Pressure-Altering Agents Affect Central Aortic Pressures More Than Is Apparent From Upper Limb Measurements in Hypertensive Patients

The Role of Arterial Wave Reflections

Charalambos Vlachopoulos, Kozo Hirata, Michael F. O’Rourke

Abstract—The pressure pulse does not have the same amplitude in central and peripheral arteries, but it is amplified toward the periphery; the degree of this amplification depends principally on wave reflection. Despite the conventional clinical and epidemiological focus on peripheral pressures, the most physiologically relevant pressures for both cardiac and vascular effects are central pressures. The reflected wave contributes differently in the configuration of the peripheral and central pressure waveform. Therefore, we hypothesized that agents that alter wave reflections could have an unequal effect on central and peripheral pressures in hypertensive patients. Thus, the effect of caffeine was investigated in 10 hypertensive subjects according to a randomized, placebo-controlled, double-blind, crossover design. Central aortic pressures and wave reflection were assessed with applanation tonometry and pulse wave analysis. After caffeine, augmentation index and augmented pressure increased by 4.6%, (P<0.005) and 5.7 mm Hg (P<0.001), respectively, indicating increased effect of wave reflection from the periphery. The increase in aortic systolic pressure was greater compared with that in radial artery pressure at 30 minutes (25%) and marginally greater at 60 minutes (21%). Furthermore, the increase in aortic pulse pressure was greater at 30 and 60 minutes (34% and 40%, respectively). The intensified reflected wave after caffeine was largely responsible for the disparate effect between central and peripheral pressures by boosting the peak of the central and not of the peripheral waveform. This study shows that pressure-altering agents might affect central pressures more than is apparent from the corresponding upper limb values because of the concomitant changes in wave reflection. (Hypertension. 2001;38:1456-1460.)

Key Words: aorta ■ arteries ■ blood pressure ■ caffeine ■ wave reflections

Conventionally, clinical and epidemiological focus is directed toward measurements of peripheral brachial artery pressures. The pressure pulse does not have the same amplitude in central and peripheral arteries, but it is amplified toward the periphery. The degree of this amplification depends on wave reflection and varies at different ages, being greater in younger subjects.1–4 Despite the conventional focus on peripheral pressures, the most physiologically relevant pressures for both cardiac and vascular effects are central pressures. Central systolic pressure is the pressure that the left ventricle has to confront, and central pressure through diastole determines the flow in the coronary arteries. In addition, pulse pressure in the central arteries causes the stretching and consequent mechanical fatigue of the elastic arteries (aorta and carotids), which are predominantly affected with aging and hypertension.5–11

With the exception of extremely stiffened arteries, the reflected wave affects the peak systolic pressure of the central but not the peripheral waveform. We hypothesized that agents that alter wave reflection could have an unequal effect on central and peripheral pressures. Caffeine, the most widely used pharmacologically active substance, is an agent that has an acute pressor effect and alters wave reflection in healthy individuals.12 Thus, in the present study we investigated whether caffeine could affect wave reflection in hypertensive patients and have an unequal effect on central and peripheral pressures.

Methods

Subjects
The study population consisted of 10 treated hypertensive patients (age, 62±7 years; 6 men). The patients were studied while on regular medications, and on each study day, they had taken their morning dose of medication. All patients abstained from caffeine, ethanol, and nicotine for ≥12 hours before each session. The study protocol was approved by the research ethics committee of St Vincent’s Hospital, and all subjects gave written informed consent.

Study Design
The study was performed by use of a randomized, placebo-controlled, double-blind, crossover design. Each subject was studied...
in the morning on 2 separate days (one with the drug and one with placebo) after an overnight fast. As baseline measurements, the patients took either caffeine (250 mg [a dose equivalent to 2 to 3 cups of coffee], No-Doz, Key Pharmaceuticals) or placebo, and all measurements were repeated at 30, 60, 120, and 180 minutes after drug intake.

Measurement of Peripheral and Central Pressures and Wave Reflection Indices

We used a validated, commercially available system (SphygmoCor, PWV Medical)\(^1\)–\(^4\) that employs the principle of applanation tonometry\(^5\)–\(^7\) and appropriate acquisition and analysis software for noninvasive recording and analysis of the arterial pulse. The technique has been described in detail previously.\(^1\)–\(^7\) The radial pressure wave and 180 minutes were recorded with a high-fidelity transducer (Millar Instruments) and were calibrated according to sphygmomanometric systolic and diastolic pressure measured in the brachial artery, because there is practically negligible pressure pulse amplification between the brachial and the radial artery.\(^1\) Noninvasive pressure waveform recordings with this technique are virtually identical to those recorded with a high-fidelity transducer within the artery.\(^1\)–\(^3\) From the radial recordings, the central (aortic) arterial pressure was derived with the use of a generalized transfer function that has been shown to give an accurate estimate of the central arterial pressure waveform and its characteristics.\(^1\)–\(^3\)\(^,\)\(^6\)\(^,\)\(^7\)

