Peripheral brachial blood pressure (BP) measurements may not provide an accurate representation of degenerative changes that characterize cardiovascular disease. Evidence is mounting that antihypertensive treatment strategies with apparently similar effects on brachial BP may have different effects on central aortic pressure (CAP), that in turn may lead to overestimation or underestimation of therapeutic efficacy. The relative importance of central and brachial BPs for predicting cardiovascular risk and clinical outcomes has been examined in several clinical studies. These studies have reported that a large proportion of individuals considered to have normal BP values based on brachial systolic pressures had high-normal BP based on CAP measurements. As additional evidence suggesting the superiority of CAP over peripheral assessments becomes more abundant, measurement of CAP may be the next important advance in the management of hypertension.

INTRODUCTION

The link between high blood pressure (BP) and increased cardiovascular risk has been established from a large body of data obtained with conventional (brachial cuff) sphygmomanometer measurements. Indeed, brachial BP parameters are reasonably predictive of cardiovascular morbidity and mortality. However, brachial BP may not completely reflect aortic degenerative changes that characterize the pathogenesis of cardiovascular disease. There is evolving evidence showing that different antihypertensive drugs with similar effects on brachial BP may have diverse effects on central aortic pressure (CAP). Central aortic pressures are influenced considerably by vascular endothelial function and provide a more accurate reflection of arterial hemodynamics. Additionally, CAP represents the BP actually perceived by the heart and brain and is therefore predictive of cardiovascular outcomes.

Blood pressure consists of a steady component (mean arterial pressure) and a pulsatile component (pulse pressure). The pulse pressure component, which is defined as the difference between brachial systolic BP and diastolic BP, has been emphasized as a surrogate marker of large artery stiffness and a possible predictor of coronary heart disease risk independent of mean arterial pressure. There is a disparity, however, between central and peripheral pulse pressure due to a rise in systolic BP, which has been attributed, in part, to conventional cardiovascular risk factors such as hypercholesterolemia, smoking, and the metabolic syndrome. This disparity diminishes with age due to aortic stiffening, for which an increase in pulse wave velocity is a surrogate.

Biophysically, CAP is determined by two major factors - cardiac output and peripheral vascular resistance. Thus, CAP should give a more accurate reflection of the hemodynamic burden on the ejecting left ventricle, coronary, and cerebral vasculature, and theoretically may correspond more closely to cardiovascular events than to brachial BP measurements.

Currently, the most widely used device for deriving CAP is the SphygmoCor (AtCor Medical; Houston, TX, USA), which uses standard cuff BP measurements and proprietary software utilizing a validated transfer function to convert the radial or carotid artery waveform measured by applanation tonography.

IMPACT OF ANTIHYPERTENSIVE DRUGS BEYOND TRADITIONAL BP REDUCTION

Evidence is accumulating that CAP may have a strong predictive value for cardiovascular disease independent of corresponding peripheral BP levels. Several important clinical trials have demonstrated marked improvements in cardiovascular endpoints without a parallel reduction in BP. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, similar reductions in brachial BP (CAP was not assessed) were found with losartan 50-100 mg ± hydrochlorothiazide (HCTZ) 12.5-25 mg and atenolol 50-100 mg ± HCTZ 12.5-25 mg. However, the losartan-based regimen appeared superior to the atenolol-based regimen in reducing the frequency of the primary composite endpoint of cardiovascular death, stroke, and myocardial infarction, and the difference was most marked in older individuals with isolated systolic hypertension. The study concluded that losartan appeared to confer benefits beyond reduction in BP. Similarly, in the Heart Outcomes Prevention Evaluation (HOPE), ramipril 10
mg showed a substantial benefit compared with placebo without producing a substantial reduction in brachial artery systolic and diastolic BP\(^5\). The 2003 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines for the management of hypertension acknowledged that central aortic BP and peripheral BP may be incongruous and recommended that total cardiovascular risk be taken into consideration in the management of patients with hypertension. The guidelines also added that subclinical target organ damage should be considered in overall risk quantification\(^6\). Since the publication of these guidelines, a growing body of evidence has strengthened the pathophysiological and clinical importance of CAP\(^7\). The 2007 revision of the ESH/ESC guidelines called for further large-scale observational and interventional studies to confirm the prognostic role of central BP measurements.\(^8\)

