THE CONCEPT OF EARLY VASCULAR AGEING – AN UPDATE IN 2015

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ABSTRACT

Arterial ageing is a process that can be quantified, at least to some degree, by measurement of pulse wave velocity along the aorta, the largest elastic artery, as a marker of arterial stiffness. In recent years the new concept of early vascular ageing (EVA) has been developed by a group of mostly European researchers and some reviews have been published. Based on a lecture given at the European Association for the Study of Diabetes (EASD) Meeting in Vienna 2014, this review was written to describe recent developments in research dedicated to EVA and new emerging aspects found in studies of families at high cardiovascular (CV) risk. This brings new perspectives related to genetics, telomere biology, and the role of gut microbiota. Even if EVA has been described in general terms there is still no unifying definition available and no direct treatment, only recommendations for conventional CV risk factor control. However, a new intervention study (SPARTE) is ongoing in France with a randomised design to treat arterial stiffness in patients with hypertension versus conventional treatment strategies. Results are expected in a few years and will be of importance in defining the role of arterial stiffness, a core feature of EVA, as a target for treatment.

Keywords: Arterial ageing, arterial stiffness, blood pressure (BP), glycaemia, hypertension, lipids, microbiota, telomere.

INTRODUCTION

From time to time, new concepts are needed to promote medical efforts to diagnose, prevent, and treat cardiometabolic (CM) risk factors and disease manifestations. For many years, the conventional risk factors for cardiovascular disease (CVD) (hypertension, smoking, hyperlipidaemia, and hyperglycaemia) were quantified and included into risk algorithms together with background factors that are not changeable (age, sex). Examples of such risk algorithms are the Framingham Risk Score,[1] the European SCORE that originated from the Danish algorithm PRECARD,[2] and a number of scoring systems that are less used internationally.[3-5] For cardiovascular (CV) complications of Type 2 diabetes mellitus (T2D), other risk algorithms have been developed in newly detected patients,[6] and also based on national registry data from T2D patients treated in Sweden.[7] The endpoints most commonly used for these algorithms were CV events (fatal or non-fatal), generally caused by atherosclerosis (ATS), plaque rupture, and thromboembolic mechanisms. In more recent years, research activities dedicated to ATS have also started to include the effects of acute or chronic inflammation on the risk of CVD, such as in patients with metabolic syndrome, for example.[8] Modern insights into the genetics of CVD and T2D have contributed to an understanding of causal pathways for these disorders, as revealed by applying 'causal inference' (based on Mendelian randomisation) methodologies.[9] These methods have proven the causal role of low-density lipoprotein (LDL) cholesterol but disproved the causal role of C-reactive protein (CRP) and high-density lipoprotein (HDL) cholesterol, which are merely risk markers. Even if substantial achievements have been accomplished both in pathophysiology and evidence-based treatment, there is a need for a deeper understanding of the early origins and features of CV and metabolic

disease, as well as elucidation of why many of these disorders tend to cluster in at-risk families, which is not directly addressed in the conventional risk algorithms. This is the background for the emerging interest in arterial stiffness (arteriosclerosis [AS]) and the development of the concept of early vascular ageing (EVA) that will be further presented in this updated review on the topic, which was first presented as a lecture at the European Association for the Study of Diabetes 2014 Meeting in Vienna.[10]

THE AGEING OF ARTERIES AND THE ROLE OF ARTERIAL STIFFNESS

Arterial ageing is a process that spans from normal ageing[11] to pathological ageing and the profound changes related to ATS. In recent years, interest in arterial stiffness has increased, with the pathology of the underlying AS (as a precursor to the more well-known and well-studied ATS) shown to be influenced by genetics, high LDL cholesterol levels, smoking, hypertension, inflammation, and overt T2D.[12] In many cases it is believed that early life programming may promote susceptibility to this increased tendency for arterial stiffening, as well as other aspects of the vascular tree such as the development of capillaries and the microcirculation. As this process is also related to ageing, it has been proposed that a process of EVA is an early sign of AS (in the media) and is also linked to early changes in endothelial function (intima), haemodynamic changes, and the influence of abnormal glucose metabolism and increased inflammation (Table 1).[13-15] New interest is now directed towards the role of the vasa vasorum in the adventitia (the outer layer of the arterial wall) because the treatment of cancer patients with anti-angiogenic drugs has been shown to cause increased arterial stiffness.[16] Taken together, these findings point to the importance of investigating all layers of the arterial wall with regard to arterial ageing, even if the changes in the media are probably the most important.

