Effect of Different Antihypertensive Drug Classes on Central Aortic Pressure

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Background: Central aortic systolic blood pressure (BP) is an important determinant of cardiac workload and cardiac hypertrophy. The relationship of central aortic systolic BP and brachial BP varies depending on the stiffness of blood vessels. It is not certain whether the different drug classes affect the brachial and aortic systolic BP in a similar manner.

Methods: In a double-blind crossover study, we measured the effects of the four major drug classes compared with placebo on central aortic pressure. Central aortic pressure and various indices were determined using the Sphygmo Cor apparatus. The study was undertaken in patients aged 65 to 85 years with systolic BP >150 mm Hg at study entry. Results are reported for 32 patients who had satisfactory applanation tonometry in all five periods.

Results: Calcium channel blockers and diuretics caused a greater fall in brachial artery systolic BP than angiotensin-converting enzyme (ACE) inhibitors or β-blocking drugs. On placebo, central aorta augmentation pressure and index were 23 mm Hg and 33.3%; on ACE inhibitors the values were 18 mm Hg and 30%; on β-blockers, 26 mm Hg and 38.5%; on calcium channel blockers, 16 mm Hg and 28%; and on diuretics, 17 mm Hg and 28.8%. The augmentation pressure on β-blocking drugs was greater than on the other three drug classes (P < .05), and augmentation pressures on ACE inhibitors, calcium channel blockers, and diuretics were less than on placebo (P < .05). The lowest central aortic pressures were achieved with calcium blocking drugs and diuretics.

Conclusions: Therapy based on brachial artery recordings may thus overestimate the effect of β-blocking drugs on central aortic systolic BP and underestimate the effectiveness of ACE inhibitors and calcium blocking drugs. The clinical importance of this discrepancy needs to be evaluated.

Key Words: Angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, β-blocking drugs, augmentation pressure, central systolic pressure, augmentation indices, pulse pressure.

Blood pressure (BP) is usually measured at the periphery (brachial artery) and a single value is recorded for systolic and diastolic BP. Although this has provided remarkable success as a means of predicting outcomes in individuals, it is an oversimplification of the true status. Brachial artery BP measurements provide a reasonably accurate measure of end-diastolic BP, which declines relatively constantly throughout diastole. However, systolic BP is not accurately recorded by this measure. The peak systolic BP is only one point on the systolic pulse wave and takes little notice of the duration of the systolic period or the shape of the systolic wave. Information related to this can be provided by applanation tonometry. There is, however, another and possibly more important problem. The significant pressure related to cardiac function and work is the pressure at the origin of the aorta. The heart expels blood against this pressure. The brachial artery diastolic pressure is a close approximation of the central aortic diastolic pressure, which is 1 to 2 mm Hg higher. However, brachial artery systolic pressure is not a good estimate of the central aortic systolic pressure.

The central aortic systolic pressure in young healthy persons is much lower than the brachial artery systolic pressure. This results from reflected waves. In normal individuals the reflected wave returns to the central aorta late in systole and there is relatively little amplification of the aortic pressure. However, it has returned to the brachial artery during contraction, resulting in amplification of the brachial artery systolic pressure, which is higher than the central aortic systolic pressure. As blood vessels become stiff because of age-related processes in our community or because of high BP or high cholesterol or both,
the pulse wave is transmitted more rapidly and returns to
the heart during contraction, resulting in a greater augmentation
of the central aortic systolic pressure.\textsuperscript{5–7} Other fac-
tors such as a slow heart rate can also affect pulse wave
velocity and augmentation of central aortic systolic pres-

In a previously published study\textsuperscript{9} we demonstrated that the
response to the four major classes of antihypertensive
drugs in elderly persons with predominantly systolic hy-
pertension varied. Calcium channel blocking drugs and
diuretics were more effective at lowering brachial systolic
BP than angiotensin-converting enzyme (ACE) inhibitors
and \(\beta\)-blocking drugs. Deary et al\textsuperscript{10} have performed a
similar study comparing five drug classes, but this was in
younger persons with diastolic hypertension. There was a
different response pattern with an ACE inhibitor and a
\(\beta\)-blocking drug achieving better brachial artery BP con-
trol than the other three classes. It is likely that this is due
to the age difference of the patients studied.

The study reported here was undertaken to determine
the effect of different classes of drugs on central aortic
pressure and aortic pressure augmentation in elderly per-
sons with systolic hypertension, using the Sphygmo Cor
apparatus (SCOR; PWV Medical, Sydney, Australia).

**Methods**

The patients in this study were a subset from a study that
has already been reported.\textsuperscript{9} The first 17 patients recruited
to that study were not included, as the Sphygmo Cor
apparatus became available only after that time. In addi-
tion, only patients eligible to receive all four drugs and
placebo were included. Thus, 44 patients 65 to 85 years of
age with a systolic BP >150 mm Hg after three clinic
visits were included in the study. No patient had been
previously treated for hypertension. The patients entered
the study after giving informed consent.

