In this issue of Hypertension, Manisty and colleagues\(^1\) provide, using wave intensity analysis (WIA), new insight into hemodynamic mechanisms of blood flow and energy transfer in conduit arteries which are relevant to the basic pathophysiology of cardiovascular disease. WIA provides a further computational approach to assessing central arterial function and determinants of central blood pressure (the authors provide a summary of the principles involved in WIA as an online supplement to their article).

The reported results are pertinent to 3 important, obviously interrelated, but as yet very incompletely understood issues:

1. A growing, but currently unproven, perception that there may be differences between antihypertensive drug types, or even intragroup differences, in their affect on cardiovascular outcome and above equivalent effects on clinic (brachial) blood pressure.
2. The likely but again unproven association of central blood pressure independent of peripheral (brachial) blood pressure with adverse cardiovascular outcome;
3. An improved understanding of the underlying mechanisms determining central blood pressure waveform, important in view of point 2 above and because of the popular application of techniques of pulse wave analysis (PWA).

There is reasonable evidence supporting the contention that brachial, and more particularly central, blood pressure indices can usefully be considered as biomarkers of cardiovascular disease (ie, of underlying arterial dysfunction) rather than as being a primary determinant of disease in their own right. This highlights growing awareness that there is more to assessment of vascular health than measurement of brachial blood pressure and traditional clinical assessment. The notion underlies interest in local and distributed arterial mechanical properties (eg, PWV, cross-sectional distensibility) as well as in PWA. PWA commonly uses the concept of augmentation pressure (AP) expressed either absolutely or as augmentation index (Alx). On this level the data of Manisty et al can be seen as dealing with some of the underlying mechanisms of pressure waveform morphology and the formation of central blood pressure.

The simplest application of PWA is calculation of pulse pressure, and pulse pressure has been shown to be prognostic of coronary- and cardio-vascular outcome.\(^2\) Attempts at a more sophisticated application of PWA by identification of other consistent features of the pressure waveform such as an inflection point in the systolic ejection phase and determination of the relative timing to this point (as a surrogate of PWV) or of other summary indices such as AP or Alx to estimate the contribution of forward and reverse going pressure waves to the central blood pressure have been widely reported and commented on in consensus statements, guidelines\(^3\) and in the wider literature. The relevance of these relatively easily measured PWA parameters has, however, remained controversial. Laurent et al\(^1\) questioned the use of “surrogates of a surrogate” and Mitchell et al\(^4\) (in 2005) suggested that AIx would have limited usefulness as a measure of change after interventions and that it was uncertain whether it would be a valuable marker of clinical risk because the appropriate long-term follow-up studies had not been performed—in 2009 a lack of definitive studies remains.

Whether agents that are well established as improving cardiovascular outcome exert significant beneficial effects via mechanisms other than their primary mode of action remains unclear and debated. A number of underlying mechanisms are proposed as important in combining to form the morphology of the central blood pressure waveform. The results of Manisty et al\(^1\) can also be interpreted in this context, and it can reasonably be asked where the information provided by WIA fits with other models of central blood pressure generation. To fully integrate and assess the results of WIA it would be necessary to establish the interrelationship (if any) between WIA and PWA, in particular with the widely used AP and Alx.

There are some recent data addressing the evidentiary void in respect to potentially differing effects of antihypertensives on central blood pressure or outcome. Two studies in particular are relevant. One is the CAFE study, (ref 8 in Manisty et al\(^1\)) from which the data of Manisty et al\(^1\) is presumably a further subset and which was itself a substudy of the ASCOT study.\(^5\) The second is the arterial mechanics component of the 2nd Australian National Blood Pressure Study (ANBP2).\(^6\) Both substudies investigated effects of differing antihypertensive treatment arms on central blood pressure, PWA, and outcome. An additional relevant study was the Strong Heart study,\(^7\) a noninterventional study in which peripheral and central pulse pressures both predicted outcome.

In the ANBP2 substudy no prerandomization or follow-up parameter of central pressure obtained by direct carotid applanation predicted outcome.\(^6\) In ASCOT, in the presence of equal lowering of brachial blood pressure, treatment based onamlodipine was associated with a better outcome than was treatment based on atenolol. In the CAFE substudy (of ASCOT) there was a clear difference in transfer function derived central SBP and AIx between the treatment groups with the atenolol group not associated with as large a central-peripheral blood pressure difference as the amlodip-
The data of Manisty et al.1 suggest decreased magnitude with no change in relative timing or local pulse wave velocity. The WRI was reasonably correlated with carotid AIx, implying a potentially reassuring consistency. Unfortunately, there were no baseline pretreatment values available but the prospective randomization procedure of ASCOT supports an effect of atorvastatin.

An important finding, not fully expanded on by the authors, was the apparent interaction of atorvastatin and amloidipine therapy on central systolic blood pressure—consistent with the effect of atenolol on heart rate evidenced in the CAFE study, although it appears that in the subgroup reported here1 the lack of decrease in central SBP (in the presence of decreased pressure augmentation) was not associated with differences in heart rate or time to the inflection point.

It is necessary to remember that the importance of a reflected pressure wave in determining central blood pressure is still unestablished. The traditional view of increasing proximal stiffness causing earlier central arrival of a larger reflected pressure wave contributing to an increased central blood pressure and increased cardiovascular risk has been questioned by evidence suggesting that with age (and presumably other conditions that accelerate CV disease) increasing proximal stiffness has the predominant effect of decreasing impedance mismatch with increased distal pressure transmission and reduced magnitude and delayed arrival of any reflected pressure component.9 Other evidence questions any relevance for reflected pressure waves.10 The data of Manisty et al.1 suggest decreased magnitude with no change in relative timing of the reflected compression wave in the stenotic group relative to the nonstenotic group with only a very small (nonsignificant) difference in central BP.

A decrease in augmentation index of 4.2% and in augmentation pressure of 2.9 mm Hg would correspond to a very moderate clinical benefit, and the main benefit of the study is to better understand potential pathophysiological mechanisms of cardiovascular disease and to establish any secondary effects of cardiovascular medication. Although WIA provides another technique of measuring potentially hemodynamically relevant parameters and of assessing underlying influences that determine central blood pressure, the unfortunate situation remains that the required outcome studies to properly determine the relevance of different analytic techniques and their associated parameters are not available.

Rather than making excessive inference from small underpowered substudies of larger trials which were designed to test different hypotheses, we must await properly designed randomized, prospective, and longitudinal trials (having base-line data) with entry criteria determined on the basis of hemodynamic parameters and with appropriately chosen end points. In the meantime studies such as that of Manisty and colleagues provide important information toward improving our understanding of mechanisms but are unlikely to be able to definitely assign causality or to provide guidance for therapy.

Disclosures

None.

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Wave Intensity Analysis and Central Blood Pressure
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