Editorial

Aortic Stiffness: Prime Time for Integration into Clinical Practice?

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Key words:
Aortic stiffness, cardiovascular risk, prognosis, pulse wave velocity.

"A man is as old as his arteries"

Thomas Sydenham (1624-1689)

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The arterial system has a dual function: first, to deliver blood to the periphery and second, to transform the periodical left ventricular ejection into a continuous flow. The second (cushioning) function is accomplished through a sophisticated arterial structure, which allows the arterial system to act like an elastic buffer; part of the energy released with every heartbeat is temporarily stored during systole in the aorta and other great arteries and is then released with the elastic recoil of arteries during diastole. The vessel with the greatest cushioning capacity is the aorta, which accommodates approximately 50% of blood volume ejected during each systole. Thus, the elastic behaviour of the aorta (quantified by various measures including aortic stiffness) is of paramount importance for proper tissue perfusion and cardiovascular performance.[1]

Aortic stiffness – pathophysiologic considerations

Aortic stiffness is largely determined by aortic structure, especially that of the tunica media. Tunica media contains the elastic components of the aortic wall, i.e. elastin fibers and collagen. Several factors influence aortic wall structure; ageing is associated with arterial stiffening through fragmentation of elastin fibers, a decrease in elastin/collagen ratio and calcification of the tunica media. This process is called *arteriosclerosis* and should be distinguished from *atherosclerosis*, which is mainly a disease of the intima. Hypertension is another major determinant of arteriosclerosis and aortic stiffening, through changes in the tunica media that take place earlier than "normal" ageing. It should be stressed that aortic stiffening is not only a consequence of hypertension but is also in itself a pathogenetic mechanism of the disease. Aortic stiffness increases in the presence of other major cardiovascular risk factors, such as smoking, hypercholesterolaemia, and diabetes mellitus.[1-5] It is also increased in patients with established cardiovascular atherosclerotic disease and it can be used as a marker of disease. It is modifiable by pharmacological and non-pharmacological means that have an effect on arterial function or structure, i.e. salt-restriction, flavonoid-rich foods, mental stress, angiotensin converting enzyme inhibitors, statins, etc.[5,6] The recently coined term "EVA" (early vascular ageing) refers to the integration of the effects of various risk factors on the arterial wall,

and aortic stiffness appears to be an ideal biomarker to express this concept.[7]

Increased aortic stiffness has several detrimental effects on cardiovascular performance. A less distensible aorta cannot efficiently accommodate the blood volume ejected by the left ventricle, which results in high systolic pressure. In addition, diastolic pressure is decreased and pulse pressure is thus increased. This pattern is a common finding in the elderly with isolated systolic hypertension. High pulsatility may be transferred down to arterioles, resulting in disruption of microcirculation, i.e. brain and kidney damage. Because of increased pulse wave velocity, reflected waves return earlier in the ascending aorta, during the systolic phase of the pressure waveform; aortic systolic pressure (and left ventricular afterload) is increased; this induces left ventricular hypertrophy and predisposes to left ventricular diastolic dysfunction. Furthermore, aortic pressure during the diastolic phase is decreased, thus decreasing coronary perfusion. The combination of left ventricular hypertrophy and reduced coronary perfusion leads to myocardial oxygen supply/demand mismatch, and further deteriorates left ventricular diastolic and systolic function.[1,5,8]

Aortic stiffness measurement

There are several indices of aortic stiffness that can be measured; aortic stiffness can be assessed locally (at a specific site), or regionally (in a greater arterial segment).[9] The index of aortic stiffness with the greatest pathophysiological and clinical background is aortic pulse wave velocity (PWV), which is commonly measured as carotid-femoral PWV, calculated by dividing the distance between the carotid and the femoral artery by the time delay of the arterial pulse between these two arterial sites.[5] A higher aortic PWV denotes increased aortic stiffness and *vice versa*.