The patients received, in randomized order, a low dose
and then a high dose of the following drugs: placebo, 1 and
2 tablets; atenolol, 25 and 50 mg; perindopril \((n = 28)\), 4
and 8 mg or enalapril \((n = 16)\) 20 mg and 40 mg; felodipine
\((n = 16)\), 5 and 10 mg or amlodipine \((n = 28)\),
5 and 10 mg; and hydrochlorothiazide 25 and 50 mg. Each
period was 4 weeks in duration. At each visit the clinic BP
was recorded as previously described.\textsuperscript{9} The study was
undertaken between 24 and 26 h after the medication was
taken. The patients had their BP measured in duplicate in
the dominant arm with a Dinamap sphygmomanometer
(Critikon Corp., Tampa, FL). They then had application
tonometer performed and their BP measured again in
duplicate. Applanation tonometry was performed in the
radial artery at the wrist using the Sphygmo Cor apparatus.
Twenty sequential wave forms were acquired; and the
system software, using a validated mathematical transfer
function, generated an average peripheral and ascending
aorta pressure wave.\textsuperscript{11} The BP values taken immediately
before and after the applanation tonometry were used as

| Table 1. Demographics of persons who completed this study |
|----------------|----------------|
| Number         | 44             |
| Male/female    | 34/10          |
| Age (y)        | 77.2, range 66–86 |
| Height (cm)    | 164.8          |
| Weight (kg)    | 74.5           |
| Body mass index|                |
| Systolic BP (mm Hg) | 166.5 ± 3.4 |
| Diastolic BP (mm Hg) | 87.3 ± 1.8 |
| Cholesterol (mmol/L) | 5.62 ± 0.17 |
| Creatinine (mmol/L) | 0.108 ± 0.006 |
| Smoker          | 4              |
| Previous smoker | 12             |
| Previous vascular disease | 16             |

BP = blood pressure.

The analysis described was performed on persons who
had successful application tonometry in all five periods of
the study. The main reason for rejection of an application
tonometer was the failure to identify the first peak. The
data was analyzed by one-way ANOVA. In addition,
paired \(t\) tests were made between the variables. \(P\) values
with and without Bonferroni’s correction are provided.
The study was approved by the ethics committee of the
Austin and Repatriation Medical Centre.

**Results**

The 74 patients randomized to the previous study\textsuperscript{9} were
distributed as follows. Of the patients, 17 had started
before the Sphygmo Cor was available. In addition, 12
other patients were ineligible to receive a \(\beta\)-blocker and
one to receive a diuretic and were not included. Thus 44
patients were entered into the study. Six patients did not
complete all study periods, and in six patients interpretable
waveforms were not recorded (usually in most study pe-
riods). Data are presented for 32 patients who completed
all periods and had successful application tonometry
during each period. Baseline data for the set of 32 patients are
indicated in Table 1.
The first comparison was made between the patients on the different ACE inhibitors and calcium blockers. Because there was no difference between the results for perindopril and enalapril or between felodipine and amlo-dipine, the ACE inhibitors and calcium blockers were treated as a group and not for the individual drug. The next comparison made was between the results on the high and low dose of each drug. The values on the high and low dose of placebo, \( \beta \)-blockers, ACE inhibitors, and diuretics did not differ. However, the values for systolic BP, both peripherally and centrally, were lower on the higher dose of the drug, which was 2 months after that medication had been started.

The brachial artery values and the various aortic indices are presented in Table 2 and the difference from the placebo value in Table 3. All drugs lower systolic and diastolic BP in the brachial artery. The systolic BP decreased more than the diastolic BP, thus reducing the brachial artery pulse pressure. This fall in pulse pressure was significant for diuretics and calcium blockers but not for \( \beta \)-blockers or ACE inhibitors (Fig. 1).

Pulse rate was reduced by 7.7 ± 1.6 beats/min with...
The changes in peripheral and central pressures are indicated in Fig. 1. From these data it can be observed that brachial artery pressure measurements underestimated the change in systolic BP in patients on ACE inhibitors and calcium channel blockers. The changes in pulse pressure were underestimated in patients on ACE inhibitors and overestimated in patients on β-blockers (Fig. 1).

**Discussion**

This study indicates that the alteration in peripheral artery BP with different drug therapies may not accurately predict the changes in central aortic pressure. This applies particularly to β-blocking drugs where the alteration in brachial artery systolic pressure overestimates the effect that has occurred centrally. β-Blockers also altered pulse rate and some of the changes may be consequent upon that effect. However, whatever the mechanism in patients on β-blocking drugs, the central systolic pressure is not reduced as much as the peripheral systolic pressure and this may lead to inadequate reduction in BP in persons treated with β-blocking drugs. This may be part of the reason that β-blockers do not reduce cardiac hypertrophy as well as other drugs, and may explain the inferior effect of β-blockers on mortality in hypertensive patients compared with diuretics. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, an angiotensin type 1 receptor blocking drug improved prognosis compared with atenolol despite similar brachial artery BP reduction. The different effects that these two drugs would have had on central aortic pressure (assuming that angiotensin type 1 blockers and ACE inhibitors are similar) may provide the explanation.

Calcium channel blocking drugs in this group of elderly patients with systolic hypertension overall had a better effect on all BP and indices compared with the other drug classes, although not all reached significance. Thus the lowest values for peripheral systolic, diastolic, and pulse pressure were recorded on calcium channel blocking drugs but was not altered with the other medications (Table 3). No correction for this slower pulse rate was made for the calculated central indices.

The first peak in the systolic waveform was reduced by each drug and the decrease with calcium channel blockers was greater than the decrease with ACE inhibitors and diuretics. The second peak in the systolic wave form was not reduced significantly by β-blocking drugs, whereas it was with the other three drugs. The peak systolic BP on calcium channel blocking drugs was lower than with the other therapies (Table 2). Systolic BP at the end of ejection was lower than placebo with all four drugs but the value with calcium channel blockers was lower than with all other drugs. The augmentation pressures calculated from the above data were reduced compared with placebo by ACE inhibitors, calcium channel blockers and diuretics (Table 3). The augmentation pressure on β-blockers was higher than on placebo, but this did not reach significance (P = .11). Central pulse pressure was reduced significantly by ACE inhibitors, calcium channel blockers, and diuretics and there was no difference between the three drugs. β-Blockers did not reduce pulse pressure significantly.

The augmentation indices are indicated in Table 2. Calcium channel blockers, and diuretics reduced the augmentation index, whereas it tended to be increased by β-blockers. The ACE inhibitors had no significant effect. The changes in augmentation indices were not as pronounced as the changes in augmentation pressure because of differences in the central pulse pressure. A comparison of the effect of the different drugs on augmentation pressure and augmentation index is provided in Figure 2. There were no differences between the effects of calcium channel blockers, ACE inhibitors, and diuretics. However β-blocking drugs caused a greater rise in augmentation pressure and had a larger augmentation index than all other drugs.

The changes in peripheral and central pressures are indicated in Fig. 1. From these data it can be observed that brachial artery pressure measurements underestimated the change in systolic BP in patients on ACE inhibitors and calcium channel blockers. The changes in pulse pressure were underestimated in patients on ACE inhibitors and overestimated in patients on β-blockers (Fig. 1).
drugs. The lowest values for BP in all the aortic pressures and indices were on the calcium channel blocking drugs. As the peripheral BP fall on the calcium channel blocking drugs was greater than with the other drug classes except diuretics, it is difficult to determine whether the lower levels of central aortic pressure are a consequence of the BP fall or some additional effect.

The response to ACE inhibitors was of interest. The ACE inhibitors caused a relatively small fall in brachial artery systolic BP (8 mm Hg), which was less than that with diuretics or calcium channel blockers, but compared with the brachial pressure measurements the fall in peak central aortic pressure was greater (13 mm Hg), which was similar to that with diuretics (15 mm Hg) but less than with calcium channel blocking drugs. Thus it is tempting to assume that both calcium blocking drugs and ACE inhibitors have a specific effect on blood vessels such as vasodilation or relaxation that reduces the augmentation pressure. Because of the short period of the drug treatments it is unlikely to be due to structural changes, but this cannot be excluded.

The importance of indices of pulse wave velocity and central pressure augmentation have been emphasized by a number of studies that have clearly shown associations between these variables and morbidity and mortality. A strong correlation with other indices of cardiovascular risk. It is likely that these results are mediated in part by a higher central aortic systolic BP in such persons. What is not clear is whether therapy based on reduction of pulse wave velocity or augmentation index as surrogates for the effect on central aortic systolic BP will lead to improvement in morbidity and mortality, although a recent large multicenter study indicated that improvement can occur with one drug therapy but not another, despite similar BP control.

This study confirms our previous conclusion that in elderly persons with systolic hypertension, calcium blocking drugs and diuretics are most effective at lowering the systolic BP. This conclusion may not be applicable to younger persons with predominant diastolic hypertension in whom ACE inhibitors and β-blockers lowered brachial BP more than the other drug classes. In the study by Deary et al., despite a lowering of brachial BP on a β-blocker patients had a marked elevation of brain natriuretic peptide, which is a marker of cardiac “stress” suggesting that the central effects may not have been as good with β-blockers as the peripheral actions. Our study suggests that calcium channel blockers may have more beneficial effects on cardiac indices than diuretics. However calcium channel blockers and diuretics lowered the central aortic systolic BP more than the other drugs. The study also infers that ACE inhibitor therapy, despite a relatively small effect on peripheral BP, had a more beneficial effect on central BP. The results of β-blockers causing further increase of the central augmentation pressure together with the poor peripheral effect indicates that they should not be the first-line therapy in elderly persons with systolic hypertension.

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References


