

Early vascular aging syndrome: background and proposed definitions

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Vascular aging is a process linked to arterial stiffness and remodeling, as well as increased pulse wave velocity (PWV). Other aspects involve structural changes in the vascular tree that might have been influenced by detrimental factors in early life, such as impaired fetal growth or preterm birth, especially in combination with a rapid postnatal catch-up growth. Based on data from several European populations, normal reference values for PWV in defined age groups were published in 2010. Thus, outliers from the normal range can be defined and thus labeled with early vascular aging (EVA), as arterial stiffness is a major marker of EVA. Another approach to define EVA is to describe the component of PWV that cannot be explained by conventional cardiovascular risk factors alone. New therapies are emerging for treatment of EVA, beyond traditional risk factor control. One option could be the breaking up of glycation linkages in arterial tissue, or the use of new antidiabetes drugs with vascular actions, such as incretin analogues or DPP-4 inhibitors, for cardiovascular protection.

Keywords: aging • arterial • brain • hypertension • pulse wave velocity • stiffness • vascular

In medical science there is a constant need for new models of understanding of the biology and pathophysiological processes behind common diseases, as documented in the history of medicine. This leads to critical discussion of older concepts that might not be fully correct or appropriate. For more than 20 years the so-called 'metabolic syndrome' has been the focus model to better understand the etiology of cardiovascular disease (CVD) in relation to abdominal obesity and metabolic abnormalities, including insulin resistance, based on a recent unifying definition from 2009 [1]. However, during the last 6 years, an increasing wave of criticism disputed the metabolic syndrome and currently some people think it should be abandoned due to its lack of precision and because it does not include important factors such as chronic inflammation [2,3]. Therefore, there is a need to find new and more precise models for both theoretical understanding and intervention on increased cardiovascular risk in order to prevent CVD manifestations. In this perspective it is, therefore, of interest to discuss the most important cardiovascular risk marker of all, the aging process, and more specifically its consequence, vascular aging. This concept is emerging as being fruitful, attracting new interest, as shown in recent reviews on vascular aging per se [4,5], or the systems biology approach to aging as outlined by TB Kirkwood [6]. Recently the early vascular aging (EVA) syndrome has been proposed [7,8] based on this concept and linked to features such as chronic inflammation, metabolic alterations and arterial stiffness, a tissue biomarker that will be further discussed in this review.

Background of cardiovascular risk: early life factors

It is well-known that traditional risk factors for CVD (age, sex, hypertension, hyperlipidemia, smoking, diabetes) are useful for calculating cardiovascular risk in general and even vascular age, based on application of algorithms from Framingham

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¹Department of Clinical Sciences, Lund University, University Hospital, S-205 02 Malmö, Sweden Tel.: +46 4033 2415 Fax: +46 4092 3272 E-mail: peter.nilsson@med.lu.se [9] as well as the European SCORE system [10]. These algorithms, however, lack a deeper understanding of the pathophysiological traits underlying the risk of CVD events, and starting already in early life. These traits could also be of importance for vascular aging *per se*.

Since early observational studies by Forsdahl [11] and Barker [12], it has been recognized that adverse factors in early life could be of great importance for adult health, especially risk of CVD. For some years the focus was mostly directed at the consequences of poor fetal growth resulting in the birth of small for gestational age babies based on intrauterine growth retardation, later growing up to become adults of increased risk for not only hypertension [13] and coronary heart disease [14], but also for insulin resistance [15] and Type 2 diabetes [16]. These observations were reported from various countries, most notably from the UK, the Netherlands and from Sweden. In the UK, Barker described these associations in follow-up studies of men and women born in Hertfordshire [17], in the Netherlands researchers made follow-up studies of babies born during the so called Dutch Winter Famine in 1944 to 1945 [18], and in Sweden, Lithell and Rasmussen have published data from cohorts either from the population in Uppsala [19] or based on data from the national military conscript register [20]. Lithell also found that impaired fetal growth was especially detrimental if combined with a rapid catch-up growth in postnatal life. The risk for cardiovascular events increased even further, especially in boys born small for gestational age and having a rapid catch up growth pattern [21]. A similar finding was found in 58 year-old men with features of metabolic syndrome, based on a population-based study from Gothenburg, Sweden. The men with the highest ratio between body weight at conscription testing at 18 years of age, and their birth weight, as a marker of pronounced catch-up growth, also had the highest risk of being diagnosed with metabolic syndrome in adulthood [22]. Studies from the UK [23] and Finland [24] have also reported similar epidemiological findings. More recently, Gluckman and Hanson systematized these observations and described the so-called 'mis-match' hypothesis [25].