Augmentation index (Alx), and augmented pressure (Ap) of the central waveform were measured as indices of wave reflection.\(^1\)–\(^4\)\(^,\)\(^14\)–\(^18\) The merging point of the incident and the reflected wave can be identified on the pressure waveform as an inflection point, which in the majority of the individuals divides the systole into an early and late systolic phase. Ap is the pressure added to the incident wave by the returning reflected one and represents the pressure boost that is caused by wave reflection and with which the left ventricle must cope. Ap is defined as maximum systolic pressure minus pressure at the inflection point. The Alx was defined as the Ap divided by pulse pressure and is expressed as a percentage. Larger values of Alx indicate increased wave reflection from the periphery and/or earlier return of the reflected wave as a result of increased pulse wave velocity (due to increased arterial stiffness) and vice versa.

Statistical Analysis

Data are expressed as mean±SD. \(P<0.05\) was considered statistically significant. Characteristics and resting cardiovascular parameters were compared between the drug and placebo groups using paired \(t\) test. Repeated-measures ANOVA was used to detect statistically significant changes in variables between caffeine and placebo session (caffeine versus placebo×5 periods [baseline and 30, 60, 120, and 180 minutes after drug intake]). Responses between central and peripheral pressures at each time point were compared with paired \(t\) test. Data analysis was performed with SPSS software, version 9.0.

Results

Baseline Characteristics

There were no differences in all baseline characteristics between caffeine and placebo sessions (Table).

Changes After Caffeine or Placebo

Heart Rate

Heart rate decreased during the study but not to a statistically significant extent (response reached a minimum of −1.9 bpm at 30 minutes).

Wave Reflection

Both Alx and Ap increased significantly during the study (\(P<0.005\) and \(P<0.001\), respectively). Response reached a peak at 30 minutes (4.6% and 5.7 mm Hg, respectively) and decreased progressively thereafter (Figure 1). A representative example of a patient is shown in Figure 2.

Pressures

Both central and peripheral systolic pressures were increased with caffeine during the study (\(P=0.01\) and \(P<0.05\), respectively), reaching a peak at 30 minutes. However, this increase was greater in aortic systolic pressures compared with radial artery pressures at 30 minutes (25%; \(P<0.01\)) and marginally greater at 60 minutes (21%; \(P=0.055\) (Figure 3). Neither central nor peripheral diastolic pressures were increased to statistically significant degree with caffeine during the study.

![Response of the Alx and AP of the aortic waveform](http://hyper.ahajournals.org/)

**Figure 1.** Response of the Alx and AP of the aortic waveform during the study. Response is defined as net caffeine effect minus placebo effect at each time point. \(P\) values on the graphs refer to repeated-measures ANOVA significance between the caffeine and the placebo session throughout the study.

**Table 1.** Baseline Characteristics of the Study Sessions

<table>
<thead>
<tr>
<th></th>
<th>Caffeine</th>
<th>Placebo</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>60.4±10.3</td>
<td>59.9±9.9</td>
<td>NS</td>
</tr>
<tr>
<td>Peripheral SP (mm Hg)</td>
<td>133.6±15.8</td>
<td>130.9±14.8</td>
<td>NS</td>
</tr>
<tr>
<td>Peripheral DP (mm Hg)</td>
<td>72.8±6.1</td>
<td>71.3±6.2</td>
<td>NS</td>
</tr>
<tr>
<td>Peripheral PP (mm Hg)</td>
<td>60.8±12.3</td>
<td>59.7±10.2</td>
<td>NS</td>
</tr>
<tr>
<td>Peripheral MP (mm Hg)</td>
<td>94.8±9.2</td>
<td>93.1±9.3</td>
<td>NS</td>
</tr>
<tr>
<td>Central SP (mm Hg)</td>
<td>122.9±14.0</td>
<td>121.0±15.0</td>
<td>NS</td>
</tr>
<tr>
<td>Central DP (mm Hg)</td>
<td>74.3±6.4</td>
<td>72.8±6.3</td>
<td>NS</td>
</tr>
<tr>
<td>Central PP (mm Hg)</td>
<td>48.6±10.2</td>
<td>48.2±10.0</td>
<td>NS</td>
</tr>
<tr>
<td>Central MP (mm Hg)</td>
<td>94.8±9.2</td>
<td>93.1±9.3</td>
<td>NS</td>
</tr>
<tr>
<td>Alx, %</td>
<td>26.8±7.8</td>
<td>26.5±6.2</td>
<td>NS</td>
</tr>
<tr>
<td>Ap, mm Hg</td>
<td>13.4±4.9</td>
<td>13.3±5.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SD. DP indicates diastolic pressure; MP, mean pressure; PP, pulse pressure; and SP, systolic pressure.
The numerical increase was similar between aortic and radial diastolic pressures (Figure 3). Both central and peripheral pulse pressures were increased with caffeine ($P=0.001$ and $P<0.05$, respectively) during the study, reaching a peak at 30 minutes. However, this increase was greater in aortic pulse pressures compared with radial artery pressures at 30 and 60 minutes (34% and 40%, $P<0.005$ and $P<0.05$, respectively) (Figure 3). These differences in the response between central and peripheral pressures can be explained on the basis that the reflected wave contributes differently in the configuration of the peripheral and central pressure waveform (see Figure 2 and Discussion).

