

**EDITORIAL**

# Estimating Is Not Measuring: The Lessons About Estimated Pulse Wave Velocity

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**A**rterial stiffness is a key indicator of cardiovascular health. It has been repeatedly associated with mortality, cardiovascular events, and stroke in all tested populations from hypertension, heart failure, diabetes to community-based populations.<sup>1</sup> Elevated arterial stiffness is also associated with incident cases of hypertension.<sup>2</sup> Altogether, arterial stiffness is indicative of generalized vascular vulnerability. Arterial stiffness can be measured non-invasively by carotid to femoral pulse wave velocity (cfPWV), as a direct measure of aortic stiffness using tonometry as reference. Alternatively, pulse wave velocity (PWV) can be measured through cuffs at arm and leg, or combinations of previous techniques, but also by ultrasound or magnetic resonance imaging.<sup>3</sup>

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**See Article by Laugesen et al.**

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Although direct measurements of cfPWV are well standardized and easy to perform, they may not be applicable in several situations, either for practical and cultural reasons, and some can consider arterial stiffness too demanding for being used in routine clinical care. This is the reason why investigators are searching for shortcuts to estimate cfPWV. Some have included age and blood pressure in the calculation of PWV by single cuff devices,<sup>4</sup> and present the result arterial stiffness true measurement, rather than an estimation.<sup>5</sup>

Our group was the first to propose estimated PWV (ePWV).<sup>6</sup> ePWV is calculated using chronological age and mean blood pressure, and their quadratic terms and interactions, using published equations<sup>7</sup> and compared it with true measurements. We showed that the overall predictive value of ePWV was not inferior to cfPWV in 2 data sets, the Monitoring Trends and Determinants in Cardiovascular Disease Danish study, and the Paris cohort.<sup>6</sup> This paper was primarily a claim to show that the effect of age and blood pressure was underestimated through linear equations, and not to promote ePWV. Second, the main result (ie, similar prediction with ePWV as with measured cfPWV) was essentially driven by the Danish cohort (general population) whereas there was a significant additive value of cfPWV over ePWV in the Paris cohort, (essential hypertensives) (P. Boutouyrie, MD, PhD, personal data).

In this issue of the *Journal of the American Heart Association (JAHA)*,<sup>8</sup> Laugesen and colleagues measured the mortality rate in a large population of patients following coronary angiography. They demonstrated that the 8.5-year mortality was predicted by estimated PWV, independently from major cardiovascular risk factors. The study is very powerful, and results are convincing, since 1 m/s excess in ePWV is associated with 20% or so excess risk of mortality, which remains significant after adjustments (including the extent of coronary disease). One must note that adjustments performed here may lead to overdetermination since

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they include age and systolic blood pressure when those two parameters are used to calculate ePWV. The main problem of the present paper (and more generally all papers using the concept of ePWV) is that it suggests ePWV can be a surrogate for measured PWV. Is it a scientifically informed decision to use ePWV as a surrogate for measured cfPWV?

ePWV is calculated on the equations based on a single data set (reference values<sup>7</sup>), itself composed of cross-sectional databases from 13 countries, between 1990 and 2010. In the reference data set, patients with hypertension were over-represented. Whether the coefficients issued from the relations in this database are universal, and whether those coefficients still apply to nowadays population is unknown. In fact, the term ePWV itself is quite an overstatement, since this is no more than a combination of age and mean blood pressure, with quadratic and interaction terms, coined into an appealing term. To put it in cruder terms, ePWV is more marketing than true science.

Measured cfPWV is associated with many other risk factors; for instance, elevated arterial stiffness is associated with major depressive symptoms, social vulnerability, and other "atypical" cardiovascular risk factors, independently from high blood pressure and age.<sup>9</sup> We can also list chronic inflammation,<sup>10</sup> family history of cardiovascular disease, low birth weight, etc. This illustrates that nonlinear dependency of arterial stiffness on blood pressure and age does not capture all cardiovascular risk associated with arterial stiffness. To illustrate this point, let us introduce early vascular aging (EVA). Measured cfPWV in particular, is considered as the best proxy for EVA. It is therefore possible to calculate vascular age (the age corresponding to the measured stiffness)<sup>11</sup> based on reference values.<sup>7</sup> EVA (and its opposite supernormal vascular aging), are observed when cfPWV is higher (or lower) than the value expected from age and blood pressure (when considering quadratic terms). We added other prominent cardiovascular risk factors (diabetes, dyslipidemia, smoking, etc) in the calculation of EVA and supernormal vascular aging. We have shown that patients with EVA (cfPWV higher than expected), had significantly altered outcome, and patients with supernormal vascular aging had improved outcome.<sup>11</sup> This illustrates the fact that age and blood pressure are not the alpha and omega of risk factors, and not the sole factors associated with arterial stiffness.

Indeed, registry papers like the Laugesen paper have no choice, because measurement of arterial stiffness was not included at baseline in the investigation methods. Longitudinal papers designed to test the value of measured PWV had to make different choices, ie, to make strong hypotheses, perform measurements, wait for events to happen, and hope for a positive result.

This collective effort was successful.<sup>1</sup> There are alternative strategies: other groups have invested in large descriptive cohorts, like the UK Biobank,<sup>12</sup> and have bet on simple techniques applicable to large numbers, although measurement is done here with many assumptions, it's better than no measurement at all. We have now simple methods for directly assessing arterial stiffness in large numbers of subjects, using methods simple enough to be integrated in connected devices, yet relying on sound physical principles.<sup>13</sup> It is tempting to shortcut all these difficulties, and use estimation rather than true measurement, because it comes free.

Calling the quadratic combination of age and blood pressure "estimated pulse wave velocity" is a misnomer. Nevertheless, it remains that the associations of age and blood pressure with risk are nonlinear, and one should consider those nonlinearities in survival studies. However, one should be prudent when launching appealing concepts such as ePWV (including the author). Estimating is not measuring; we hope that each time a pilot lands an aircraft, he/she measures speed and altitude for safe landing, rather than estimate it from charts. We expect a similar rigor from doctors when evaluating their patient's risk.

## ARTICLE INFORMATION

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### Disclosures

None.

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