The difference between the concepts of arterial ageing and EVA is that the latter also encompasses the smaller arterioles and the microcirculation, based on the crosstalk between the macro and microcirculation as evident in the origin of vascular brain damage.[17] EVA is now being extensively studied in different population-based cohorts, both in Europe and in Latin America, but no general definition has yet been agreed upon.

Table 1: Components of the early vascular ageing syndrome.

Established features:
Arterial stiffness
Haemodynamic ageing
Endothelial dysfunction, nitric oxide
Chronic inflammation
Hyperglycaemia
Dyslipidaemia
Emerging features:
Early life influences
Telomere shortening/increased attrition rate
Cognitive dysfunction and brain ageing
Dysbiosis of the gut microbiota
Arterial media calcification

One way to define EVA could be to use the outliers according to the normal range of carotid–femoral pulse wave velocity (c–f PWV), i.e. those more than two standard deviations from the normal distribution of c–f PWV based on data from the European reference group.[18] Another way to describe EVA is based on statistical methods in which arterial stiffness (as determined by c–f PWV), which is a central aspect of EVA, is used as the dependent variable in multiple regression analyses, with a number of risk markers used as independent variables, based on data from population-based studies. As the influence of haemodynamic changes and sympathetic nervous system (SNS) stimulation on the arterial tone is substantial, the data are normally adjusted for mean arterial pressure (MAP) and heart rate (HR), the latter being a marker of SNS activity.

In Malmö, Sweden, we have examined elderly individuals (mean age: 71 years) and this has revealed that markers of glucose metabolism and dyslipidaemia (elevated triglycerides, low HDL cholesterol levels) as well as waist circumference (a marker of active abdominal fat tissue with inflammatory action) are significantly associated with arterial stiffness (c–f PWV), but not LDL cholesterol, smoking, or cystatin C (a marker of impaired renal function) after adjustment for MAP and HR.[19] The findings therefore point to two different clusters of CV risk factors involved in the development of AS and ATS, respectively.

THE PREVALENCE OF EARLY VASCULAR AGEING IN DEFINED POPULATIONS

There are no conclusive studies addressing the prevalence of EVA in a systematic way. However, new data from the Portuguese Guimarães study have shown higher than expected prevalence rates in young individuals.[20] The results indicated that the overall prevalence of EVA was about 13%, although more striking findings were recorded in younger age groups, with 26% of those <30 years presenting with PWV values above the 97.5th percentile of the expected mean value for their age. In a widened analysis, >34% of the population <40 years were above the 90th percentile for expected PWV. These findings are especially relevant with regard to the high stroke risk in this population in northern Portugal. The study is ongoing and also includes evaluation of neurocognitive function, which is yet to be reported. The principal investigator of the Guimarães study, Dr Pedro Cunha, has already organised three international symposia dedicated to EVA syndrome at the Minho University, with international lecturers and students invited. The next course is planned for November 2015, and will be based on experiences from the 2014 EVA course.[21]

When should EVA be suspected? One approach is to consider a positive family history of early onset of obesity, hypertension, T2D, and CVD, and to screen relatives. Another approach is simply to use clinical skills and look for general signs of early biological ageing (facial appearance, gait, skin turgor, etc.), as was tested in a Danish study of identical twins which found that older-looking twins (as judged by lay people provided with facial photos) displayed a higher risk-factor burden, shorter telomere length, and a worse prognosis during follow-up.[22] A limitation of this study was that arterial stiffness was not measured among the risk factors.

GENETIC FACTORS ARE DIFFERENT FOR HYPERTENSION AND ARTERIAL STIFFNESS

There is still a need to better define EVA in different age groups and also in relation to gender and ethnicity, as well as based on genetic studies, for improved classification.[23] Some people would argue that EVA is simply a construct describing one example of target organ damage (arterial stiffness) in individuals at high CV or metabolic risk, and primarily influenced by haemodynamic changes and blood pressure (BP) levels. However, modern genetic investigation of hypertension and BP regulation, based on a global study, could not show any marker on chromosome 13,[24] whereas a study from Sardinia, Italy, with independent replication in another American cohort, found a genetic locus for arterial stiffness on this chromosome (the *COL4A1* gene, which is involved in collagen metabolism).[25] The genetic determinants of arterial stiffness have recently been reviewed in more detail, including a description of other markers.[26] These findings show that even if arterial stiffness (and EVA) is strongly influenced by the BP load (MAP), HR, and SNS activity, there may exist some other important components (collagen protein synthesis and structure) and vascular risk factors (hyperglycaemia, dyslipidaemia, inflammation) independent of BP regulation. If shown to be true, for example after analysis based on Mendelian randomisation methodology, this opens up new possibilities to target these mechanisms of protein/collagen synthesis with new drugs to reduce arterial stiffness. Such studies have been considered and drafted, but the results will not be ready for presentation in the near future.