The time delay of the arterial pulse between two arterial sites can be measured non-invasively using a variety of techniques; while it can be measured with Doppler ultrasound,[10] nowadays this has largely given way to specifically designed devices that use mechanotransducers or tonometers applied to the skin over the arterial sites of interest (i.e. carotid and femoral artery). Aortic PWV can also be measured with magnetic resonance imaging and other techniques.[9]

Prognostic value of aortic stiffness

There are several studies examining the prognostic value of aortic stiffness. Initial studies were conducted in specific high-risk populations, such as patients with end-stage renal disease; subsequent studies focused on broader patient groups, such as hypertensive patients and diabetics; and more recent studies examined the prognostic value of aortic stiffness in the general population. In the seminal study by Blacher et al,[10] aortic PWV was measured with Doppler ultrasound from the aortic arch to the femoral artery; age and aortic PWV were the strongest predictors of cardiovascular and all-cause mortality in this high-risk population. Subsequently, Pannier et al[11] measured carotid-femoral PWV in end-stage renal patients and confirmed previous results: aortic PWV was a significant and independent predictor of outcome. Interestingly, only aortic PWV was of prognostic value; neither brachial artery nor femotibial artery stiffness was able to predict cardiovascular outcome. In studies conducted in broader populations, Laurent et al[4] demonstrated that aortic PWV was significantly associated with all-cause and cardiovascular mortality in hypertensive patients, independently of previous cardiovascular diseases, age, and diabetes. The independent predictive value of aortic PWV has also been shown in diabetic patients[3] and in patients with chest pain.[12] Finally, in the general population, it has been shown that aortic PWV is an independent predictor of cardiovascular and all-cause mortality[13,14] and of incident coronary heart disease[15] during follow up. Recently, Mitchell et al[16] reported results from the Framingham Study and confirmed the independent predictive value of aortic PWV in the general population. When PWV was added to the standard risk factor model, risk discrimination was improved, particularly in subjects with intermediate risk according to Framingham Risk Score.[16]

In a recent meta-analysis conducted by our group,[17] comprising but not limited to the abovementioned studies and including more than 15,500 individuals, we found that high aortic stiffness (arbitrarily defined in studies included in the meta-analysis) conferred a relative risk (RR) of 2.26 (95% confidence interval [CI]: 1.89 to 2.70) for cardiovascular events, 2.02 (95% CI: 1.68 to 2.42) for cardiovascular mortality and 1.90 (95% CI: 1.61 to 2.24) for all-cause mortality (Figure 1). Furthermore, an increase in aortic PWV by 1 m/s increased the risk of cardiovascular events, cardiovascular mortality and all-cause mortality by 14%, 15% and 15%, respectively, after adjustment for age, sex and traditional cardiovascular risk factors (Figure 2), while an increase in aortic PWV by 1 standard deviation (SD) was associ-

