Healthy vascular ageing

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Decisions on preventative treatments can be based on single parameters but in most cases clinicians take more than one risk factor into account, as some negative indicators of risk can be outbalanced by other more favourable factors. This concept has led to the development of risk scores that integrate a multitude of cardiovascular risk factors; the Framingham Risk Score is one notable example [1]. Whilst these scores work well on the population level they are of limited use for individual risk prediction. A tendency to overestimate risk; differences in risk between populations, ethnicities, social classes; general changes in population health from derivation of scores in historic samples and application to modern societies; and the fact that not all damaging and protecting factors that could play a role in an individual patient are taken into account explain why as clinicians we are often confronted with patients at seemingly high risk who do perfectly well even at advanced age and with patients at seemingly low risk who are struck by premature CVD. In this era of precision medicine [2] we would like to offer not only individualised treatment options but also individualised preventative strategies to our patients.

An alternative approach is therefore based on early detection of cardiovascular disease rather than prediction of cardiovascular disease risk. The concept of the cardiovascular continuum where advanced disease develops not without earlier functional and structural subclinical changes forms the theoretical basis of this approach [3]. One can assume that an individual's "position" on the continuum from health to overt cardiovascular disease is determined by the integrated action of genetic, environmental and other risk factors and could therefore inform decision rules on initiation of preventative and therapeutic strategies [4].

Assessment of vascular function and structure is a key element of the mapping of an individual's cardiovascular health. For example, it is well established that pulse wave velocity (PWV; a measure of vascular stiffness) is an independent predictor of cardiovascular events [5]. The clinical experience that vascular function and structure can be disproportionally impaired compared to an individual's risk profile has led to the concept of early vascular ageing (EVA), describing the development of cardiovascular diseases from a vascular perspective [6]. Other measures of vascular function and structure include assessment of endothelial function (e.g. by flow-mediated dilation or peripheral artery tonometry); pulse wave analysis (to study features of the waveform and to estimate central blood pressure); and imaging studies to assess atherosclerotic changes (e.g. ultrasound studies into carotid intima-media thickness and carotid plaques) and vascular calcification (e.g. coronary calcium scores assessed by computed tomography). The European Society of Hypertension (ESH) and European Society of Cardiology (ESC) therefore suggest that comprehensive assessment of the vascular phenotype can help in the assessment of an individual's cardiovascular risk and thereby in the choice of antihypertensive treatment strategies [7]. However, the idealised view of a stepwise and continuous development of vascular damage from early functional to advanced structural changes is not what we observe in individual patients where these processes can develop in parallel and at different rates [6]. Moreover, most of the non-invasive tests that could be used in large clinical studies and ultimately in clinical practice assess large vessels and do not directly study the microvasculature, thereby neglecting the essential cross-talk between large and small vessels [8]. It is therefore not surprising that the ESH/ESC, other than providing a list of

techniques, cannot recommend a specific hierarchy or order of tests and how they should exactly be interpreted [7].

In this issue of *Hypertension*, Teemu Niiranen and colleagues [9] have taken a simple and pragmatic approach to assess vascular health in participants of the Framingham Heart Study. They took advantage of this well-characterised, longitudinal general population cohort to confirm that a marker of vascular structure (PWV) is independently associated with cardiovascular outcomes when adjusted for traditional risk factors. What make the paper unique is that the authors looked at flip side of the coin and focussed on individuals with a healthier vascular phenotype to show that they experience a lower cardiovascular event rate compared to those with participants whose vessels are less healthy. The other unique feature is that Niiranen at al. have gone beyond PWV to define the condition of the vasculature and defined "healthy vascular ageing" (HVA) as a composite of low PWV and normal blood pressure where blood pressure is an indirect readout of a variety of vascular, including microvascular, changes. Maybe not surprisingly, HVA was associated with a favourable profile of traditional risk factors both when these markers were studied individually using multiple regression models and when they were combined categorically using a cardiovascular health score. However, a beneficial profile of traditional risk factors did not fully explain a healthy vascular phenotype and other features including genetic and environmental factors will help to explain why some people have healthier vessels than others despite similar traditional risk factors. Niiranen et al. provide some clues in their paper by looking at a range of biomarkers and

genetic risk. These additional data and a range of sensitivity analyses make the present paper more convincing and will stimulate future research in this field.

