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Stiff vessels approached in a flexible way: Advancing quantification and interpretation of arterial stiffness☆

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Abstract *Introduction:* Although pulse wave velocity (PWV), a proxy of arterial stiffness, is a strong predictor of cardiovascular complications, it is confounded by blood pressure (BP) and heart rate at the time of examination. Furthermore, establishing whether an artery behaves stiffer or less stiff does not inform a clinician on the *cause* of the stiffening.
Quantification of arterial stiffness: This paper focuses on BP as a confounder of PWV. We developed a method to patient-specifically determine the dependence of PWV on BP — on average 1 m/s per 10 mmHg diastolic BP — and used it to disentangle BP-dependent and -independent stiffening in hypertension and cancer patients. We furthermore showed that the so-called cardio-ankle vascular index (CAVI) — a measure deemed BP-independent — shows a residual BP-dependence that is readily correctable using a modified equation ($CAVI_0$). Both developed methods are directly applicable to clinical measurements in individual patients.
Interpretation of arterial stiffness: We developed a computer modelling procedure to disentangle contributions of the individual wall components — collagen, elastin, and smooth muscle — to arterial stiffening as observed in patients. Our model-based approach shows that with ageing, the biomechanical phenotype shifts from elastin-dominated to collagen-dominated load bearing.

Model-based assessment of arterial wall mechanics provides a promising tool to further improve interpretation of arterial stiffness measurements in patients. Further development

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of such methodology applied to various mouse models may improve the understanding and interpretation of arterial stiffening in ageing and disease.

Introduction

With each heartbeat, the heart ejects its stroke volume into the large arteries. If these are compliant, they store this temporary excess blood volume and its associated energy during systole, and release it during diastole. However, if the arteries are stiff — e.g., because a person has diabetes or is very old — this storage function is lost,[1] which implies that more work is required from the heart to maintain its output.

Clinically, arterial stiffness is most often quantified by measuring pulse wave velocity (PWV): the velocity with which the pulse wave that is generated by the heart, propagates along the large arteries.[2] If these arteries are compliant PWV is low (4–6 m/s), but if they are stiffened PWV will be increased (8–12 m/s).

Two types of PWV measurement can be distinguished: transit time PWV and local PWV.[3] Transit time PWV (Fig. 1A) is obtained by measuring blood pressure at two different sites: proximally, typically at the carotid artery, and distally, typically at the femoral artery. One can then quantify the time difference of wave arrival at these sites. Dividing the distance between the sites[d] by this time difference yields an estimate of regional PWV. Local PWV (Fig. 1B) is mostly obtained by measuring arterial pressure as well as diameter at the same site, which are then converted into PWV using the Bramwell–Hill equation (Fig. 1, legend).[8]

Quantification of arterial stiffness

PWV as a measure of arterial stiffness is confounded by blood pressure[9–11] and heart rate[12,13] at the time of measurement. In addition, local PWV measurement may be confounded by head orientation during ultrasonography.[14] This paper will focus on blood pressure as a confounder of PWV.

PWV increases with blood pressure[10] because intrinsic (material) wall stiffness increases with pressure.[e,17] The importance of this pressure dependence is illustrated by the white coat effect — the phenomenon that in some patients, in-clinic blood pressure is much higher than out-of-clinic blood pressure.[18] This increased in-clinic blood pressure also causes an (artificially) increased in-clinic PWV, which is unrelated to intrinsic arterial stiffening.

The blood pressure dependence of PWV can be handled in two ways: statistically as well as "mechanics model based".[19] Statistical correction has the disadvantage that it is only applicable in a *cohort* of patients, whereas a model-based approach is applicable to individual patient data. Model-based approaches can be subdivided into 1) *correcting* for the pressure influence, yielding a pressure-corrected PWV in e.g., metres per second, or 2) using *pressure-independent indices*, which are generally dimensionless.

Correcting for the blood pressure influence on pulse wave velocity

Model-based correction is based on the relationship between arterial pressure and diameter (Fig. 2A). This relationship is approximately exponential.[20,21] The slope of this relationship is a measure of the stiffness of the artery, and is related to the PWV. Using a PWV and a diastolic blood pressure (DBP) and systolic blood pressure (SBP) measurement, this relationship can be characterised. Subsequently, using this relationship, the PWV fluctuation that is solely due to pressure can be predicted.[9]

We used this technique to quantify the pressure-independent effect of anti-hypertensive medication on local PWV (Fig. 2B).[9] Our approach was to measure pressure and diameter in hypertension patients at baseline, when their medication was temporarily discontinued. Using these data, we obtained an estimate of local PWV, but also a model of the pressure–diameter relationship. After baseline measurements, medication was reinstalled or changed. At 3-month follow-up, we again measured local PWV and, additionally, we also used the baseline model, together with follow-up blood pressures to predict PWV, under the assumption that the pressure–diameter model had remained unchanged. We then compared the measured PWV at follow-up to the predicted PWV. Being equal this would imply that the artery's *intrinsic* stiffness remained unchanged, whereas any difference would imply intrinsic

[d] Formally, the actual path travelled by the pulse wave would be required, which is difficult to determine non-invasively. Several distance approximations have therefore been proposed and evaluated.[4,5] Current recommendations propose the use of 0.8 times the direct distance between the measurement sites.[6] However, arterial tortuosity developing with ageing and especially with several genetic arteriopathies complicates the use of this approximation.[7]

[e] The Moens–Korteweg equation shows that $PWV = \sqrt{E_{inc} h / 2 r_i \rho}$.[15,16] With an increase in pressure, inner radius (r_i) increases and wall thickness (h) decreases, which, from the equation, would lead to a *decrease* in PWV. Despite this, the incremental Young's modulus (E_{inc}, a measure of material stiffness) shows a large, nonlinear increase with blood pressure that outweighs the r_i- and h-effects. ρ, blood mass density.

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