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COMMENT

Potential adverse effects of vasodilatory antihypertensive medication on vascular stiffness in elderly individuals

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Introduction

The mechanical and structural properties of blood vessels differ along the vascular tree. There are two categories of large arteries: elastic and muscular arteries. Elastic arteries are close to the heart, contain more elastin per unit of area and play an important role in buffering the ejected blood volume, also called Windkessel function [1]. This results in smoothing of the pressure pulse and maintenance of blood flow during diastole [1]. More distal muscular arteries have a higher smooth muscle cell content. They regulate wall tension and shear stress by adjusting the vascular tone [1] and transport blood to the smaller resistance vessels that control blood flow.

With increasing age, the structural and cellular components of the arterial wall change. Mechanistically, the arterial wall is largely dependent on the balance between elastin and collagen [2] and their interplay with vascular smooth muscle cell (VSMC) contraction. This balance is disrupted during aging, leading to a higher collagen content, a lower elastin content, more elastin fragmentation, and more cross-linking of both collagen and elastin [2, 3]. On a cellular level, vascular aging is related to endothelial dysfunction and impaired nitric oxide bioavailability [2, 3], leading to reduced endothelium-dependent vasodilation and therefore more pronounced vasoconstriction [2, 3]. These microstructural and functional changes are typically thought to result in an overall stiffening of the arterial wall, which is a marker for increased risk of cardiovascular diseases, including myocardial infarction, heart failure, and stroke, as well as dementia and renal disease [2]. The hemodynamic consequence of arterial stiffening is increased arterial pulse pressure due to impaired Windkessel function [2]. This increased pulse pressure translates to an increased systolic blood pressure, causing an increased load on the cardiac left ventricle, as well as reduced efficiency of cardiac ejection and coronary perfusion [2]. Although vascular aging (i.e., the deterioration of the structure/function of the arterial wall) is a natural process that occurs with increasing chronological age, other pathological states and risk factors may accelerate this process [2, 3]. As such, hypertension is inherently associated with early vascular aging [2, 3], leading to endothelial dysfunction, vascular inflammation, remodeling, and hypertrophy [2]. In contrast to chronological aging, hypertension may not lead to an increase in the intrinsic stiffness of the wall material but to a (partly) reversible increase in structural stiffness through thickening of the arterial wall [2].

In this issue of *Hypertension Research*, Pewowaruk et al. [4] investigated how nitroglycerin (NTG)-mediated vasodilation acutely affects vascular stiffness and whether this differs between elastic and muscular arteries. NTG is an organic nitrate and acts as a nitric oxide (NO) donor [5]. In their study, arterial stiffness was measured both regionally using carotid-femoral pulse wave velocity (cfPWV) and locally at the carotid and brachial arteries using the pressure-diameter relation. Arterial diameter was assessed using ultrasound. Brachial blood pressure was measured oscillometrically and was subsequently converted to central blood pressure using radial tonometry and a generalized transfer function. This central pressure was then used to determine the carotid pressure-diameter relationship. The study population of veterans (>60 years old) with and without hypertension is very relevant in light of vascular aging and how the latter may be accelerated by hypertension [1].

Since most stiffness parameters are intrinsically pressure-dependent [6], Pewowaruk et al. used their previously

