Editors' view

Blood pressure as a drug target: what should we be measuring?

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BP as risk factor: cause, consequence or bystander?

Clinicians and researchers have traditionally relied on estimates of systolic and diastolic pressure in the brachial artery to predict cardiovascular risk and guide individual therapy. There is overwhelming evidence that usual BP measured in this way is a powerful predictor of future cardiovascular events [1], but the mechanistic link(s) between pressure and pathology (atheromatous disease and arterial thrombosis) is (are) incompletely understood. The distinguished statistician Ronald Fisher (of Fisher's exact test) pointed out the excellent correlation between the incidence of lung cancer in the twentieth century and sales of washing machines in a tobacco-industry funded pamphlet mocking the then available evidence that smoking causes cancer. His point was that association does not prove causality, but nor does it disprove it, and the subsequent evidence assembled by Richard Doll resolved the smoking/cancer issue definitively.

Evidence from placebo-controlled randomized trials shows that experimental interventions that lower brachial artery blood pressure also reduce cardiovascular events [2]. This not only underpins clinical decision making but also supports the notion that high BP actually causes cardiovascular disease, rather than being a consequence of it. However, this is not the end of the story. Systolic and diastolic BP (SBP, DBP) are correlated with one another, both are lowered by drug treatment, but DBP behaves strikingly differently from SBP in predicting future risk. Subjects aged 50–79 years in the Framingham cohort were grouped according to SBP (<120, 120–139, 140–159, >160 mmHg) to control for the strong association between SBP on DBP and reduce the effect of SBP on risk within each group [3]. DBP in each group was found to be *negatively* correlated with

cardiovascular risk (i.e. the *higher* the DBP the *lower* the risk). This unexpected observation underlies the utility of pulse pressure (SBP – DBP) as a risk factor in older adults, and has impacted on clinical practice: whereas previously a clinician with an older patient with isolated systolic hypertension might have felt reassured by a 'low' DBP of say 60 mmHg he or she now knows to take the elevated SBP of say 160 mmHg even more seriously than if the DBP had been 110 mmHg. Drug treatment of isolated systolic hypertension is highly effective in reducing cardiovascular events [4].

Should clinicians be measuring central rather than brachial BP?

Brachial artery BP differs substantially from aortic root pressure ('central' pressure). Brachial SBP is, paradoxically, greater than central SBP, a phenomenon known as 'amplification', and the shape of the pressure wave differs markedly in central elastic and peripheral muscular arteries [5]. The proximal parts of the coronary and carotid arteries are exposed to central rather than to brachial pressures so it seems self-evident that central SBP should better predict pathological events at these sites. Direct measurement using intra-arterial transducers is not appropriate for population studies or in guiding treatment of otherwise healthy hypertensive people, but central BP can be estimated non-invasively using applanation tonometry to measure the pressure waveform and calibrating this using the brachial artery BP measured by a standard indirect method. Applanation involves flattening a small area on the surface of a superficial artery that is supported posteriorly by firm tissue, using a surface probe that incorporates a high fidelity pressure transducer. In the hands of a

skilled practitioner this method is feasible in the carotid artery, where the waveform closely approximates the aortic waveform. This method predicts mortality in patients with renal failure [6]. Applanation tonometry is technically easier to perform in the radial artery at the wrist where the artery is both superficial and well supported by underlying bone. Unlike the carotid waveform the radial waveform differs markedly from the aortic pressure wave, but the central waveform can be estimated from it electronically by mathematical transformation using a generalized (population derived as opposed to subject specific) transfer function with remarkable fidelity under many conditions [5]. The late systolic shoulder of the radial pulse closely approximates central systolic pressure [7], and can be read directly from the pressure trace providing a simple and direct measure of central SBP.

In addition to the evidence that central SBP is more closely associated with cardiovascular outcome than is brachial SBP, there is also evidence that it can be differently affected by drug treatment, notably by nitrates and by β -adrenoceptor antagonists, than is brachial SBP [8]. Thus the physiological importance and pathological and pharmacological relevance of central BP are unquestionable. Are the currently available methods of estimating central pressure sufficiently robust and clinically predictive that they should be adopted into routine clinical practice? In the present issue of the Journal Laurie Tomlinson and Ian Wilkinson review this important question [8].

Barriers to adopting measures of central BP into clinical practice

Unlike the discovery by Stanley Franklin and his colleagues of the importance of peripheral pulse pressure mentioned above [3], which is readily applicable at the bedside, clinicians have been wary of adopting central BP into clinical practice. There are several reasons for this, some better than others:

- The cost of new kit and need to acquire new skills and expend more operator time.
- The need to measure brachial BP is not eliminated, since indirect methods of estimating central BP are calibrated using brachial BP in routine practice. The inaccuracies of indirect methods (auscultatory or oscillometric) are therefore not obviated [9].
- Unfamiliarity with the clinical meaning of central SBP vs. familiarity with implications of brachial SBP in clinical practice.
- Uncertainty as to how much extra predictive power adoption of central in place of brachial SBP could be hoped to provide in diagnosing hypertension and monitoring the response to drug treatment.

- Incompleteness of the evidence that this strategy would translate into better clinical outcomes.

In the not too distant past the great and good of the hypertension community (including the WHO) supported the use of an unvalidated method of measuring brachial artery blood pressure that eliminated observer bias (the Hawksley random zero sphygmomanometer), despite early indications that this was unreliable, probably because its rationale was so plausible. Unfortunately this method indeed proved to be inaccurate [10]. The harm done is hard to quantify but was considerable, and there were red faces. Once bitten twice shy and it is appropriate to expect the highest standards of evidence validating not only new methods of measurement of central BP (where so far much progress has been made [8]) but also defining clinical outcomes of different strategies of dose initiation and titration using brachial vs. central BP, compared ideally in randomized controlled trials. Here, the evidence is much more limited. There are however strong hypotheses to test, and such clinical trials would be of considerable academic interest and could also attract funding from devices manufacturers.

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