Box 1. The association of aging with traditional cardiovascular risk factors.

- Increasing systolic blood pressure and pulse pressure.
- Increase of cholesterol levels after menopause.
- Less muscle tissue and impaired insulin sensitivity.
- Increasing glucose levels.
- Accumulation of body fat deposits, especially in the abdomen.
- Elevated levels of uric acid.
- Impaired renal function.

This implies that babies adapt their metabolism and physiology to the conditions expected after birth. If there is fetal malnutrition, the fetus adapts to develop a mechanism to increase insulin resistance. When the postnatal life is not characterized by a shortage of calories, but instead a surplus of calories, the new-born baby or child grows rapidly and will later be prone to develop obesity, metabolic syndrome and CVD manifestations [25]. One aspect of this is also increased hemodynamic load and being prone to hypertension, supported by findings in animal studies [26]. This could be influenced not only by the mechanisms linked to insulin resistance, but also to a rarefication of capillaries and less developed vascular function, a phenotype that could also be found in babies born preterm, as described by Bonamy et al. [27]. It has been shown that babies born prematurely, or in combination with being small for gestational age following intrauterine growth retardation, are more susceptible to risk factors increasing hypertension and arterial stiffness later in life [28,29]. This could, therefore, represent a link between factors in early life and the development of EVA in adult life [30].

Aging & arterial stiffness

Following early life developments there is maturation, and then the aging of organs and functions becomes gradually visible during the life course and can be measured. Aging is not only the major risk marker for CVD, as it correlates with a number of conventional risk factors or risk markers (Box 1), but is also an important determinant of arterial stiffness (arteriosclerosis) and pulse wave reflection. One measure of arterial stiffening is increased pulse wave velocity (PWV). Several reviews have now concluded that PWV, normally measured across the aorta between the carotid and the femoral arteries, predicts cardiovascular events, based on data from more than 13,000 subjects from 12 studies [31]. Another recent review showed the same risk magnitude, and, in addition, the risk for total mortality in an expanded dataset consisting of 17 longitudinal studies that evaluated aortic PWV and followed up 15,877 subjects for a mean of 7.7 years [32].

The arterial wall consists of different layers and the elasticity is determined not only by hemodynamic forces and endothelial reactivity but also by the content of elastin and collagen. With aging, the elastin content decreases and the collagen fibers will become more prone to cross-linkages and this combination will change the mechanical properties of the arterial wall [33]. This means that an increased arterial stiffness, as measured by carotid-femoral (c-f) PWV, is one marker of early arterial aging included in EVA [7,8,30]. The risk increases linearly with c-f PWV elevation, but is especially increased above 12 m/s, which is currently recommended to be a threshold for increased cardiovascular risk according to the 2007 European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension [34], and further addressed in the 2009 document 'Reappraisal of European Guidelines' from the European Society of Hypertension [35].

The arterial stiffness of large arteries can be determined by use of direct measurements of c-f PWV, but also between the carotid artery and the brachial artery [31]. Recently, evaluation of arterial stiffness in retinal arteries has also become possible with advanced technologies [36]. This is of great importance, as the retinal vascular and neural bed represents an extended part of the CNS. Another approach is to use ultrasound devices to investigate the distensibility of local arteries, for example the carotid arteries. Most types of bi-dimensional vascular ultrasound devices have been tested for this purpose to determine diameter at diastole and stroke changes in arterial diameter. Another technology is the magnetic resonance imaging of large and small arteries. For practical purposes in screening studies it is often the best choice to go for determination of c-f PWV as a marker of arterial stiffness, as c-f PWV is also the variable that has the strongest support for prediction of future cardiovascular events [31,32], even compared with other measures, such as augmentation index (Aix) of the pulse wave reflection or central aortic pressure, that could both be determined by pulse wave analysis in Arteria brachialis [31]. Other technologies are very useful to describe local morphological details or changes following pharmacological interventions, but cannot compete with c-f PWV as a predictor of future cardiovascular events [31].

