Arterial waveform and central blood pressure: The complex links between large and small arteries

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Arterial wave reflections (AWR) are determined by arterial pulse wave velocity (PWV), the distribution and distance of the reflection points (RP) from the heart and the magnitude of these reflections. Pulse waves are reflected at sites of changing impedance. Substantial changes in impedance occur at branching of arteries and when approaching microvascular beds, but the continuous change in impedance along the arterial tree also generates continuous, diffuse reflection patterns, complicating the overall interpretation of wave reflection. This shows that the conceptual view of pulse waves reflected at a discrete site is far too simple.

Apart from structural aspects, also functional changes can largely influence AWR. Vasodilation decreases AWR by decreasing stiffness and moving the RP further from the heart. The opposite holds for vasoconstriction.

With ageing, stiffness of elastic arteries is progressively increasing, while muscular arteries stiffen much less. This disturbs the progressive increase in arterial stiffness from central to more peripheral medium-sized arteries. Also in hypertension, at the operating pressure arterial stiffness increases in the elastic aorta while it remains unchanged in the muscular radial artery, again changing the progressive change in impedance. It has been speculated that this reduces the impedance mismatch between central and peripheral arteries, leading to higher pulsatile load of the microcirculation and hence contributing to target organ damage in the brain and kidney.

These examples show that wave reflections and the consequent changes in arterial waveform and central blood pressure are influenced by a complex interplay between the large and small arteries.

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Introduction: arterial wave reflections, central pressure, central pressure waveform

The shape and magnitude of the central arterial pressure waveform are determined by a complex interaction between the functioning of the heart and circulation. At the onset of systole, the heart ejects a volume of blood into the circulation at a given pressure, generating a forward wave into the arterial tree. This wave is reflected at sites of impedance mismatch and returns to the heart, augmenting the forward wave as it passes through the arterial tree. The characteristics of this reflected wave (which is actually the resultant of all reflected waves, but is conveniently considered as a single reflected wave), the timing of its return and its amplitude, are determined by the speed at which the forward and reflected waves travel (the pulse wave velocity, PWV, in turn determined by arterial stiffness), the distribution and distance of the reflection points (RP) from the heart and the magnitude of the reflections generated at each reflection point.

Shifts in wave reflection characteristics, be it due to functional or structural arterial changes, may have important clinical repercussions. The change of wave reflection patterns with age for instance, is the main driving force of increasing (central) systolic and pulse pressure with advancing age, which has been shown to significantly influence cardiovascular risk. In younger subjects, relatively low pulse wave velocities and reflection points which seem to be located at relatively large distances from the heart result in reflected waves predominantly augmenting pressure during diastole, with the beneficial effect of increasing diastolic coronary perfusion. With age however, increased arterial stiffness results in higher pulse wave velocities and reflection points seem to move closer to the heart, resulting in reflected waves which interact with forward waves during systole, increasing systolic and pulse pressure.

Devising successful strategies for mitigation of deleterious changes in arterial wave reflections depends on a thorough understanding of their origins, their effect and the driving forces behind observed changes in wave reflections. There has therefore been considerable research interest in the determinants of arterial wave reflections and how different forms of therapy may influence the resulting pressure wave through modification of these determinants. Investigating wave reflections is, however, not straightforward, both from a technical point of view - acquiring information about the forward and reflected wave from the observed waveform - as well as for the proper interpretation of the results obtained from this separation. Due to the gradual increase of arterial stiffness and decrease in size from the central to the peripheral arteries, wave reflections do not just occur at specific sites of impedance mismatch such as branches or terminal vascular beds, but are also continuously and diffusely generated all along the arterial tree. Furthermore, arterial wave reflections are the resultant of an interplay between central and peripheral arteries and between macro- and microvasculature; an interplay which changes with age, disease and intervention. Many of these aspects are, to date, still not completely understood and the subject of ongoing debate.

