Abstract

Although hypertension is defined according to absolute blood pressure (BP) threshold levels, it is well recognised that the risk related to BP effects increases linearly from levels well below those currently identified. Therefore, international guidelines differ as to the BP level that requires antihypertensive therapy. Previous studies have identified the possibility that central arterial BP may refine the ability to identify those with BP levels within normotensive ranges who are at risk. In the present thesis I evaluated the determinants of central arterial BP that may enhance risk prediction within the normotensive BP range.

Prior reports on the contribution of aortic forward (Pf) and backward (Pb) wave pressures to age-related increases in aortic pulse pressure (PPc) have been confounded by the use of participants receiving antihypertensive therapy. Therefore, before assessing the changes in aortic function that occur in the normotensive BP range, I assessed the relative contribution of Pf and Pb to age-related increases in PPc in 892 community participants having never received antihypertensive therapy. On product of coefficient mediation analysis, in those participants <50 years of age, independent of several confounders and mean arterial pressure (MAP), Pb ($p<0.005$), but not Pf contributed to age-related increases in PPc. In contrast, in those participants ≥50 years of age, independent of several confounders and MAP, Pb ($p<0.005$) and Pf ($p<0.01$) contributed to age-related increases in PPc, and Pb effects were markedly diminished by adjustments for Pf (0.26±0.002 vs 0.52±0.003 mm Hg per year, $p<0.0001$ for comparison). Thus, independent of the effects of antihypertensive therapy, aortic backward waves contribute to age-related increases in aortic PPc across the adult lifespan, but at an older age, this effect may be attributed in-part to the impact of forward on backward wave pressures.

Whether age-related changes in aortic function occur in the normotensive BP range is unknown. I therefore evaluated the extent to which an abnormal brachial BP control accounts for age-related variations in aortic function in 1185 participants from a community sample (age>16 years)(36.4% uncontrolled BP). With adjustments for distending pressure (MAP), no increases in PPc, Pb, or aortic stiffness (pulse wave velocity [PWV]) and decreases in PP amplification (amp) were noted in those with an uncontrolled brachial BP younger than 50 years of age. In those older than 50 years of age with an uncontrolled brachial BP, MAP-adjusted aortic hemodynamic variables were only modestly different to those with a controlled brachial BP (PPc, 46±14 vs 42±15 mm Hg, $p<0.02$, Pb, 23±8 vs 21±8 mm Hg, PWV, 8.42±3.21 vs 8.19±3.37 m/sec, PPamp, 1.21±0.17 vs 1.21±0.14). Nonetheless, with adjustments for MAP, marked age-related increases in PPc, Pb and PWV and decreases in PPamp were noted in those with uncontrolled and controlled brachial BP across the adult lifespan ($p<0.0001$). Thus, brachial BP control in the general population fails to account for most distending pressure-independent, age-related changes in aortic hemodynamics across the adult lifespan. Age-related changes in aortic dysfunction therefore occur equally as strongly in the normotensive as

in the hypertensive brachial BP range.

In 1307 community participants I subsequently determined the extent to which the adverse effects of blood pressure (BP) are mediated by pulsatile haemodynamic changes across the normotensive as compared to the hypertensive adult brachial BP range. In normotensives (50.5%) independent of steady-state pressure (mean arterial pressure), significant relations between aortic backward wave pressure (Pb) and LVMI (partial $r=0.16$, $p<0.001$) or IMT (partial $r=0.15$, $p<0.005$) and between aortic pulse wave velocity (PWV) and eGFR (partial $r=-0.18$, $p<0.0001$) were noted, effects which in hypertensives were observed for LVMI and eGFR, but not IMT. In normotensives, as compared to brachial pulse pressure (PP) or systolic BP (SBP), Pb showed a greater slope (β-coefficient) of the relation with LVMI (0.99 ± 0.24 vs 0.47 ± 0.10 and 0.41 ± 0.09 mm Hg, $p<0.05$) and IMT (0.0045 ± 0.0013 vs 0.0013 ± 0.0006 and 0.0013 ± 0.0005 mm Hg, $p<0.05$) and a stronger association with left ventricular hypertrophy (Odds ratios [95% CI], 1.125 [1.059 to 1.195] vs 1.054 [1.027 to 1.082] and 1.042 [1.020 to 1.066, $p<0.05$). However, in hypertensives only the slope of the Pb-LVMI relationship was greater than that of PP- and SBP-LVMI relations. Thus, beyond brachial BP, pulsatile haemodynamics rather than steady-state pressures account for end-organ effects more consistently across the normotensive than the hypertensive BP range.

In conclusion, in the present thesis I show that age-related increases in both forward and backward wave pressures account for increases in aortic pulse pressure; that age-related increases in aortic backward wave pressures and stiffness as well as decreases in pulse pressure amplification are as striking in the normotensive as in the hypertensive brachial BP range; and that increases in aortic backward wave pressures and stiffness account for more end-organ changes beyond brachial BP in the normotensive than the hypertensive brachial BP range. These data suggest that the assessment of aortic function may identify those with brachial BP values in the normotensive BP range that are most at risk for a cardiovascular event.