much has been published about arterial stiffness in patients with diabetes mellitus (DM), a lot of studies demonstrating that, among patients with established DM, arterial stiffness is closely related to the progression of complications of DM, including nephropathy, retinopathy, and neuropathy. They conclude that potential mechanisms of arterial stiffness acceleration in DM, with particular emphasis on the role of advanced glycation end products and nitric oxide dysregulation which can be expressed even in pre-diabetic populations with impaired glucose tolerance. The presence of diabetes and prediabets is associated with increased PWV (arterial stiffness) and DM contribute in part to increased CV risk in diabetic patients. The early signs of asymptomatic and advanced atherosclerosis presented as elevated carotid intima-media thickness was found even in young adults with type 1 diabetes [31]. The stiffness advancement is particularly prominent when age and diabetes come together synergistically. Synergistically effect on vascular stiffness expressed diabetes and hypertension, too. In our previous study [12], by multiple regression study we found predictable values of independent variables (hypertension: = 1.73, P = 0.009, diabetes: β^{st} = 0.4595, P = 0.0046) on the dependent variable PWV as a vascular stiffness measure.

DISCUSSION AND CONCLUSION

Age is an important determinant of PWV. By incorporating carotid-femoral Doppler PWV measurement into regular diagnostic tool for estimation of arterial stiffness, not only elderly, but also even young patients with increased CV risk can be pinpointed earlier, with recommendation for preventive appropriate stiffness, hypertension or diabetes treatment. By measuring arterial stiffness with Doppler it is possible to noninvasively assess age of the arteries and thus the risk of CV event. Increased aortic stiffening is a hallmark of the aging process. It is a results of the real aging accompanied of many disease states, such as diabetes, hypertension, atherosclerosis, and chronic renal compromise [23,31]. Vascular stiffening likely begins much earlier and progresses more rapidly in hypertensive, diabetic and hemodialysis patients. In this population, the chronological age is greater than biological age, expressed through the increased vascular stiffness. The bone mineral loss and consequential deposition of calcium in the blood vessels result with rise of artery stiffness most often observed in older people and in women after menopause. Many different biomarkers such as calcium-regulating hormones, vitamin D deficiency, serum calcium and calcium-phosphorus product contribute to accelerated bone resorption and atherosclerosis. In our previous study [32], we found association between them.

We found a positive correlation between aortic calcification and BMD as an independent variable. Aortic calcification is the main carrier of arterial stiffness and elevation of PWV. Lebrun et al. [33], in a cross-sectional study among postmenopausal women, provides evidence that most of the established cardiovascular risk factors are determinants of aortic PWV. Increased PWV marks an increased risk of stroke, coronary heart disease, and death within 10-12 years in postmenopausal women [33].

The first use of PWV measurement was reported in 1922 in a study examing an association between age and arterial stiffness [34]. Despite his great and before proven role, PWV as an indicator of artery stiffness has never been ascertained as a CV risk marker. Even in recent years, many new studies have confirmed that PWV is strongly correlated with presence and extent of atherosclerosis and constitutes a forceful marker for CV disease. The main carrier and responsible factor for stiffness is abdominal aorta. The greatest impact on the increased vascular stiffness has aortic calcification. Human associations studies suggest that older age, chronic kidney disease and osteoporosis are the most important risk factors for abdominal aortic calcification [35]. *Aortic wall calcifications* are increasingly recognized as strong predictors of cardiovascular events and all-cause mortality. The vascular calcification that occurs in elderly and osteoporotic patients is likely responsible for a substantial increase in vascular stiffness as measured by PWV [36]. The reasons for that are a dynamic bone during osteoporosis, excessive bone resorption with rapid accrual and removal of calcium and phosphorus from the bone. Poor bone mineralization and excessive calcium and phosphorus in the circulation likely favor deposition of hydroxyapatite crystals in soft tissues [14].

Despite aging as one of the main reasons for stiffness advancing, in our studies we found strong correlation of PWV with diabetes and PWV with hypertension. The bone loss is potentiated in diabetes, but the reason is still unknown. Insulin-like growth factors and other cytokines may influence diabetic bone metabolism [37]. Hypertension state is responsible to alteration in calcium metabolism leading to increased calcium losses and secondary activation of the parathyroid gland that caused increased movement of calcium from bone.

With the aid of this fast, cheap and non-invasive method such as Doppler, we can estimate the arterial stiffness. Any increase of arterial stiffness above 9 m/s, which is not correlated with chronologic age, can suggest and direct us to investigate additional comorbidities such a diabetes, hypertension or chronic renal disease that increase arterial stiffness and hence cardiovascular mortality.

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