Those declared dead live longer

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In general, the vascular endothelium represents a selective barrier to prevent mechanically the diffusion of macromolecules into the interstitial space. In addition, the endothelium is known to regulate vascular tone e.g. by releasing nitric oxide (NO) or prostacyclin (PGI₂) and to regulate markedly the degree of inflammation, vascular growth, and platelet aggregation and coagulation. Many studies have provided evidence that dysfunctional endothelium is a hallmark of patients with cardiovascular diseases having even the potential to predict the progression of the atherosclerotic process including cardiovascular event rates in a number of patients cohorts, including those with COVID-19. Importantly, it has also been shown in the correction of endothelial dysfunction is associated with an improvement in prognosis. The underlying mechanisms of endothelial dysfunction (ED) are likely to be multifactorial and include a decreased vascular NO bioavailability due to increased oxidative stress secondary to an infiltration of the vascular wall with phagocytic macrophages and an uncoupling process of the endothelial nitric oxide synthase. It is important to note that the increase in oxidative stress is not restricted to the endothelium and also involves the media and the adventitia, which will contribute significantly to the reduction of NO production signaling within vascular tissue. The vascular side effects of this NO deficit is the initiation and continuation of the atherosclerotic process including vasoconstriction, platelet and leukocyte adhesion and migration, and a proliferation of smooth muscle cells. We are aware that the atherosclerotic process begins early in life and ED, which may be considered as a biomarker, is reflecting function changes of the endothelium that in general precedes morphological vascular changes. Thus, the techniques assessing the vasodilation resulting from the release of NO and other molecules will inform us about the functional integrity of the endothelial cell layer, thus providing an insight on “total vascular health”. Within the last 25 years, several techniques have been employed to quantify vascular endothelial function.
in humans. Of these, the methodology of flow-mediated dilation (FMD), where an increase in shear stress leads in turn to enhanced vasodilation, can be taken as surrogate of overall endothelial functions and that measurements in the peripheral circulation reflect the status of more noble vascular territories, is likely the most commonly used clinically (Figure 1). Multiple methodological guidelines have been published in order to standardize this method and improve its reproducibility. Although the introduction of this relatively complex but non-invasive method has initiated a tremendous research interest research in this area, we completely failed to introduce this vascular function test into our clinical routine and this methodology is not even mentioned e.g. in the guidelines for cardiovascular prevention. So, currently, FMD may be described as clinically dead.

With the present studies, Heiss et al. (insert Ref of Heis et al) provide important information to resuscitate this methodology for clinical use by introducing an age-adapted frame of FMD reference intervals in apparently healthy individuals for use as a biomarker of cardiovascular health. A similar analysis was performed recently by Holder et al, yielding similar results. They collected results from databases published from 2001 to 2021 using standardized protocol and training requirements for operators, which yields consistent performance and reproducibility. These studies were performed by 22 FMD operators at 6 different institutions. Available data from individuals that were classified as healthy were collected and presented (n=1579). To put the FMD data into the international context, the authors also performed a systematic review and meta-analysis of FMD values in healthy study participants.

Considering that almost all cardiovascular risk factors lead to the development of ED, and that successful fighting of risk factors in general leads to a better FMD has been previously taken as evidence in support of the concept that FMD could be used as a tool to quantify of
the overall exposure to cardiovascular risk factors (the “exposome”). In their database of 1,579 apparently healthy individuals (aged 18-76), FMD values (data from 44 studies, 6 institutions, 22 operators) were normally distributed and inversely univariately correlated with age, body-mass-index, glucose, cholesterol, blood pressure, and brachial artery diameter. Associations were shown in multivariate analysis with age (-0.4%/decade), BMI (0.04%/kg/m2), smoking (-0.7%). Together with resting brachial artery diameter, these factors explained only 19% of the variability of FMD. Whether measurements errors or other yet unknown factors determine the remaining 81% remains unclear. Brachial artery diameter at rest has been demonstrated to represent a major determinant of FMD and to interfere with the power of FMD in predicting cardiovascular events. Whether this reflects the resting status of the endothelium or is simply the result of the mathematical equation for the calculation of FMD remains debatable.

In the paper by Heiss et al, individuals with higher cardiovascular risk SCORE had FMD values in the low tertile (<5.4%), while those with lower scores had FMD in the higher tertile (>6.8%), were younger, had smaller brachial artery diameter, lower blood pressure and cholesterol. Consistent with their internal data, after adding data from 385 patients with stable coronary artery disease (CAD), ROC analysis showed that FMD of >6.5% excluded CAD and FMD <3.1% excluded 95% healthy individuals. A meta-analysis and meta-regression of 82 clinical trials (11 countries, n=3,509) using similar FMD methodology showed that despite considerable heterogeneity FMD in healthy individuals was on average 6.4% with no significant differences between countries but a significant age-dependent decline. The authors conclude that this age-adapted frame of FMD reference intervals in apparently healthy individuals is suited to be a biomarker of CV health.

Taken together, as cardiovascular risk results from traditional, environmental, genetic and several other unknown factors, there is a need for a technique that allows a comprehensive...
assessment of the individual exposome. The paper by Heiss et al. provides important information to this scope and keeps the methodology as an important vascular function test alive. Thus, one might say: Those declared dead live longer. Whether this measure may also serve as a target for individualized cardiovascular prevention or therapy, still remains to be determined however.

Conflict of interest: none declared.
**Figure Legend**

**Figure 1:** We place the sphygmomanometer cuff at the proximal forearm and inflate it up to 200 mmHg for a period of 5 minutes. When the cuff is released, we record the reactive, flow-dependent dilation of the brachial artery using a 12 MHz flow probe. The amount of dilation largely reflects endothelial function and therefore the vascular NO bioavailability. Thereafter we measure the total vasodilator capacity of the vessel by testing the dilation in response to nitroglycerin (NTG) 0.8 mg sublingually. In the present example, the artery dilates in response to increased flow by 9% and in response to nitroglycerin (NTG; sublingually), as an endothelium independent but NO vasodilator (NDD), by 16%.
References


