Wave reflection and central pressure augmentation

Recently, Cheng et al [1] proposed that central pressure augmentation may be principally determined by left ventricular systolic function rather than vascular wave reflection. We would like to make three comments.

First, we question Cheng et al's interpretation of published work about the role of wave reflection in pressure augmentation. Specifically, [2] and [3] were cited to suggest that the contribution of reflected waves is small or absent in the aorta, while it was stated that [4] "failed to find evidence supporting any predominant effect of wave reflection on pressure augmentation". However,

1) Manisty et al [2] studied carotid (not aortic) waveforms, reported reflection coefficients of ~0.5 (not small or absent) and stated that "[wave] separation clearly demonstrated that [higher AIx in individuals randomized to atenolol-based rather than amlodipine-based regimen occurred] because of increased wave reflection". It is true that in one example in [2] (Figure 1, right panel), a small forward compression wave labelled '$c^{+}1$' mainly caused the pressure augmentation. Although this wave could conceivably have a direct ventricular origin, it has not been observed in the aorta [5-7] and thus probably arises when reflected waves from elsewhere in the body (e.g. the brachiocephalic artery) are transmitted forwards into the carotid artery [8].
2) The conclusion of Davies et al [3] that augmentation index (AIx) is mainly due to changes in reservoir pressure, not wave reflection, was based on a controversial modification of wave intensity analysis, namely the 'reservoir-wave paradigm', which we have recently shown underestimates actual wave reflection by 40-100% [9]. Moreover, the view advanced in [3] is moot because, as we [9] and others [10] have pointed out, the reservoir pressure is generated by wave reflection.

3) Baksi et al [4] concluded that changes in the *timing* of wave reflection do not account for the increase in systolic blood pressure with age. However, the authors stated that age-related increases in AIx were consistent with marked increases in the magnitude of wave reflection and that their results should not be interpreted as excluding this mechanism [4]. While the discordance between time to the systolic inflection (Ti) and pulse wave velocity (PWV) in [4] might be considered evidence against wave reflection if the aorta were a uniform tube with a discrete distal reflection site, aortic tapering causes distributed wave reflection [11] and a wave 'horizon effect' [5]. In short, the 'reflected wave' arises from a complex series of events that muddies its relation to PWV and Ti. To complicate matters further, the foot of the reflected wave is not reliably estimated by Ti [12, 13].
4) Ample evidence exists that wave reflection underlies aortic pressure augmentation as depicted in Figure 1 of [1]. Without wave reflection, pressure and flow waveforms are identical, and their ratio is equal to characteristic impedance [14]. However, pressure augmentation is accompanied by a decrease in flow [14], a divergence shown by wave separation to be caused by the arrival of a backward-running (i.e. reflected) pressure wave [15, 16]. This view has solid mathematical grounding [14], does not require quasi-periodicity [17], and is supported by in-vitro [18] and computational studies [9, 13]. Most 'evidence' against wave reflection does not stem from non-validity of wave separation theory, but from unrealistic models of the aorta [11].

Second, we are somewhat puzzled that Cheng et al [1] showed examples of positive AIx in Figures 1 and 2, whereas the carotid and radial artery group data AIx in Figure 3 were *negative*, as would be expected in young subjects [19]. A negative AIx is thought to be caused by the natural outflow pattern of the left ventricle [20, 21], with

the pressure rise (if any) after Ti indicating wave reflection. Hence, in the absence of wave separation or truly representative pressure waveforms, it is impossible to judge the degree of systolic wave reflection (if any) in the study participants of [1]. While Cheng et al were rightly cautious in extrapolating their conclusions, their data may not be relevant for "question[ing] the prevailing concept of wave reflection as the genesis of the systolic inflection" [1] if study participants exhibited little systolic wave reflection from the outset, as is likely.

Third, although Cheng et al [1] found a weak association between Ti and the time of peak velocity of longitudinal shortening, it is unclear how deceleration of longitudinal shortening could produce a pressure-increasing compression wave (e.g. a $c^{+}1$ wave [2]) needed to explain a pressure augmentation. One would instead expect this ventricular event to generate a forward expansion (pressure-decreasing) wave related to inertial effects, as explained in [22]. This so-called 'X' wave has been found in the aorta [6] and peripheral arteries [2, 8, 22, 23] and is more prominent when AIx is negative. In subjects with negative AIx, one might therefore expect a relation between the times of peak longitudinal shortening and peak pressure (rather than Ti) in the aorta. Importantly, though, the X wave in carotid, brachial and radial arteries probably arises from a different mechanism to the aortic X wave, namely re-reflection of a primary backward-running reflected wave [23].

Whilst we commend the goal of [1] to explore the contribution of ventricular and vascular phenomena to the central pulse waveform, we suggest that analysis of AIx and Ti is not the optimal approach because "[positive] augmentation is a manifestation, not a measure of early wave reflection" [24] and, as pointed out in the editorial [25] accompanying [1], AIx is affected by many factors. Wave separation (including 'traditional' wave intensity analysis [9]) remains the gold standard

technique for investigating features of the pressure waveform [12]. Although uncertainties may exist when interpreting the relatively complex carotid (or more peripheral) arterial wave patterns, aortic wave patterns clearly demonstrate that pressure augmentation is predominantly caused by wave reflection [5-7].

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