Probably the strongest and most reassuring message from this paper [9] is that HVA can be achieved and that it can be found also in the elderly, albeit much less commonly than in younger people. Age remains the main determinant of vascular age and we probably have to accept the fact that vascular ageing cannot be prevented indefinitely. The Lancet Commission on Hypertension has recently used the concept of normal (cardio)vascular ageing to identify clinical and research priorities in order to avoid the accelerated development of cardiovascular diseases in some patients and to push the "normal" lifecourse of disease development towards an "ideal" lifecourse that provides a much longer disease-free lifespan [10]. Niiranen et al. [9] have provided an important piece of research by defining some of the factors that are associated with HVA and probably even more so by identifying what we do not know about HVA yet. The fact that the Framingham cohort may not be fully representative of the general population in the United States and elsewhere probably limits the generalizability of the results.

Nevertheless, there are limitations of the present paper by Niiranen et al. [9]. First, whilst there are good reasons for including blood pressure in their definition of vascular age it mixes up a risk factor (blood pressure) with its consequences (altered vascular phenotype). We appreciate that the interaction between blood pressure and vascular function/structure is particularly complex and that blood pressure can at the same time be cause and consequence of vascular changes. However, the assumed notion that a healthy vasculature is impossible in people with

high blood pressure contradicts clinical experience where we see patients who have surprisingly little vascular damage despite their high blood pressure – presumably because of the strong influence of other protective factors.

Second, the authors have only assessed PWV and no other vascular phenotypes. Clearly a simple number in metres per second cannot fully represent the complexity of vascular disease, and low PWV does not mean that all function and structure of all vascular beds is normal or "healthy". More comprehensive assessment using a variety of markers applied to a variety of vascular beds would give a more precise picture. Interpretation of such complex data will, however, be challenging and could result in more confusion than in useful guidance. The pragmatic approach in the present paper may therefore have its clinical advantages.

Third, how will information on HVA inform clinical practice? It is reassuring that HVA can be observed in some and whilst we should strive to achieve it in all people it remains unclear which advice we should give to people with HVA. Would we withhold preventative therapy in those with HVA despite an unfavourable traditional risk profile or high risk score? Specific algorithms that integrate subclinical phenotypes and traditional risk factors will have to be developed, and these will require studies in additional and larger cohorts. In this context the timing of vascular assessments would be particularly important: a healthy vasculature in the elderly will indeed indicate lower risk whereas its predictive value in younger people will be more limited. Given the low costs and low adverse effect rate of drugs used for cardiovascular protection one would need good reasons for not offering such treatment to a group of people.

So what do we learn from the paper by Niiranen et al. [9]? First and foremost, HVA is possible. This is good news for our patients even if they have multiple risk factors. Second, HVA is associated with a beneficial profile of traditional risk factors but other yet unidentified factors contribute significantly. Third, there is no uniform definition of HVA and no generally accepted best practice how to assess vascular age. Niiranen et al. have to be congratulated on their pragmatic approach even if it is far from perfect. Fourth, the immediate clinical consequences of this work are not fully clear yet.

Most importantly, the present paper encourages us to perform studies that focus on a particularly healthy cohort in order to understand the factors that are associated with their phenotype. This is in contrast to the traditional approach where researchers studied the most diseased in order to understand risk factors for disease. In fact, the latter is where the Framingham Heart Study made major contributions in the past. The present study by Niiranen et al. [9] paves the way for future research into protective factors that will not only improve our understanding of the pathophysiology of vascular diseases but also offer new predictive, diagnostic and therapeutic tools. There is a bright future for the Framingham cohort, and the acronym FHS already points in this direction as the "Framingham Health Study".

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Disclosures

None.

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