One speculative example involves the truncated and aberrantly farnesylated lamin A protein called progerin, which is found in children with the extremely rare and fatal premature ageing syndrome Hutchinson–Gilford progeria syndrome (HGPS). Recently, 25 patients with HGPS received the farnesyltransferase inhibitor lonafarnib for a minimum of 2 years.[27] The primary outcome for measuring success was the rate of weight gain, with secondary outcomes including changes in arterial PWV and carotid artery echodensity; all patients improved in one or more of these outcomes. According to the authors, the results from this clinical trial in children with HGPS provide preliminary evidence that lonafarnib may improve vascular stiffness, bone structure, and audiological status.[27] Whether these findings are applicable or not to other patient groups is not known at present.

RISK PREDICTION BASED ON ARTERIAL STIFFNESS

Based on two recent meta-analyses, stiffening of the large arteries has been shown to be an important risk factor for future CV events and mortality beyond other well-known CV risk

factors.[28,29] Measurement of arterial stiffness is preferably performed by use of c–f PWV,[30] with a risk threshold of 10 m/s according to an updated consensus document from 2012.[31] This can be achieved by both direct and indirect methods that are reasonably well correlated with one other in most cases, although the direct measurement via c–f PWV is preferred. Arterial stiffness is known to be strongly associated with age and hypertension,[32,33] which are findings also confirmed in a longitudinal study from the USA.[34] Arterial ageing is tightly inter-correlated with BP and causes the increase in pulse pressure (PP) seen in aged individuals. In some individuals, the arterial stiffening seen with increasing age is more pronounced and occurs earlier in life, a marker of EVA.[13]

As previously mentioned, a number of non-haemodynamic components are thought to affect arterial ageing, such as hyperglycaemia and dyslipidaemia. Several cross-sectional studies have shown an association between arterial stiffness and diabetes, as well as with markers of impaired glucose metabolism.[35-37] The roles of insulin resistance and hyperinsulinaemia, as well as changes in incretin regulation, are not well understood here. Individuals with end-stage renal disease are also known to exhibit an increased central arterial stiffness, but results from studies investigating the association between arterial stiffness and clinical stages of chronic kidney disease (CKD) have presented conflicting results.[38] Results from a prospective study showed that central obesity predicts arterial stiffness over a time period of 16 years,[39] whereas a 20-year follow-up study of men indicates that heavy smoking, CRP, and PP are predictors of arterial stiffness. These data reinforce the importance of chronic inflammation for the development of EVA.

FAMILIES AT HIGH CARDIOMETABOLIC RISK

A specific target group for research and preventive cardiology is the well-known example of families at high CM risk.[40] This has been documented in several epidemiological studies and also brought into focus for genetic studies. One conceptual problem to understand is the limited power of combined genetic risk scores (GRS) to explain more than a tiny proportion of this family-associated disease risk. This is why researchers have now tried to define the 'missing heritability' (non-GRS) that is believed to involve the influence of gene–environment interactions (epigenetics), lifestyle, early life programming, and even the role played by the gut microbiota with its high degree of family resemblance.[41] In fact, the role of the gut microbiota in influencing the risk of CM disease is emerging but, even if links have been shown with ATS,[42] there have still been no studies that have reported on the association between gut microbiota patterns and arterial stiffness. Such analyses are ongoing in the Malmö Offspring Study.

TELOMERE BIOLOGY IN RELATION TO EARLY VASCULAR AGEING

A number of studies have suggested that shorter leukocyte telomere length (LTL) in peripheral blood cells could be a marker of ageing, and early studies reported an association between increased PP, as a marker of arterial stiffness, and shorter LTL.[43] More recent studies have had difficulty in replicating these observations when both LTL and arterial stiffness were measured by more accurate technologies.[44] One explanation could be that most studies have only been cross-sectional by design and what is really needed is the calculation of telomere attrition rate based on repeated measures over time.[45] No such studies are currently available, and nor is a study analysing levels of telomerase and arterial stiffness. The opinion of the author of the present review is that the question is not settled and more studies are required.