On the other hand, the interest in central blood pressure was facilitated by the findings in the CAFE study, where it was shown that antihypertensive treatment based on the calcium antagonist amlodipine was more favorable than a therapy based on the β-receptor blocker atenolol for central blood pressure control, even if there was no difference in the brachial blood pressure [37]. There is no doubt that central blood pressure is a more relevant hemodynamic variable than brachial blood pressure for associations with target organ damage, such as left ventricular hypertrophy [38]. It is also the central blood pressure that exposes the brain to a direct hemodynamic load and thus increases the risk of stroke or vascular dementia. On the other hand, the bulk of evidence so far is more in favor of c-f PWV as a predictor of future events [31]. It has also been shown that long-term blood pressure control in hypertensive patients is able to reduce c-f PWV, even Box 2. Features of the proposed early vascular aging syndrome.

- Increased arterial stiffness and carotid–femoral pulse wave velocity.
- Impaired endothelial function and vasodilatation.
- Chronic vascular and perivascular inflammation.
- Intima media thickness and early atherosclerosis.
- Hemorheological disturbances of blood flow.
- Capillary rarefaction and dysfunctional regulation.
- Shorter telomere length and lower telomerase activity.
- Impaired glucose and lipid metabolism.
- Insulin resistance.
- Oxidative stress.
- Arterial calcification.
- Increased deposition of matrix substances.
- Small vessel degeneration in brain and kidney.
- Increased left ventricular heart load with hypertrophy.
- Cognitive decline secondary to brain aging.

partially independent of the blood pressure control itself [39].

Role of inflammation & hyperglycemia for cardiovascular risk

During recent years the role of chronic inflammation in the pathogenesis of CVD has been highlighted and documented in observational studies [40]. There are several markers of inflammation that have been investigated, most notably fibrinogen [41], C-reactive protein [42] or an index of inflammatory acute phase reactants as used in a number of epidemiological studies from Malmö, Sweden [43]. These markers were determined from blood samples from the general circulation, but there is also evidence to support the existence of local, perivascular inflammation and influences from cytokines secreted from local perivascular fat deposits, of great importance for local hemodynamic regulation [44]. Furthermore, there is evidence to suggest that inflammation plays an important role not only for atherosclerosis but also for arterial stiffening and defects in microcirculation [45]. Therefore, it is likely that chronic inflammation might also increase the process of EVA itself (Box 2). A simple, but far from perfect, clinical marker of arterial stiffness is increased brachial pulse pressure. Markers of inflammation [46], as well as hyperglycemia [47], are predictors of increased pulse pressure levels during longterm follow-up. This indicates that chronic inflammation and hyperglycemia are supposed co-factors in the EVA process. Clinical examples include the arterial stiffening seen in patients with rheumatoid arthritis and systemic lupus erythematosus [48]. Underlying mechanisms include endothelial dysfunction, induced matrix metalloproteinases (including MMP-9), medial calcifications, as well as changes in proteoglycan composition and cellular infiltration around the vasa vasorum leading to vessel ischemia.

Treatment of hyperglycemia & glycosylation

Glycemic changes in vessel wall proteins (glycosylation) could further increase the degree of arterial stiffness, often encountered in patients with Type 2 diabetes [49], but also in subjects with hyperglycemia and features of metabolic syndrome [50]. This glycosylation process is mirrored by the glycemic control in general, via HbA_{1c} levels, but also by more direct measurements of the Advanced Glycation End (AGE) products [51]. It was shown in Finnish women with Type 2 diabetes that AGE might predict cardiovascular events, even if no correlation with plasma glucose levels or HbA_{1c} was found [52]. Against this background a search is ongoing for so-called AGE breakers, drugs able to break up glycosylation and thus have the potential to decrease arterial stiffness [53]. These drugs have so far been fairly unsuccessful in humans, but are being further developed in patients with chronic heart failure, for example [54].

How to define EVA?