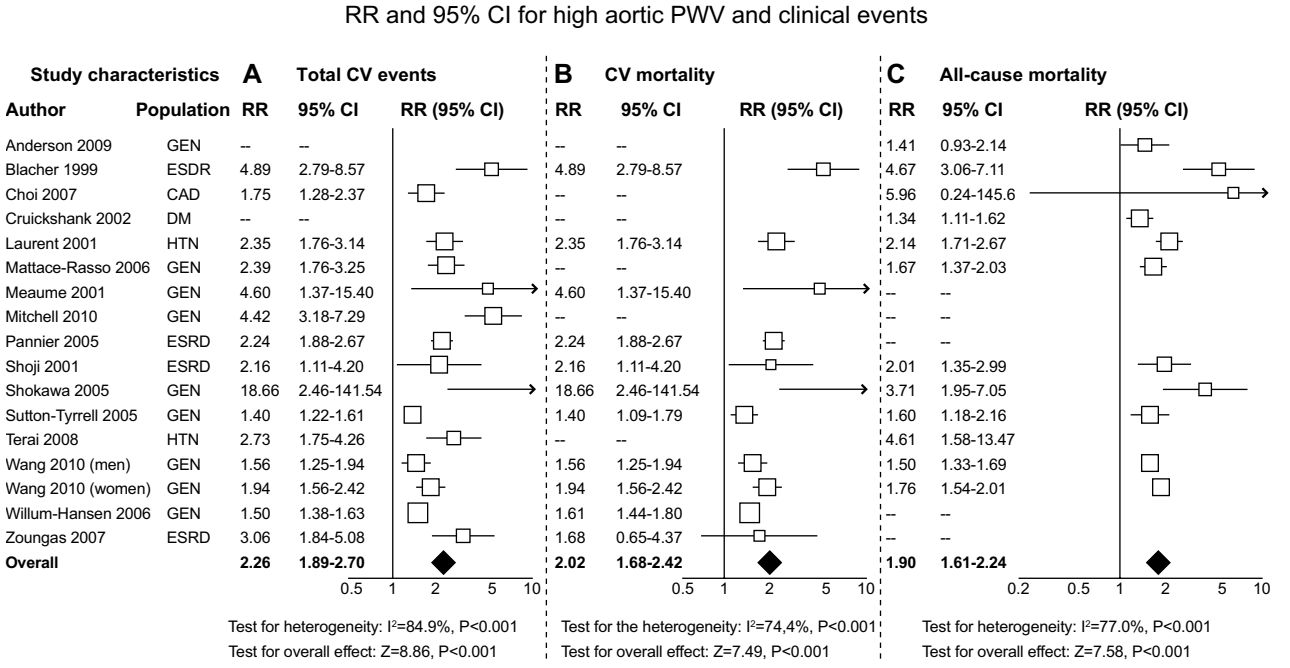

Figure 1. Relative risk (RR) and 95% confidence interval (CI) for high aortic pulse wave velocity (PWV) and total cardiovascular (CV) events **(A)**, CV mortality **(B)**, and all-cause mortality **(C)**. Studies are listed alphabetically. *Boxes* represent the RR and lines represent the 95% CI for individual studies. The *diamonds* and their width represent the pooled RRs and the 95% CI, respectively. CAD, coronary artery disease; DM, diabetes mellitus; ESRD, end-stage renal disease; GEN, general population; HTN, hypertension. Reproduced with permission from Ref # 17.

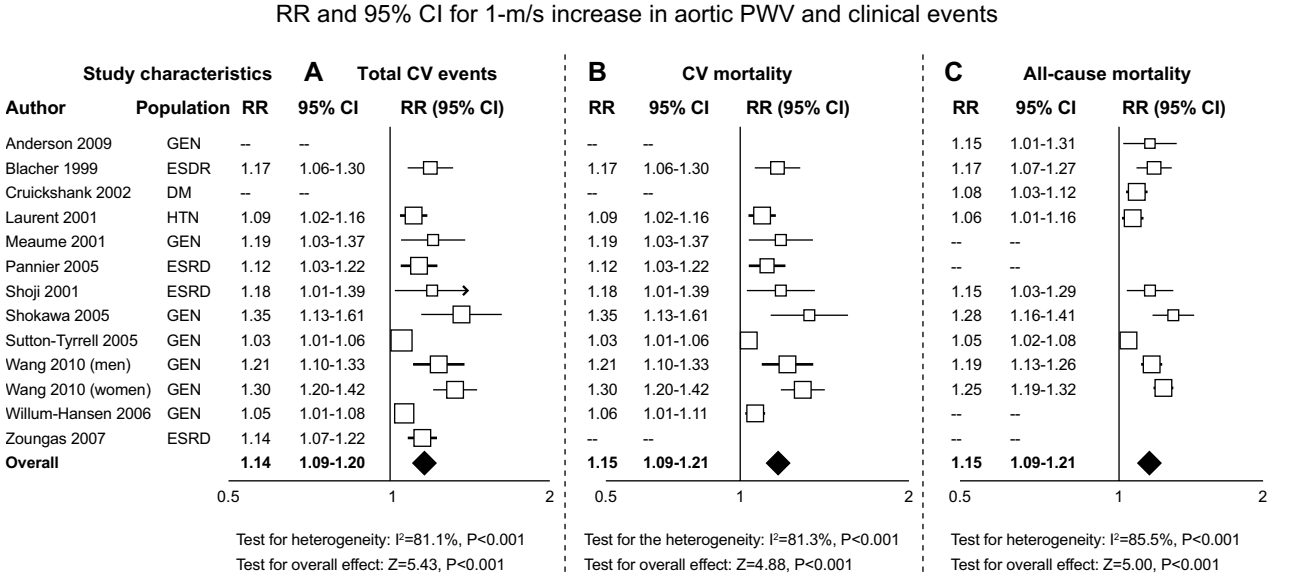

Figure 2. Relative risk (RR) and 95% confidence interval (CI) for a 1-m/s increase in aortic pulse wave velocity (PWV) and total cardiovascular (CV) events **(A)**, CV mortality **(B)**, and all-cause mortality **(C)**. Studies are listed alphabetically. Symbols and abbreviations as in Figure 1. Reproduced with permission from Ref # 17.

