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Review Article

Hemodynamic Aging as the Consequence of Structural Changes Associated with Early Vascular Aging (EVA)

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ABSTRACT: An increase in peripheral vascular resistance at rest is not routinely observed in healthy older persons, but often associated with increased stiffness of central elastic arteries, as hallmarks of aging effects on the vasculature, referred to as early vascular aging (EVA). In clinical practice, the increased arterial stiffness translates into increased brachial and central systolic blood pressure and corresponding pulse pressure in subjects above 50 years of age, as well as increased carotid-femoral pulse wave velocity (c-f PWV), a marker of arterial stiffness. A c-f PWV value ≥ 10 m/s is currently defined as a threshold for increased cardiovascular risk, based on consensus statement from 2012. Prevention and treatment strategies include a healthy lifestyle and the control of risk factors via appropriate drug therapy to achieve vascular protection related to EVA. New drugs are under development for vascular protection, for example the selective Angiotensin II (AT2) receptor agonist called compound 21. One target group for early intervention could be members of risk families including subjects with early onset cardiovascular disease.

The biology of aging in humans in general is of great importance to understand cardiovascular aging and its clinical consequences. The structural changes of the arterial wall in large elastic arteries associated with aging have been well characterised and include increased stiffening caused by a decrease in the elastin content of the arterial media, as well as a relative dominance of collagen content and associated increased non-enzymatic cross-linkages between collagen structures. This process will contribute to early vascular aging (EVA) as described in a number of reviews during recent years [1-3]. EVA provides a working model to understand one part of the aetiology leading to increased cardiovascular risk in addition to atherosclerosis, plaque formation and plaque rupture that will finally end in cardiovascular events, for example myocardial infarction or stroke. As these morphological changes, linked to arterial stiffness and arteriosclerosis, are also possible to measure in a quantitative way via carotid-femoral pulse wave velocity (c-f PWV) for arterial stiffness this provides an imaging biomarker that can be used as a cardiovascular risk marker in clinical practice [3,4]. A threshold above 10 m/s of c-f PWV has been proposed as a level above which cardiovascular risk rapidly increases and different interventions are motivated [4]. This is mirrored in current European guidelines on the detection, diagnosis and treatment of arterial hypertension, as recently published by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) in the 2013 edition of their joint ESH/ESC Guidelines [5]. In the most recent meta-analysis of 16 cohorts showing evidence for the predictive power of c-f PWV for total mortality and cardiovascular endpoints, it was shown, based on individual data, that c-f PWV is an independent risk marker even adjusted for a number of other cardiovascular risk factors, including measures of blood pressure [6].

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This was also evident in a number of subgroups, and more pronounced in younger as compared to older subjects, probably representing more differential biological and vascular aging in the younger than in older subjects [6]. The details indicated that of 17,635 participants, 10% had a cardiovascular (CVD) event. The pooled age- and sex-adjusted hazard ratio (95% CI) per SD change in log-transformed aortic PWV was 1.35 (1.22, 1.50, p<0.001) for coronary heart disease (CHD), 1.54 (1.34, 1.78, p<0.001) for stroke, and 1.45 (1.30, 1.61, p<0.001) for CVD. After adjusting for conventional risk factors, PWV remained a significant predictor: CHD 1.23, (1.11, 1.35 p<0.001); stroke 1.28, (1.16, 1.42 p<0.001); and total cardiovascular events 1.30 (1.18, 1.43, p<0.001) [6].

Haemodynamic effects of vascular aging

However, as arterial stiffness is a characteristic of vascular aging based on morphological changes in the arterial wall there is also a need to understand its haemodynamic consequence. More specifically, what are the consequences of normal aging on blood pressure and pulse rate regulation in western populations and what is outside this normal range? A starting point is to try to list different characteristics of haemodynamic aging and to try to understand the association with underlying morphological changes in the arteries (Table 1).