Discussion

In the present study, we showed that caffeine, a pressure-elevating agent, increases wave reflection in hypertensive patients and affects central systolic and pulse pressure to a greater extent compared with the corresponding upper limb values. These findings have important pathophysiological, clinical, and epidemiological implications.

Since the advent of sphygmomanometry, clinical and epidemiological focus has been directed toward the measurement of peripheral blood pressure. However, despite the indisputable contribution to the determination and reduction of cardiovascular risk, this reliance on peripheral pressure measurements has shortcomings, which stem from the fact that pressure pulse does not have the same amplitude in central and peripheral arteries. Indeed, the pulse is amplified toward the periphery mainly owing to an increase in systolic pressure and, to a lesser degree, a decrease in diastolic pressure. This amplification of the pulse depends principally on wave reflection and on the nonuniform elasticity of the arteries along the arterial tree, with stiffness increasing as the distance from the aortic valve increases.1–3

Central pressures have a predominate effect on both cardiac and vascular function and integrity. Increased ascending aortic and, hence, left ventricular systolic pressure increases left ventricular metabolic demands and predisposes to left ventricular hypertrophy, impaired diastolic relaxation, and ultimately pump failure. Furthermore, the distending pressure in the central arteries is very important because these elastic arteries (aorta, carotid) are those that are predominantly affected and degenerate in aging and hypertension, in contrast to the less affected muscular peripheral arteries such as the brachial and radial.5–9 Studies have shown that intima-media thickness in the carotid arteries is related to central and not to brachial pulse pressure.10 In addition, in patients with Marfan syndrome, central pulse pressure is a major determinant of ascending aorta diameter, whereas brachial pulse pressure is not.11 Furthermore, it has been shown that the pulsatility of the ascending aortic pressure waveform is a powerful predictor of restenosis after angioplasty.25

Thus, the findings of our study imply that the true impact of pressure-elevating or lowering agents on the cardiovascular system might be underestimated when only peripheral pressure measurements are taken into account. Our results are in parallel with previous studies in which the unequal effect of nitrates on peripheral and central pressures was investigated using invasive techniques.26 Noninvasive pulse wave analysis using applanation tonometry and transfer function is a reliable tool for assessing central hemodynamics. This approach acquires particular importance for long-term studies or studies involving large number of patients.

The difference between central and peripheral pressure response observed in our study can be explained on the basis of wave reflection. With the exception of extremely stiffened arteries, the reflected wave does not affect the peak systolic pressure of the peripheral waveform, whereas it contributes significantly to the formation of the peak systolic pressure in the aorta.1–3 Thus, the reflected wave, which is intensified after caffeine, alters the configuration of the descending systolic part of the peripheral waveform, but it does not affect its peak. In contrast, by boosting the peak systolic part of the aortic waveform, it augments peak systolic pressure, thus leading to an unequal increase in peripheral and central systolic and pulse pressures (Figure 2).

Wave reflection along the arterial tree is an important determinant of the pulsatile load of the heart and is involved...
In conclusion, our results show that caffeine increases wave reflection in hypertensive patients and affects central systolic and pulse pressure to a greater extent compared with the corresponding upper limb values. Given the importance of central pressures for cardiac and vascular effects, these findings indicate that assessment of drug effects should not be confined to peripheral pressure measurements. Pulse wave analysis using applanation tonometry is particularly useful for the monitoring of the true impact of pharmacological interventions.

References

13. Vlachopoulos C, O’Rourke M. Wave Reflections; Central and Peripheral Pressures. 1459


Pressure-Altering Agents Affect Central Aortic Pressures More Than Is Apparent From Upper Limb Measurements in Hypertensive Patients: The Role of Arterial Wave Reflections

Charalambos Vlachopoulos, Kozo Hirata and Michael F. O'Rourke

Hypertension. 2001;38:1456-1460
doi: 10.1161/hy1201.098767

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/38/6/1456

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/