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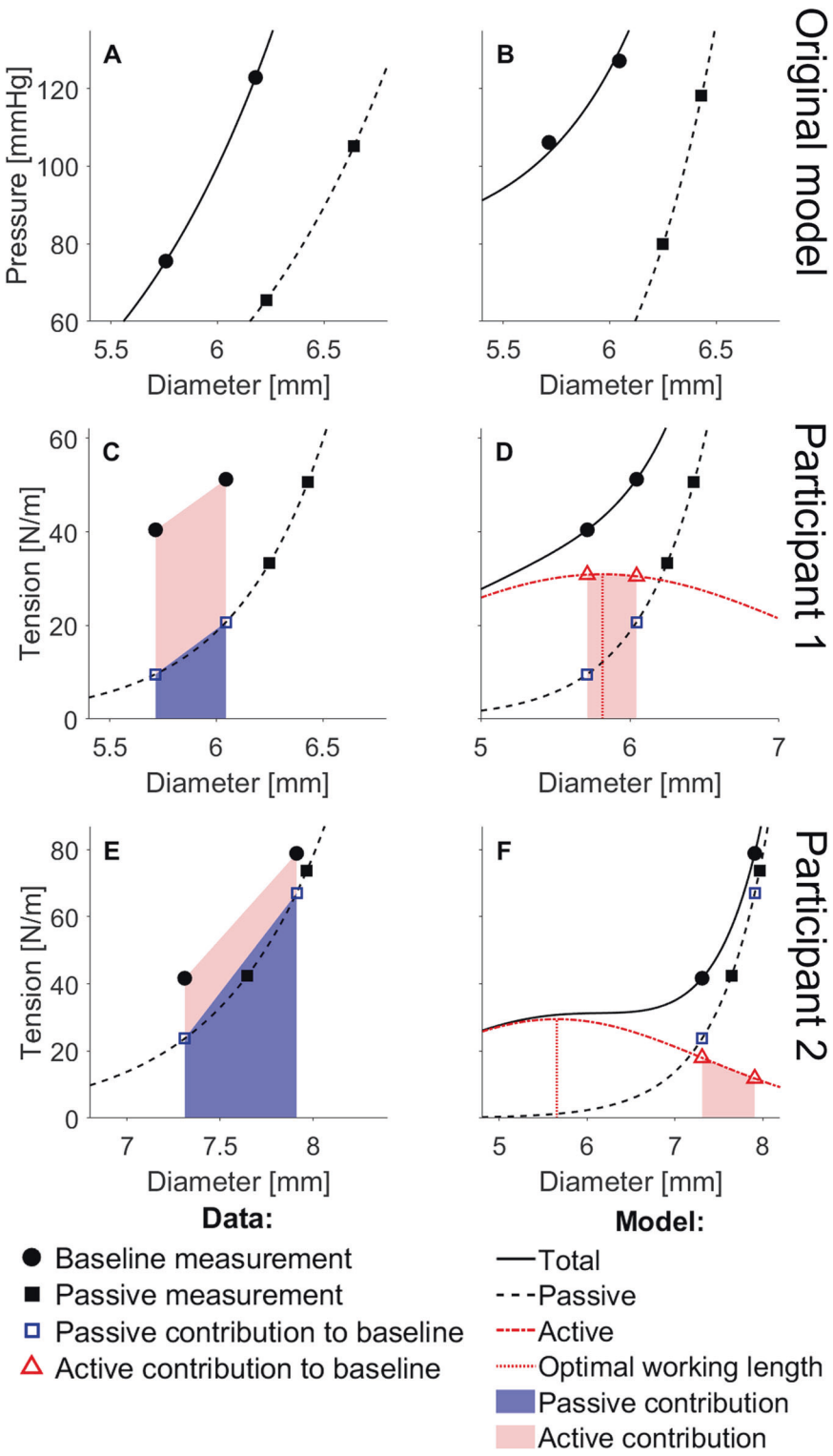

Fig. 1 Results from the original model from Pewowaruk et al. [4] (**A**, **B**), and after implementation of length-dependent VSMC contraction (**C**–**F**). **A**, **B** Examples of the original model fit without and with residual errors respectively; **C**, **E** Passive and active contributions to baseline data of participants 1 and 2, respectively; **D**, **F** Total and contraction model curves of participants 1 and 2 respectively

proposed clinically applicable model [7] to fit a combined passive-active exponential function to the pressure-diameter data and calculate stiffness at a common 120/80 (systolic/diastolic) mmHg reference pressure (Fig. 1A). This model distinguishes between the mechanical contribution of the passive extracellular matrix (ECM) and the active VSMCs, which may be useful to unravel the mechanism of altered stiffness in vasodilation. With its four fitted parameters, the model is applicable when clinical data of at least two pressure-diameter datapoints (e.g., diastole and systole) are available in at least two contractile conditions, resulting in 4 datapoints to ensure a unique parameterization of the four

parameters. The model's active and passive stiffness index parameters also represent relevant information about the stiffness contributions of both components.

Discussion

Pewowaruk et al.'s results show that the arterial stiffness of the carotid artery and the regional cfPWV is, as expected, higher in hypertensive individuals than in controls, but this was not observed in the brachial artery [4]. Stewart et al. [8] also obtained similar results for the carotid artery of middle-aged individuals. Furthermore, the observed response to NTG-mediated vasodilation of the different arterial beds analyzed in the study of Pewowaruk et al. is noteworthy; while the stiffness of the elastic carotid artery, as well as cfPWV, increased, the stiffness of the muscular brachial artery did not change significantly. These findings were independent of hypertensive status. In contrast, Stewart et al. [8] observed a decrease in stiffness in response to NTG in control participants but no change in hypertensive individuals. Further model analyses by Pewowaruk et al. revealed that in the carotid artery, the active VSMC stiffness index parameter was lower than the passive ECM stiffness index, whereas these two indices were almost equal in the brachial artery. This leads to the hypothesis that the different stiffness responses to vasodilation are a result of the ratio of active to passive stiffness contributions, which is in line with previous research these researchers performed with their model using data available from other clinical studies [7]. When this difference is positive (active stiffness > passive stiffness), decreasing arterial tone will decrease the overall wall stiffness as the active contribution decreases. In contrast, when this difference is negative, vasodilation will lead to an increase in stiffness. This could potentially explain the discrepancy between the present results and those of Stewart et al. [8]; in the older age group in the study by Pewowaruk et al., vascular aging is likely to be more pronounced than in a middle-aged group, which causes more stiffening of the (passive) ECM [1, 2]. This could reverse the ratio between the active and passive stiffness components and therefore cause the observed stiffening (rather than destiffening) in response to vasodilation.