Quantifying wave reflections

Proper investigation of arterial wave reflection requires separation of the observed pressure wave in its forward and reflecting components, which can be done using measurements of both aortic pressure and flow. As this is often inconvenient, alternative approaches - mostly based on the detection of a characteristic point on a single measured waveform indicative of the timing of the return of the reflected wave - have been proposed, though these may introduce inaccuracies and additional difficulties in interpretation.

The choice of analysis tool is important, as it may influence results obtained from studying wave reflections. Segers et al. investigated several parameters of wave reflection, including effective length - a synthetic measure representing the theoretical length of the arterial tree calculated from the timing of the return of the reflected wave and the measured pulse wave velocity assuming all reflections to originate from a single, theoretical reflection point -, timing of the reflected wave and reflection magnitude calculated either through wave separation analysis (WSA) - based on measurements of aortic flow and velocity - and waveform analysis (WFA) - based on detection of a characteristic point on a pressure wave -, and found results to differ depending on the method used. Reflected wave timings obtained from WSA and WFA did not correspond and effective lengths changed differently with age, decreasing for WSA-based measures and in some cases increasing for WFA-based measures. Similarly, Westerhof et al. investigated the change of the timing of the reflected wave with WSA and WFA in an anatomically accurate model of the human arterial system and found that reflected wave timings did not necessarily reflect the travel time from the heart to a theoretical reflection site and back due to phase differences introduced at the reflection sites which induce an additional time delay. Ideally, estimates of effective length or the timing of the return of the reflected wave should thus be based on the gold standard separation in forward and reflected waves using a combination of aortic pressure and flow. In practice however, waveform analysis remains an important tool for quantification of wave reflections, though its limitations and even its dependence on the type of characteristic point used should be taken into account when analyzing results.

The choice of the parameter to investigate wave reflections is highly important as well. Though central arterial stiffness gradually and continuously increases with age, some proposed parameters of wave reflection, like augmentation index (Alx), do not follow suit. Augmentation index is defined as the ratio of augmented pressure over pulse pressure. The augmented pressure represents the pressure increase due to wave reflection, positive for reflected waves arriving mostly in early systole and negative for reflected waves arriving later. Though initially increasing with age, Alx values have been shown to level off in older age groups. This behavior is most likely due to the inclusion of the stiffness dependent pulse pressure in its calculation, which confounds the use of Alx for determining wave reflections in elderly subjects where PP will be elevated due to increased arterial stiffness.
Wave reflection driving forces: macro- and microvasculature

The response of different segments of the arterial tree to changing circumstances can differ. With ageing for instance, stiffness of the elastic arteries is progressively and continuously increasing, while muscular arteries only stiffen to a much lesser extent.\(^5\)–\(^10\) Similarly, in hypertension, at the operating pressure, arterial stiffness increases in the elastic aorta while it remains unchanged in the muscular radial artery.\(^1,\)\(^11\) The microvascular structures in the arterial tree finally are, next to the main determinant of mean arterial pressure as sites of vascular resistance, also the origin of a considerable part of the wave reflections. Changes in the structure and function of the microvascular bed determine wave reflection coefficients at these sites.\(^12\) Rizzoni et al. found that, in hypertensive patients, changes in the microcirculation and the mechanical properties of large arteries were the two most important factors in predicting outcome and suggested that structural changes in large and small vessels may be reciprocally interrelated.\(^13\)

Changes in macrocirculatory function have important effects on the microvasculature. Due to the progressive loss of the dampening function of the large elastic arteries with age, pressure pulsatility is increasingly transferred to the microvasculature. Especially for high-flow organs, like the brain and kidney, exposure to excess pulsatility may induce extra risk. To protect organs from damage, the structure of the microvasculature changes to accommodate to this increased pulsatility by increasing myogenic tone and microvascular remodeling, but at the cost of in turn increasing mean arterial pressure and thus, indirectly, further increasing arterial stiffness.

