Arterial response during cold pressor test in borderline hypertension

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Laflèche, A. B., B. M. Pannier, B. