Noninvasive Pulse Waveform Analysis in Clinical Trials: Similarity of Two Methods for Calculating Aortic Systolic Pressure

Audrey Adji, Kozo Hirata, Sonja Hoegler, and Michael F. O’Rourke

Background: Concerns persist about the validity of generalized transfer function-derived, aortic blood-pressure measurements during the administration of vasoactive agents in clinical trials. Hence, we compared this transfer-function method with another, which estimates aortic systolic pressure directly from the late systolic shoulder of the radial pressure wave, after administration of placebo, ramipril, or atenolol.

Methods: We recorded radial pressure pulse waveforms, using a commercially available system, in 30 subjects with ≥1 coronary risk factor in an acute study of ramipril at 10 mg and atenolol at 100 mg. Directly recorded radial and derived aortic pressure pulse waveforms were examined individually and were ensemble-averaged, and the difference between radial and aortic pressure responses was examined.

Results: The late systolic shoulder response from radial waveforms was reduced by 15.8 mm Hg (SD, 12.2 mm Hg) more with ramipril than with atenolol. This was similar to a difference of 14.6 mm Hg (SD, 11.2 mm Hg) calculated for the aortic systolic pressure response using the transfer-function technique. Ramipril caused a greater reduction in the aortic systolic pressure response (22.2 mm Hg), whereas with atenolol, there was a modest decrease (7.6 mm Hg). The mean difference between aortic systolic pressures measured from direct radial waveforms and from derived aortic pressure between 3 and 5 h after dosing under all circumstances was 1.6 mm Hg (SD, 8.9 mm Hg).

Conclusions: Central pressure derived from radial pressure waveforms using a generalized transfer function gave similar results for central pressure measured directly from radial waveforms. The hemodynamic benefits of angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and calcium channel blocker over β-blocker antihypertensive therapy in recent trials were confirmed by this study. Am J Hypertens 2007;20:917–922 © 2007 American Journal of Hypertension, Ltd.

Key Words: Aortic systolic pressure, radial pressure waveform, generalized transfer-function technique.
systolic pressure, we were assured by the conclusions of Smulyan et al.10 that the main source of measurement error in the Sphygmocor system (AtCor Medical, Sydney, Australia) is the variability and inaccuracy of cuff pressure used in the calibration of radial artery pressure.

Methods

Data were collected from a group of 30 subjects (25 men and 5 women; mean age, 67 years; SD, 10 years) with ≥1 coronary risk factor (hypertension, diabetes mellitus, hypercholesterolemia, or smoking). Of these subjects, 10 had myocardial ischemia, and 18 had angiography-proven angina. Details of this study were previously described.10 Briefly, the study was performed according to an acute, randomized, placebo-controlled, double-blind crossover method. Subjects’ regular vasoactive medications were withdrawn for at least five half-lives before the session, and they received either 10 mg of ramipril, 100 mg of atenolol, or placebo. Measurements were made at baseline, and at 30, 60, 120, 180, 240, and 300 min after baseline. The study protocol was approved by the Research Ethics Committee of St. Vincent’s Hospital, and all subjects gave written, informed consent.

After 15 min of rest in a quiet, temperature-controlled room, brachial blood pressure was taken in the supine position with a standard adult-size cuff mercury sphygmomanometer, using the Korotkov technique, and Phase 5 was taken as the diastolic pressure. As in the REASON and CAFE Trials, radial pressure pulse waves were calibrated using the Sphygmocor system,3–5 calibrated by cuff systolic and diastolic pressure obtained from the brachial artery. For each series of radial pressure waves, the corresponding aortic pressure pulse waveform was generated, using the generalized transfer function.

We focused on the effects of ramipril and atenolol during steady state (measurements taken 180, 240, and 300 min after oral administration). The pressure pulse waveforms from directly recorded radial and derived aortic were ensemble-averaged between 180 to 300 min from drug administration. Central systolic pressure was determined by two methods: (1) the peak of the aortic derived pressure waveform, and (2) the late systolic shoulder of the directly measured radial pressure waveform (inflection technique). Student’s t-test was employed to examine the difference between central systolic pressures calculated by Methods 1 and 2, with P < .05 considered statistically significant.

Results

During the steady-state period (180 to 300 min after active therapy), the reduction in central systolic pressure estimated by Method 2 was 15.8 mm Hg (SD, 12.2 mm Hg) greater with ramipril than with atenolol (Fig. 1). This value was similar to the reduction in central systolic pressure calculated by Method 1 (14.6 mm Hg; SD, 11.2 mm Hg). No significant difference was found between those values. The reduction in systolic pressure determined by both methods was calculated from the average of all individual responses in systolic pressure with each active therapy.