Traditionally, the aforementioned early return of the wave in aged subjects during early systole has been attributed to the gradual stiffening of the elastic arteries, leading to higher pulse wave velocities, and a gradual shift of the reflecting sites towards the heart.\(^1\) More recently, Mitchell et al.\(^14\) investigating central (carotid-femoral) elastic artery and peripheral (brachial-radial) muscular artery stiffness and wave reflections from PWA in a subgroup of 521 subjects from the Framingham study, proposed an alternative view. They state that increases in central aortic stiffness and forward wave amplitude, rather than reflected wave amplitude, are the primary mechanisms for increased central systolic and pulse pressure in healthy adults. They hypothesize that due to the increased stiffening of central compared to peripheral arteries, the impedance mismatch between central aorta and proximal muscular arteries diminishes, reducing wave reflections at their interface and thus shifting the reflecting sites towards the periphery. They suggest the increase of forward pressure amplitude to be the result of increasing aortic impedance due to increasing aortic stiffness.\(^14\) In a subgroup of subjects with systolic hypertension, they additionally reported a decrease in aortic diameter, further increasing aortic impedance and forward wave amplitude.\(^15\) These findings oppose the traditional view and have been the subject of some debate. In a comment, O’Rourke and Nichols attributed the findings to the limitation of identifying the timing of the reflected wave using PWA.\(^4\)

Segers et al. comparing WFA with WSA also found increasing effective lengths with age for women in the Asklepios study when using WFA, but decreasing lengths if wave reflection was studied using WSA.\(^5\) The increased forward pressure wave due to increased impedance further implies a contribution of cardiac function.\(^5\)

Origins of wave reflections

Though wave reflection occurs continuously along the arterial tree, large wave reflections are thought to especially occur at the terminal microvascular beds, where pressure drops significantly over a short distance. In order for reflected waves to contribute to an increased systolic central pressure, wave reflections should arrive during early systole. With realistic pulse wave velocities it remains debatable whether waves returning from the peripheral vascular beds, such as in the lower legs, which are at distances of 1 m or more of the heart, are just able to return in early systole and boost the pressure peak. Pressure reflections from sites more proximal to the heart seem more likely to have a large influence on central pressure augmentation based on these rough distance estimations alone.

While it is in essence a strictly theoretical concept, the effective reflection site (or effective length of the arterial tree) is often examined to direct attention to specific regions of the arterial tree considered to be of particular interest. The fact that with age, central arterial stiffness (and pulse wave velocity) continues to rise, while pulse transit time seems largely unaffected has led to the common concept of the effective arterial length to ‘move’ with age, indicating to a certain degree a shift in relative importance of vascular territories for arterial wave reflections. Determination of effective lengths depends on identification of the return of the wave and the measured pulse wave velocity. Using PWA, in which return times are estimated from just a pressure waveform, Mitchell et al. found effective reflection sites at about 50–60 cm from the heart.\(^14\) Segers et al. using both WFA and WSA, found effective reflecting sites between 40 and 60 cm from the heart.\(^5\) Qasem and Avolio reported a real reflection site at the distal aorta.\(^16\) Though effective length calculations should be interpreted with care,\(^6\) the implied focus they put on reflections occurring somewhere in the lower abdomen are in line with results previously reported by Karamanoglu et al.\(^17\) In a simplified model they investigated the contribution of three different vascular territories (upper limb, lower limbs and trunk) and found central pressure waveforms to be determined mostly by reflections returning from the trunk. They furthermore found that the impedance mismatch from peripheral to central arteries effectively limits the effect observed centrally of waves returned from peripheral arterial sites.

These combined observations all seem to point towards the lower abdominal area as an area of potential interest for the examination of wave reflections, though it should be kept in mind that the “effective length” is a theoretical concept and does not (necessarily) relate to the presence of a discrete reflection site. On the other hand, the
abdominal area does contain short branches of the aorta towards several high-flow organs, such as the kidneys, and perhaps more importantly, the splanchnic bed, with its extensive microvasculature.

Conclusions

In studying wave reflections and their influence on the central pressure waveform, the interplay between large and small vasculature is clearly of significant importance, though the exact mechanisms of this interaction are of yet not fully understood. Examining the contribution of different arterial territories to wave reflection, especially those segments situated in the trunk may be of significant importance and warrant further investigation.

References