ated with respective increases of 47%, 47% and 42%. Interestingly, high aortic stiffness did not have an impact of the same magnitude in all populations studied; in high-risk populations high aortic stiffness conferred a higher risk than in low-risk populations; in end-stage renal disease patients the RR of high aortic stiffness was 2.81 (95% CI: 1.97 to 4.02), in hypertensive patients RR was 2.46 (95% CI: 1.93 to 3.13), and in the general population RR was 1.68 (95% CI: 1.45 to 1.96). These results indicate that aortic stiffness has a better ability to predict future events in high-risk populations compared to low-risk populations. Another finding was that, while there was no difference in the risk prediction ability of PWV in relation to age in the general population or in hypertensive patients, PWV was better able to predict cardiovascular events in younger patients with end-stage renal disease. This could reflect a "selection" phenomenon, with patients with end-stage renal disease who reach older age being less vulnerable to the harmful effects of aortic stiffening.[17]

A crucial issue is whether an improvement in prognosis can be mediated through a reduction in aortic stiffness. To date, only one study has addressed this: despite the same decrease in blood pressure between survivors and non-survivors with end-stage renal disease, only survivors reduced aortic PWV.[18]

Normal and reference values

The wide application of aortic PWV measurement has been hampered by the absence of normal or reference values and by differences in the distance taken into account for its measurement. These issues have recently been addressed in a large multi-centre project involving 13 different centres across Europe and more than 16,500 subjects and patients.[19] The "Reference Values for Arterial Stiffness" collaboration reconciled differences in the methodology of PWV measurement and provided reference and normal values. Differences in PWV measurement included differences in the calculation of the distance between the carotid and the femoral sites of measurement, as well as differences in the algorithm used by each device for transit time measurement. Reference PWV values were obtained from subjects who had no overt cardiovascular disease or diabetes and were not under treatment with antihypertensive or hypolipidemic drugs (n=11,092). Normal values were obtained from a subgroup of the previous population who had optimal/normal blood pressure (n=1455). Normal values increase with advancing age, from mean value (-2SD to +2SD) of 6.2 (4.7 to 7.6) m/s in subjects less than 30 years old to 10.9 (5.5 to 16.3) m/s in subjects ≥70 years old. The reference values depend on the level of blood pressure and increase as pressure increases (Figure 3).[19] While PWV increases with age in subjects with optimal/normal blood pressure, in other groups (i.e. with higher blood pressure or with cardiovascular risk factors) the increase in PWV with age is even steeper; this probably reflects the lifetime accumulation of detrimental effects on the aortic wall from high blood pressure and/or other cardiovascular risk factors.

The verdict

Carotid-femoral pulse wave velocity is easy to measure with specifically designed devices or with simple Doppler ultrasound. It is not only a marker of disease but also an independent predictor of cardiovascular events, cardiovascular mortality and all-cause mortality. High aortic stiffness doubles the risk of cardiovascular events or mortality compared to low aortic stiffness, and the predictive value of high PWV is greater in high-risk patients, such as patients with hypertension or end-stage renal disease. Aortic PWV expresses the cumulative effect of various risk factors on the arterial system and their interplay with genetic predisposition. In contrast to cardiovascular risk factors, such as blood pressure or cholesterol, that may fluctuate over time, PWV is relatively stable, since it is mostly influenced by arterial wall structure, which takes more time to change. The 2007 European Society of Hypertension & European Society of Cardiology guidelines for the management of hypertension rightfully included increased carotid-femoral PWV as subclinical target-organ damage, and recommended aggressive management of patients with high PWV.[20] Since then, more studies showing the independent predictive value of carotid-femoral PWV have been published, especially in the general population, and reference and normal values have been determined. Thus, aortic PWV convincingly fulfils the criteria of a biomarker: it has a solid pathophysiological background, it can be assessed easily and reproducibly in clinical practice, it confers an incremental prediction in cardiovascular risk, and its modification has an impact on prognosis. Measurement of aortic PWV should be integrated in the examination and risk stratification of our patients. It is prime time for its use.

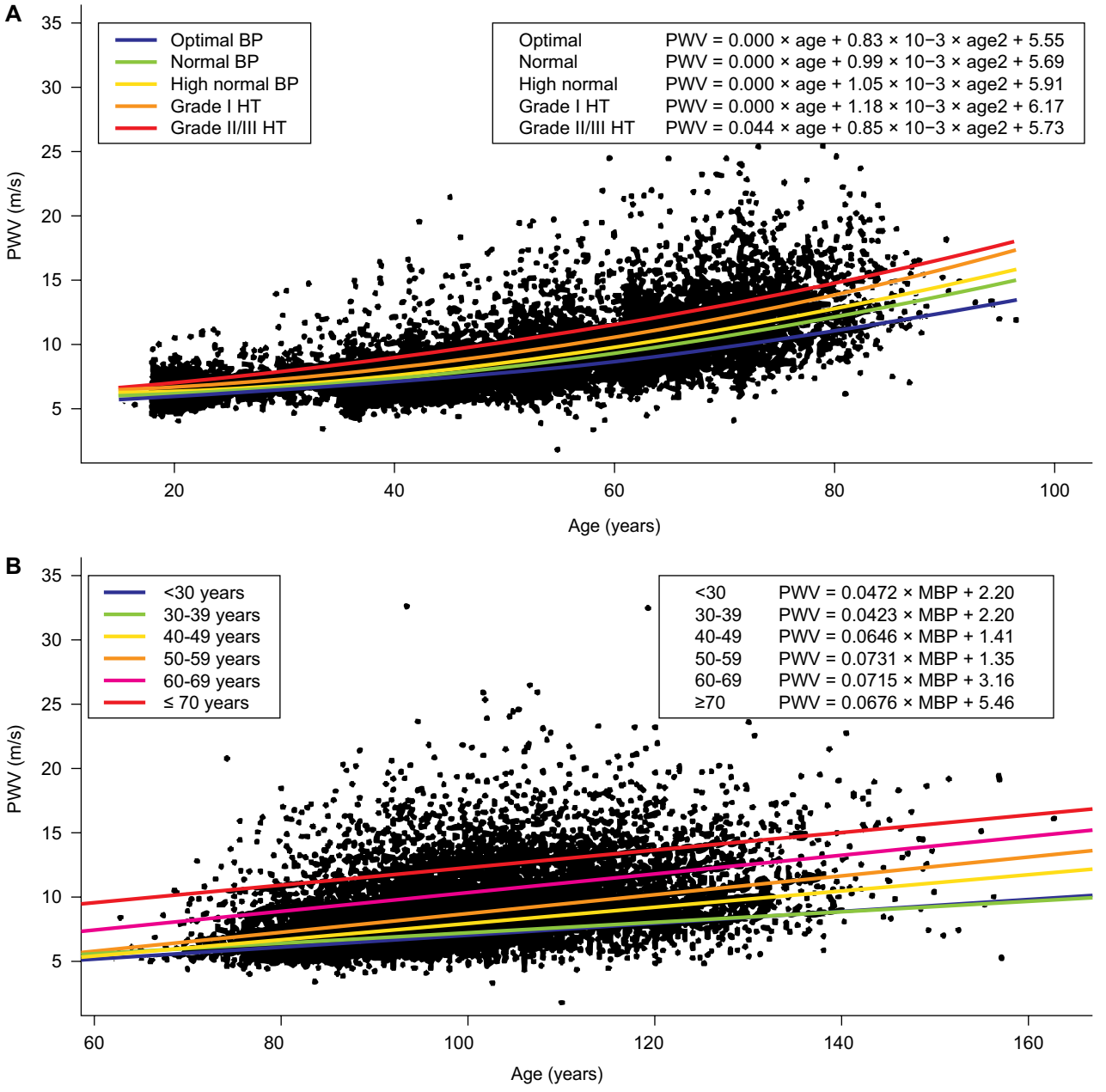

Figure 3. A. Pulse wave velocity (PWV) versus age in the reference value population (11,092 subjects). Regression lines denote the results of regression on age^2 for different blood pressure (BP) categories. The box in the right upper corner presents regression equations for PWV versus age according to blood pressure category. B. Pulse wave velocity versus mean blood pressure (MBP) in the reference value population (11,092 subjects). Regression lines denote the results of linear regression on mean blood pressure for different age categories. The box in the right upper corner presents regression equations for PWV versus mean blood pressure according to age category. BP – blood pressure; HT – hypertension. Modified with permission from Ref #19.

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