### COMPARISON OF CENTRAL AND PERIPHERAL BP MEASUREMENTS;

#### Clinical Significance

Some studies have evaluated the effect of antihypertensive drugs on both peripheral and central BP levels. In a double-blind crossover study in patients aged 65 to 85 years with systolic BP >150 mm Hg, the effect of four antihypertensive drug classes on both CAP and brachial BP was assessed\(^9\). Patients received, in randomized order of a placebo, a β-blocker (atenolol, 25 and 50 mg), an angiotensin-converting enzyme (ACE) inhibitor (perindopril 4 and 8 mg, or enalapril 20 and 40 mg), a calcium channel blocker (CCB; felodipine 5 and 10 mg, or amlodipine 5 and 10 mg), and a diuretic (HCTZ 25 and 50 mg) for 4 weeks for each drug. At the end of active treatment, the CCBs and the diuretics produced a greater brachial artery systolic BP reduction compared with the β-blocker or ACE inhibitors. The lowest central aortic systolic BP values were obtained with the CCBs and diuretics. It was postulated that brachial BP measurements may have overestimated the efficacy of the β-blocker and underestimated the effectiveness of the ACE inhibitors and CCBs\(^10\).

Since the benefits of ACE inhibitors could not be explained by corresponding reductions in brachial arterial pressure, an acute study was performed on 30 patients with one or more coronary risk factors in which measurements included cuff brachial pressure, radial artery tonometry with generation of CAP, and pulse wave velocity for aorta, upper limb, and lower limb arteries\(^1\). Patients received either ramipril 10 mg, atenolol 100 mg, or placebo. Central and brachial BP measurements were taken 30 minutes after administration of these treatments and repeated every 60 minutes for 5 hours. Significant differences in therapeutic effects between brachial and central pressures were seen for systolic BP (P < 0.0001), but not diastolic BP. Ramipril produced a substantial reduction (average change in steady state) in systolic BP that was greater in the aorta (-13.8 mm Hg) than in the brachial artery (-11.9 mm Hg), whereas atenolol produced little change in either aortic (+0.8 mm Hg) or brachial (-2.5 mm Hg) systolic BP. During steady state, brachial systolic BP fell by -20.3 mm Hg with ramipril and by -10.9 mm Hg with atenolol (both P < 0.0001). However, the fall in aortic systolic BP was -22.2 mm Hg with ramipril (P < 0.0001) and only -7.6 mm Hg with atenolol (P = 0.0002). The investigators noted that measurements of brachial systolic BP underestimated the benefit of ramipril on aortic pressure, but overestimated the benefit of atenolol\(^1\). Furthermore, treatment with an ACE inhibitor significantly reduced the central aortic augmentation index, which is an index of arterial stiffness\(^1\).

In a similar comparison between drug classes, the hemodynamic effects of atenolol 50 mg and eprosartan 600 mg were evaluated in a double-blind, randomized, crossover study (N = 21) that assessed central BP and augmentation index using pulse wave analysis, and examined aortic pulse wave velocity\(^1\). Peripheral BP reductions were similar, yet there was a significantly greater reduction in central aortic BP observed in patients treated with eprosartan.