Against this background of contributing pathophysiological factors, it is of interest to discuss how EVA syndrome [7,8] should best be defined (Figure 1). One might argue that there is not a need for a definition as this concept is more like a biological model of understanding cardiovascular risk, and not a fixed model. On the other hand it should be possible to analyze the distribution of c-f PWV, as a marker of arterial stiffness and EVA, in various age-groups, stratified for gender. EVA could then be defined as the outliers beyond +2SD of the distribution for a specific population and in relation to age-group and gender. This is something that was made possible based on European collaboration within an extensive database (n = 16,867) on c-f PWV measurements, when data from 1455 healthy and normotensive subjects were analyzed



Figure 1. The early vascular aging concept. CVD: Cardiovascular disease.

to define normal ranges [55]. An important aspect is how c-f PWV or arterial stiffness is most effectively measured, as different methods exist (Complior®, Sphygmocor®, Arteriograph® or ultrasound devices) and should be validated against each other [31,55–57]. Currently the Sphygmocor® (AtCor®) device is most often used as the gold standard for determination of c-f PWV.

However, it should be kept in mind that the arterial wall is damaged by two axes; one is a longitudinal (i.e., damages in central artery and damages in peripheral artery including microvasculature); another is a short axis (i.e., endothelial damage and arterial medial layers damage). PWV is a marker mostly reflecting damages to the central artery and those of arterial medial layers. However, aging and also fetal programming may directly affect the endothelium and also the microvasculature. PWV is not a suitable marker to assess these abnormalities. Arterial stiffness of large arteries in combination with arterial wall remodeling (increased media thickness) may thus be only one of several phenotypes of EVA syndrome; however, this requires further study.

A second proposed method to define EVA would be to analyze the remaining part of c-f PWV (dependent variable) that is not explained by conventional cardiovascular risk factors (independent variables) in a multiple regression analysis, when adjustment is made for factors such as age, gender, blood pressure, hyperlipidemia, smoking, hyperglycemia and (eventually) ongoing drug treatment. This is still something that is not fully explored and, therefore, represents work in progress. One question is whether markers of inflammation should also be included in such a statistical model or not.

EVA is associated with markers of functional aging

There might also exist different ways to approach the EVA concept. In a recent publication from the Whitehall II study (UK), the authors wanted to analyze associations of arterial stiffness with age on the one hand, and subjective, as well as objective measures, of physical functioning, and self-reported functional limitation in 5392 men and women aged 55-78 years [58]. Arterial stiffness was strongly associated with age with a mean difference (SE) per decade: men, 1.37 m/s (0.06 m/s); women, 1.39 m/s (0.10 m/s). Participants took an 8.00 ft (2.44 m) walking speed test, a spirometry lung function test, and completed health functioning and (instrumental) activities of daily living questionnaires. Associations of stiffness and blood pressure with physical function scores were compared. One-SD higher stiffness was associated with

lower walking speed and poorer lung function adjusted for age, sex and ethnic group. This supports the concept of vascular aging and was reinforced by the observation that arterial stiffness (PWV) is a robust correlate of physical functioning and functional limitation in early old age.

Brain aging in relation to arterial aging

A new aspect of EVA is to look for the association between vascular aging and brain aging as measured by impaired cognitive function and development of dementia. It is well known that some important cardiovascular risk factors, most notably hypertension, are also important risk factors for cognitive decline and vascular dementia [59]. Attempts have been made to try to define the structural changes associated with brain aging, including white matter lesions, as well as functional changes [60]. By use of more sophisticated technologies it should be possible to describe intracerebral arterial changes and stiffness, for example the PWV in retinal arteries [36]. In addition, many mental test instruments can be used for evaluation of cognitive function, for example the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MOCA) scale. In a recent position paper from the American Heart Association a review has been conducted regarding risk factors and prevention of mild cognitive impairment and dementia [61]. It was concluded that some risk factors are of great importance to control, most notably hypertension where the evidence-base is strongest. The evidence for the benefits of controlling hyperlipidemia and diabetes in this respect is comparatively weaker.

Interestingly enough there are also some reports on the association between impaired cognitive function in early life and later an increased risk of coronary heart disease, independent of confounding factors such as family social background during childhood [62,63]. This is another proof of the importance of evaluating cardiovascular risk in a life course perspective, as early life neurocognitive development builds a functional reserve to protect from cognitive decline in later life.