Table 1. Features of hemodynamic ageing and its relationship to arterial stiffness

Age-related changes in brachial BP
Isolated systolic hypertension (ISH)
Elevated pulse pressure (PP)
Age-related changes in central BP
Increased central systolic BP and PP
Increased BP variability
Linked to arterial stiffness
Decreased heart rate variability
Linked to arterial stiffness
Impaired endothelial function
Less vasodilation, linked to arterial stiffness
Impaired baroreceptor function, orthostatic hypotension
Linked to arterial stiffness

Well-known changes include an increase in brachial systolic blood pressure and a flattening off of the diastolic blood pressure to be followed by a decrease in diastolic blood pressure above the age of approximately 60-65 years. This will lead to increased risk of isolated systolic hypertension (ISH) and elevated pulse pressure (PP), both

conditions being associated with increased prospective risk of cardiovascular events [7]. The same holds true for corresponding changes in central systolic blood pressure and pulse pressure, because around the chronological age of 50 years the blood pressure amplification between the central and peripheral circulation decreases, and thus central and brachial blood pressures tend to become more similar. This is, however, not the case in younger subjects when the central pressure is substantially lower than the peripheral (brachial) blood pressure and amplification thus plays a more important role. These changes according to conventional blood pressure and central blood pressure recordings have previously been discussed in detail by Stanley Franklin *et al.* [7,8]. For example, in participants from the Framingham Heart Study who were free of CVD events and anti-hypertensive therapy, in all 1439 CVD events occurred between 1952 and 2001. In pooled logistic regression with the use of BP categories, combining SBP with DBP and PP with mean arterial pressure (MAP) improved model fit compared with individual BP components. Significant interactions were noted between SBP and DBP (p=0.02) and between PP and MAP (p=0.01) in multivariable models. The combination of PP + MAP (unlike SBP+DBP) had a continuous relation with risk and may provide greater insight into haemodynamics of altered arterial stiffness versus impaired peripheral resistance but is not superior to SBP+DBP in predicting CVD events [7].

Arterial stiffness as a core characteristic of age-related haemodynamic changes

There are, however, also other features of haemodynamic aging less well characterised, but all linked to arterial stiffness as an underlying contributing factor, and thereby also explaining most of the risk associated with these different features. One of them is increased blood pressure variability (BPV), linked to increased cardiovascular risk, i.e. for stroke [9]. Increased BPV can be evaluated on a visit-to-visit basis with weeks or months between visits, but also based on shorter time intervals (days, hours, even beat-to-beat timing), as recently reviewed by Gianfranco Parati *et al* [10]. An underlying feature is arterial stiffness, and it is reasonable to believe that this factor might explain most of the increased risk associated with increased BPV, even if also some mechanical risk mechanisms could play a role based on changes in blood flow, shear stress or transmission of increased pulse wave energy to small arteries and the peripheral circulation [10].

In a corresponding way it has been reported that a decrease in heart rate variability (HRV) is a marker of aging and increased cardiovascular risk, but also

associated with increased arterial stiffness, for example in patients with type 1 diabetes [11].

Furthermore, it is well known that episodes of orthostatic hypotension are associated with increased cardiovascular risk during follow-up, based on data from several epidemiological studies. Also for this clinical example we notice underlying arterial stiffness as a common denominator, as shown in the Rotterdam study of elderly subjects [12]. The link could be the impaired stretching (compliance) of the carotid arterial wall close to the baroreceptor due to arterial stiffness and superimposed atherosclerosis, leading to impaired baroreceptor function in response to change of body position. This could contribute to the role of arterial stiffness being the true risk marker behind orthostatic reactions, often seen in aged subjects with for example diabetes of long duration. These orthostatic reactions should be separated from benign vasovagal reactions with orthostatic reactions in younger subjects.

It is conceivable to think that more widespread changes in innervation and the autonomic nervous system could contribute to the aging of the neural system and thus linked to vascular aging and decreased baroreceptor function as well as imbalance between sympathetic and parasympathetic activity. One recent study tested the relationship between direct measures of sympathetic traffic and PWV in healthy humans [13]. The authors examined MSNA (microneurography), PWV (Complior device), heart rate and blood pressure in 25 healthy male participants (mean age 43 years). It was reported that PWV correlated significantly with age (r = 0.63), SBP (r = 0.43) and MSNA (r = 0.43) but not with BMI, waist circumference, waist-to-hip ratio, heart rate, pulse pressure or DBP. Multiple linear regression analysis revealed that only age and MSNA were linked independently to PWV (r^2 = 0.62, p <0.001), explaining 39 and 25% of its variance, respectively. Individuals with excessive PWV had significantly greater MSNA than individuals with optimal PWV. Thus the relationship between MSNA and PWV is independent of age, BMI, waist circumference, waist-to-hip ratio, heart rate, pulse pressure or blood pressure [13].

A cross-talk between the sympathetic nervous system and the renin-angiotensin system takes place in the arterial wall. The effects of this interaction will further decrease elasticity and promote vascular aging [14].