The Japan-Combined treatment with Olmesartan and a calcium channel blocker versus olmesartan and diuretics Randomized Efficacy (J-COR-E) study was designed to study the effects on central aortic systolic BP and brachial ambulatory systolic BP of a CCB and diuretic when either were used in combination with an angiotensin receptor blocker\(^2\). In this prospective, randomized, open-label, blinded endpoint study (N = 207; mean age, 68.4 years), patients received olmesartan medoxomil 20 mg monotherapy for 12 weeks, followed by randomized olmesartan medoxomil/azelnidipine 20 mg/16 mg (n = 103) or olmesartan medoxomil/HCTZ 20 mg/12.5 mg (n = 104) for 24 weeks. The between-group difference in brachial systolic BP reduction was not significant. However, the reduction in central systolic BP was significantly greater with olmesartan medoxomil/azelnidipine compared with olmesartan medoxomil/HCTZ (between-group difference [95% confidence interval], 5.2 [0.3 to 10.2] mm Hg; P = 0.039)\(^3\). These findings confirmed a previous finding that a CCB significantly decreased the aortic pulse wave velocity but a diuretic did not.\(^3\)

### CAP AND CARDIOVASCULAR RISK OBSERVATION FROM OUTCOMES STUDIES

The relative importance of central and brachial BPs for predicting cardiovascular risk and clinical outcomes was examined in several large trials. In a cross-sectional substudy of the Anglo-Cardiff Collaborative Trial II, CAPs were derived in >10 000 adult patients followed by calculation of the pulse pressure ratio, the ratio between aortic and brachial pulse pressures\(^4\). For each age group, there was a considerable variability in the PP ratio. Compared with healthy individuals at baseline, the pulse pressure ratio was significantly increased (central systolic BP was relatively higher) in individuals with cardiovascular risk factors. The largest pulse pressure ratio was in men with diabetes and cardiovascular disease and in women with hypertension, diabetes, and cardiovascular disease\(^4\). Furthermore, the investigators found that the difference between peripheral and central pulse pressure decreases with increasing age until the age decade of 50 to 60.
and women, respectively. A key finding from this study was the estimated average difference of 11 mm Hg and 8 mm Hg in men and women, respectively. In another major outcomes clinical trial, the Conduit Artery Function Evaluation (CAFÉ) study, a substudy of Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), investigators compared a stepwise regimen of amlodipine 5-10 mg ± perindopril 4-8 mg with an atenolol 50-100 mg ± bendroflumethiazide K 1.25-2.5 mg regimen on CAP in treated patients with hypertension (N = 2199). Although brachial systolic BP reductions were similar between treatment groups, there were significant reductions in CAP with the amlodipine regimen, a finding that may explain the differences in outcomes between the two treatment groups (Fig. I)\(^1\).

The Strong Heart Study was a longitudinal study of prevalent and incident cardiovascular disease in a population of Native Americans\(^2\). The relations of brachial and central pressures to carotid artery hypertrophy, extent of atherosclerosis, and incident cardiovascular events were examined in 3520 participants. Central aortic pressure readings were more prognostic than standard brachial pressure for vascular measures of atherosclerosis including carotid plaque burden (\(P < 0.001\)), carotid intimal-medial thickness (\(P < 0.002\)), and vascular mass (\(P < 0.05\)). Both central and peripheral measures of pulse pressures were more closely tied to atherosclerosis than systolic BP (\(P < 0.001\))\(^3\).

**CONCLUSIONS**

Major antihypertensive drug classes have differential effects on CAP despite having similar effects on brachial pressure. Evidence is mounting to suggest that central pressures more closely correlate with measures of cardiovascular risk than brachial pressure and that central pressures independently predict future cardiovascular events and responses to antihypertensive therapy. Disparities between CAP and brachial BP measurements pose a challenge to the guidelines for the management of hypertension, as these are usually determined by conventional brachial cuff measurements. As the cost of required equipment comes down and additional persuasive evidence of its superiority over peripheral assessments becomes more abundant, assessing CAP may be the next important advance in the future clinical management of hypertension.

**ACKNOWLEDGEMENTS**

Kathryn Leonard, BSc, of Wolters Kluwer Pharma Solutions, Inc., provided editorial assistance in the preparation of this manuscript, which was supported by Daiichi Sankyo, Inc.

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