Telomere length: a marker of biological aging

Another marker of biological aging is changes in telomere biology, and most notably a time-dependent decrease of telomere length [64]. This has been reported as a characteristic of clinical conditions associated with age-related disorders such as coronary heart disease [65] and Type 2 diabetes [66]. The length of telomeres normally shortens with aging in relation to the number of cell divisions in nongerm line cells, but not in a uniform way in all subjects as there are also reports of telomere elongating in a minority (15–25%) of subjects during follow-up [67]. It is believed that the telomere length in cells is determined at birth and influenced by genetic factors to a substantial degree [68], but also by some lifestyle factors such as obesity and smoking [69]. Previous publications have reported on shorter telomeres in the placenta of children born prematurely or small for gestational age [70,71]. Therefore, there could exist a link between alterations in telomere biology in the placenta and the clinical consequences of being born prematurely or small for gestational age, with a disposition to arterial stiffness, hypertension and CVD [72-75]. However, there is still a lack of studies to confirm this relationship in various populations.

Concluding remarks

In summary, the EVA syndrome [7,8] is proposed as a useful concept for better understanding of the pathophysiological background of increased cardiovascular risk found in subjects with markers of early biological aging, also of their arteries [76-78]. It is measurable and can be followed over time, for example involving changes in c-f PWV. This is a process linked to arterial stiffness [31] and changes in telomere biology [30]. Even self-percieved or observerpercieved early aging is associated with an increased burden of risk factors and shorter telomere length [79,80]. The broad evaluation and treatment of risk factors is necessary to achieve long-terms benefits, as most visibly shown in the Steno-2 study for patients with Type 2 diabetes, hypertension and microalbuminuria [81]. The goal for systolic blood pressure in Type 2 diabetes is still, however, not well defined, but is propably 130-135 mmHg based on a recent meta-analysis [82]. Ideally future intervention studies should include additional measurement of c-f PWV [83] and telomere biology [84,85] to further elucidate on EVA and whether this condition is reversible or not. As with all new concepts, the EVA concept is far from being finalized. A critical debate needs to scrutinize if EVA brings additional new understanding or not, especially in comparison with risk algorithms that calculate arterial age based on conventional risk factors [9,10]. The history of medicine clearly shows that even very established dogma can be changed when new findings challenge old beliefs, for example, the history of how Helicobacter pylory infections helped to explain the epidemiology of gastric ulcers [86], leading almost to eradiction of old surgical treatments.

Future perspective

It is very likely that the broader concept of EVA will have a potential to gradually replace, or at least complement, the older concept of the metabolic

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syndrome now being criticized, especially among diabetologists. If drugs or interventions could be developed to counteract arterial stiffness and lessen the influence of glycation linkages, as aspects of EVA, there is a chance for a pharmacological break-through that goes beyond the traditional risk factor interventions directed towards hypertension, hyperlipidemia and hyperglycemia.

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Executive summary

- The metabolic syndrome has been a clinical concept in use for more than 20 years, but recently criticized due to lack of important information on risk factors (inflammation) and doubts whether the syndrome represents a better risk prediction than individual risk factors.
- As aging is the most important risk marker of cardiovascular risk it is natural that an increasing interest in the biological aging also translates into an interest in the prerequisites of cardiovascular aging and its clinical consequences.
- The concept of early vascular aging (EVA) has emerged as a way to describe vascular aging in susceptible subjects, for example showing increased arterial stiffness as measured by pulse wave velocity in the abdominal aorta.
- EVA is still not well defined, but major features consist of arterial stiffness, endothelial dysfunction, metabolic alterations (including impaired insulin sensitivity and glucose intolerance), chronic inflammation and organ involvement, for example impaired cognitive function as a marker of brain aging.
- Factors acting in early life could be of great importance for influencing EVA, for example the combination of intrauterine growth retardation and rapid postnatal catch-up growth patterns.
- New developments in telomere biology are promising to find new markers of biological aging in general, also of importance for vascular aging.
- The treatment of EVA is based on traditional lifestyle interventions and control of risk factors, most importantly hypertension. Additionally, new drugs are currently being tested to counteract arterial stiffness and vascular risk, for example the so-called AGE-breakers or the new incretin acting drugs.

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