Endothelial dysfunction linked to vascular aging

Endothelial dysfunction is another pathophysiological link to cardiovascular disease. It correlates not only with aging but also with smoking, insulin resistance, hyperglycaemia, metabolic syndrome, chronic inflammation and other cardiovascular risk factors [15],

and this could further contribute to impaired vasodilation and the arterial stiffness phenotype. This is well documented in numerous studies. Endothelial dysfunction has been difficult to establish as an independent risk marker of future macrovascular events, for example by use of impaired forearm vasodilation that could represent both endothelial-derived and endothelial-independent pathways [16]. The reason could be that the underlying or concomitant arterial stiffness contains or represents much of the risk information provided by impaired endothelial function itself. For example, in recent studies, reduction in coronary flow velocity reserve (CFR) has been demonstrated in patients with increased aortic stiffness and in one study increased aortic stiffness could predict impaired CFR in patients with suspected CAD [17].

Cardiac-arterial coupling influenced by arterial stiffness

Finally, it is self-evident that haemodynamic changes associated with aging are not possible to describe without taking cardiac changes into account. In fact, there is a so called cardiac-arterial coupling process that can be illustrated by echocardiography examinations [18]. There is thus a cross-talk between cardiac function and the general circulation in the arterial tree. With increasing stiffening of the proximal thoracic aorta the reflected wave from the periphery back to the central circulation and the heart can no longer be accommodated. Instead this pulse wave energy will impact on the heart with increased pressure waves and augmentation during systole leading to increased strain on the left ventricle, causing left ventricular hypertrophy (LVH), and a decreased perfusion pressure during diastole, leading to impaired blood flow in the coronary circulation. These two trends combined will increase the risk of morphological changes (LVH) in combination with coronary ischaemia, thus increasing the risk of CHD events. This is therefore a hemodynamic mechanism explaining some of the risk potential of arterial stiffness, as measured by increased PWV, for the development of CHD. It contributes to what has been called the cardiovascular aging continuum by O'Rourke, Safar and Dzau [19].

Drug treatment to influence haemodynamic aging

Most blood pressure lowering drugs are equally effective in reducing brachial blood pressure, but may differ according to mechanisms and effects on central blood pressure and arterial stiffness. Treatment based on beta-receptor blockers has been reported to be less efficacious for control of central blood pressure, i.e. when atenolol-based treatment was compared to an amlodipine-based treatment in the ASCOT study [20]. Long-term effective blood pressure control will also lower arterial stiffness

and reduce c-f PWV, an effect that seems to go beyond blood pressure lowering per se [21].

In France, recently the SPARTE intervention study started for a randomised intervention in patients with hypertension, half of them randomly treated for reduction of arterial stiffness (PWV) as the treatment target and half of the patients randomised to be treated according to general guidelines [22].

New drugs are under development for vascular protection, for example the so called compound 21, a specific angiotensin II (AT2) receptor agonist, with promising results in animal studies to reduce arterial stiffness but not primarily affecting blood pressure [23,24]. Compound 21 may also ameliorate streptozotocin-induced diabetes in animals by protecting pancreatic islets via anti-oxidative and anti-apoptotic effects [25]. Human studies are awaited during coming years.

A number of new anti-hypertensive drugs are being developed, most of them also acting on the renin-angiotensin system, but also from new pharmacological classes such as vasopeptidase inhibitors and aldosterone synthase inhibitors [26].

Conclusions

In conclusion, the development of morphological changes in the wall of large arteries associated with arterial stiffness has got consequences for increased cardiovascular risk, discussed within the EVA concept for understanding the age-dependent development of cardiovascular risk [1-3]. One mediating factor of risk could be the haemodynamic changes described in this review, that could represent different aspects of what could be called the haemodynamic aging syndrome (HAS). Therefore the link between EVA and HAS could be represented by arterial stiffness. If not possible to measure arterial stiffness directly by use of c-f PWV, or aortic PWV indirectly by an oscillometric method in the upper arm, shown to predict mortality and total cardiovascular events [27], another approach could be to evaluate different aspects of HAS. This includes not only ISH and increased brachial pulse pressure, as distant and not too accurate measures of arterial stiffness, but also increased blood pressure variability and orthostatic reactions in the elderly, as well as decreased heart rate variability. This approach could provide useful and clinically meaningful insights into the panorama of haemodynamic aging and eventually the coupling to changes in cardiac function. Thomas Sydenham (1624-1689) once told that *"A man is as old as his arteries"*. This statement could now be complemented with the notion that these arterial changes become more visible

through age-related hemodynamic changes in a predicted way. EVA has finally met HAS.

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