Since only NTG is used as a vasodilatory agent, the magnitude of the vasodilation-induced change in stiffness may not be directly comparable to that induced by other vasodilatory drugs. Nevertheless, sublingual NTG administration is easily applicable in research because of the rapid onset of vasodilation and its short half-life and action time [5]. As an organic nitrate, NTG generates the vasodilatory compound NO [5]. At therapeutic doses, NO-mediated vasodilation is most prominent in the veins [1, 5] but also affects arteries and even other types of smooth muscle cells [5]. Other antihypertensive drugs may also induce vasodilation via different pathways, including the inhibition of the renin-angiotensin-aldosterone system or blocking calcium influx [5]. Although the amount of vasodilation and stiffness modulation induced by different compounds may differ, Pewowaruk et al.'s results highlight a potential adverse effect of antihypertensive drugs on vascular stiffness.

By developing a computational model, Pewowaruk et al. [4] were able to extrapolate the measured datapoints to the overall mechanical behavior of the vascular wall and eventually investigate stiffness independently of the confounding influence of blood pressure. The nature of the model also gives insight into the separate mechanical contributions of the passive and active components of the arterial wall. Other researchers also investigated the role of VSMC contraction on the arterial wall [9–11], resulting in models of varying degrees of complexity. The strength of Pewowaruk et al.'s model [4] is its applicability to situations with limited clinical data due to the low number of fitting parameters. However, the inherent assumptions and constraints therein also result in limitations in the use of the model. In particular, in the carotid artery data of three participants, their model was not able to capture the mechanical behavior without residual errors (Fig. 1B), despite having enough degrees of freedom [4]. In two of these participants, the active contribution to pressure decreased from diastole to systole. This could not be described by the model, given the assumption of an exponential VSMC pressure contribution with positive parameter constraints. Physiologically, VSMC contraction is generated by actin-myosin interactions, leading to length-dependent force generation, showing a maximum at optimal filament overlap while decreasing above/below this optimum [9–11]. We, therefore, hypothesized that in these two participants, VSMCs operated beyond their optimal length.

We adjusted the original model to include the length dependency of active VSMC tension as a Gaussian-shaped function [9] to capture the decrease in active pressure contribution from diastole to systole in two participants:

$$T(D) = \frac{1}{2} P_{\mathrm{ref}} D_{\mathrm{ref}} \left[e^{\beta_{0,\mathrm{pas}} \left(\frac{D}{D_{\mathrm{ref}}} - 1 \right)} + \frac{k}{k_{\mathrm{ref}}} e^{-\frac{\left(\frac{D}{D_{\mathrm{ref}}} - c_{\mathrm{act}} \right)^2}{\omega_{\mathrm{act}}^2}} \right], \quad (1)$$

where P_{ref} and D_{ref} are the reference pressure (fixed at 80 mmHg) and diameter [7], respectively; $\beta_{0,\mathrm{pas}}$ is a passive stiffness index parameter [7]; k and k_{ref} govern the contractile state ($k_{\mathrm{ref}} = 0.1$) [7]; c_{act} is a normalized optimal working length [9]; and ω_{act} governs the width of the Gaussian function [9]. This implementation showed that the VSMC contribution to tension was nearly diameter independent in Participant 1, indicating VSMCs were near their maximum contraction length (Fig. 1C, D). In

Participant 2, the VSMC contribution showed a strong negative relationship with diameter (Fig. 1E, F), indicating that VSMCs were beyond their maximum contraction length. This approach also has its own limitations, as it requires three parameters to describe the width, mean, and maximum of the Gaussian curve, compared to only two parameters for the exponential active curve in the original model. Given that only four datapoints are available, this is not enough to fit all five fitting parameters of the new model. Therefore, ω_{act} is set constant to 0.374, as suggested by Carlson and Secomb [9]. Moreover, since the active and passive contributions are no longer represented by a similar exponential function, the passive and active stiffness terms cannot be directly compared anymore through comparison of two β_0 parameters, as was possible in the original model [4]. However, a comparison in terms of passive vs. active pressure load bearing remains possible. Furthermore, as previously indicated by Giudici and Spronck [12], Pewowaruk's model may not be able to capture passive behavior at small diameters, since the elastin contribution is not described well by the exponential function. This could also (partially) explain the fitting problem observed for these two participants. However, given the old age of the participants, the impact of this limitation is expected to be limited [12].

In summary, the research from Pewowaruk et al. [4] showed 1) how the degree of vasoconstriction could alter vascular stiffness in both the muscular brachial artery and elastic carotid artery and 2) how clinical research benefits from innovative modeling approaches. Their study highlights the importance of investigating whether vasodilatory drugs, used as antihypertensive medication, have an adverse effect on large arteries by increasing their stiffness, which has inherent potential cardiovascular risks.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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