THE ROLE OF COGNITIVE AND BRAIN AGEING IN RELATION TO EARLY VASCULAR AGEING

It is evident that the different forms of dementia, such as Alzheimer´s disease and cerebrovascular dementia, have more in common than was previously thought. This is based on the understanding that most common CV risk factors, especially uncontrolled hypertension, are able to predict both of these types of dementia in population-based studies. Therefore, an increasing interest has focussed on the role of haemodynamic changes and arterial stiffness in white matter lesions and cognitive decline. In the Malmö population, a non-linear relationship has been shown to exist between c–f PWV and cognitive dysfunction according to tests of speed and executive function, but not according to the Mini Mental State Examination memory test which reflects the function of the grey matter.[46] Similar

associations between vascular ageing and brain ageing have been reported in other studies, sometimes derived from neuroimaging data as in the Reykjavik Study.[47]

TREATMENT OF HYPERTENSION AND ARTERIAL STIFFNESS

It has been shown that prolonged control of hypertension reverses early vascular changes and has a long-term beneficial influence on arterial stiffness, with decreasing c–f PWV levels over time, beyond the control of BP itself.[48] However, an ongoing randomised controlled study in France (SPARTE) aims to compare a treatment strategy for the reduction of arterial stiffness (as assessed by c–f PWV) by various means (including drugs that specifically influence the renin–angiotensin system) with another treatment strategy (control) involving implementation of the control of conventional risk factors (including BP) as suggested in guidelines.[49] SPARTE is planned to continue for a number of years (until a sufficient number of CV endpoints have accumulated) in order to show potential differences in outcomes between the treatment arms, and recruitment still ongoing.

Blockade of the renin–angiotensin system is supposed to be beneficial for the reduction of arterial stiffness beyond BP control per se.[50] There are few data regarding the role of aliskiren, a direct renin inhibitor, on the central haemodynamics and endothelial function of patients with uncontrolled arterial hypertension. One study assessed the addition of aliskiren to other antihypertensive drug treatments for arterial stiffness and endothelial function.[51] Thirty patients with uncontrolled hypertension (mean age: 60.4 years) without any other CV risk factors were enrolled. Augmentation index (AIx) and c–f PWV were measured by applanation tonometry at baseline and after 6 months of aliskiren titrated to 300 mg once per day. The addition of aliskiren had no effect on central AIx but significantly improved c–f PWV (9.4±2.7 m/s versus 8.7±2.5 m/s; p=0.04). In addition to improving systolic and diastolic BP, the addition of aliskiren to concomitant antihypertensive drugs may therefore be effective in improving aortic stiffness and endothelial function in patients with uncontrolled hypertension. However, endpoint studies are needed in order to prove the overall benefits; the ALTITUDE study[52] was previously unable to show added CV benefits in patients with T2D. Other groups of non-diabetic patients should be evaluated following blockade of the renin–angiotensin system, for which many new drugs are currently being developed.[53]

Finally, new discoveries relating to vascular calcification have opened up the therapeutic field for new interventions. There is substantial and relevant clinical and basic science evidence to suggest that modulating the receptor activator for nuclear factor κB (RANK), the RANK ligand (RANKL), and osteoprotegerin (OPG) (i.e. RANKL–RANK–OPG signalling), and also the receptor for advanced glycation end-product signalling and the associated pro-inflammatory milieu is able to alter the natural course of CV complications and outcomes in people with overt diabetes.[54] Vascular calcification is also a hallmark of changes seen in the abdominal aorta of patients with CKD.[55] These new treatment alternatives have to be further tested in controlled clinical studies.

THE IMPORTANCE OF MULTIPLE CARDIOVASCULAR RISK FACTOR CONTROL

As increased c–f PWV has been documented to be an independent risk marker for future CV events and all-cause mortality in recent meta-analyses,[28,29] there is a need to target it with multiple risk factor control, aiming for c–f PWV <10 m/s that represents the current threshold for increased risk.[31] Whether this also holds true for patients with established T2D is currently unknown, but it is plausible and very likely that it will take a multi-drug intervention to achieve positive results in these patients because of the advanced stage of vascular disease and the combination of AS, ATS, and chronic inflammation further enhanced by hyperinsulinaemia, insulin resistance, and hyperglycaemia. This strategy is also emphasised in the recent European guidelines on risk factor control in patients with diabetes or impaired glucose metabolism.[56]

CONCLUSION

Knowledge regarding morphological changes (imaging) and physiological changes (imaging and haemodynamics) in the arterial wall will make it possible to better understand the double process of AS and ATS leading to CVD manifestations. Current medical and surgical therapies will be expanded in the future in order to achieve better control of these pathological processes and even

for the control of arterial ageing. EVA is a new concept to explain some of the increased CV risk observed in patients with diabetes. New interventions are needed to address the role of glycaemia and advanced glycation end-products in worsening EVA, and to counteract this detrimental influence on the arterial wall.

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