As we reported previously,10 ramipril caused a greater reduction in brachial systolic pressure (from 140.8 mm Hg at baseline to 128.9 mm Hg at steady state) compared with atenolol (141.4 mm Hg at baseline to 138.9 mm Hg at steady state) (Table 1). This reduction was even greater in aortic systolic pressure with ramipril (from 130.9 mm Hg at baseline to 117.1 mm Hg at steady state), whereas aortic systolic pressure did not change with atenolol (131.2 to 132.0 mm Hg) (Table 1). There was no significant difference between baseline pressure and measured pressure during steady state between ramipril, atenolol, and placebo (Table 1). Significant differences were found between the change in systolic pressure (or net response) measured in both brachial and aortic, due to ramipril, atenolol, and placebo.

The mean difference between central systolic pressures measured from radial (Method 2) and aortic (Method 1), described by the Bland-Altman method, was 1.6 mm Hg (SD, 8.9 mm Hg) (Fig. 2). However, the estimation of central systolic pressure from radial pressure wave (Method 2) appeared less reliable. We were unable to estimate central systolic pressure using Method 2 in one subject: the late systolic shoulder could not be identified, whereas the peak of all aortic pressure waves, used in Method 1 to calculate central systolic pressure, could be readily determined.

Our previous study reported that the reduction of aortic systolic pressure with ramipril over atenolol was 5 to 6 mm Hg greater than recorded in the upper limb.10 The fall of late systolic shoulder in radial pressure wave calculated, as the reduction of aortic systolic pressure (Method 2), was even greater—i.e. 1 to 2 mm Hg more than estimated with the first method (Fig. 3).

To confirm our finding that the two methods were equivalent in practice, we also analyzed a patient database that consisted of recordings from 1505 patients attending an outpatient cardiology department. The majority of these adult patients suffered from ischemic heart disease, hypertension, or cardiac failure, and thus were similar to the groups studied in the previous trials. The mean difference in systolic pressure measured by Methods 1 and 2 was 1.3 mm Hg (SD, 5.0 mm Hg) (Fig. 4).

Discussion

The important message of the REASON and CAFE Trials is that the benefits of ACEIs and CCBs over β-blocker therapy for hypertension are attributable to a...
greater reduction in central rather than brachial systolic pressure. There was some unease about this interpretation, because the SphygmoCor method for calculating aortic pressure employed the same generalized transfer function process under all circumstances, and it was assumed that the drugs utilized did not alter the transfer function. There is strong evidence to support such a view.3,4,11–15 The upper-limb transfer function shows little change with doses of nitroglycerine that cause profound changes in the contour of arterial waves. Such changes as are seen (eg, reduction in peak amplitude of the modulus) with a vasodilator agent would show less, rather than more, effect with a vasodilator such as ramipril on aortic systolic pressure. Modeling studies16,17 showed that relatively large changes in upper-limb vascular properties have little effect on the transfer function and even less on the compound wave generated in the aorta. Further, in the REASON Study,1 carotid pressure waves were recorded together with radial waveforms, and virtually identical results were seen when these carotid waves were used to describe the differential effect of an ACEI-and-diuretic combination versus atenolol. Similar beneficial effects on carotid systolic pressure were seen with a vasodilating

Table 1. Reduction in brachial systolic pressure with ramipril compared with atenolol

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Average 180, 240, and 300 min after therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ramipril</td>
<td>Atenolol</td>
</tr>
<tr>
<td>Brachial SBP (mm Hg)</td>
<td>140.8 (17.1)</td>
<td>141.4 (16.5)</td>
</tr>
<tr>
<td>Aortic SBP (mm Hg)</td>
<td>130.9 (16.9)</td>
<td>131.2 (15.7)</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure.
In the present study, when no transfer process was used, the reduction in central pressure with ramipril compared with atenolol was similar when the direct radial contour technique was used instead of the SphygmoCor process. These data provide further support for the view that such “new” arterial vasodilating antihypertensive agents as ramipril, losartan, amlodipine, and perindopril are superior to atenolol because of their ability to reduce central carotid and aortic pressure to a greater degree than bra-

\[\text{FIG. 2. Bland-Altman plot of differences in individual data points of late radial systolic shoulder as representation of central systolic pressure (Method 2) and of aortic pressure peak as systolic pressure (Method 1). Data were collected from 30 patients during steady-state period (180, 240, and 300 min after drug administration). In total, 87 points were obtained, because the system was unable to identify any late systolic radial shoulder in one subject. There was no significant difference between measures taken at the two sites. Dashed lines indicate } \pm \text{ 2SD.} \]

\[\text{FIG. 3. Left: As a consequence of the differential effects of ramipril and atenolol on central and peripheral systolic pressure, the difference in the effect on aortic compared with upper-limb systolic pressure was underestimated by 5.2 mm Hg between 3 to 5 h after dosing. The difference in the effect on aortic in comparison with late systolic shoulder in radial pressure was similar (7.2 mm Hg) during this period. Error bars indicate } \pm \text{ 1 SD. Right: The difference between values of systolic pressure fall by the two methods described on bottom left panel, with error bars indicating } \pm \text{ 1 SEM. SEM = Standard error of measurements.} \]
chial pressure. A recent study comparing an ACEI (enalapril) versus a diuretic (indapamide) as monotherapy showed the superiority of the ACEI over the diuretic in the reduction of central aortic pressure without change in heart rate.19

References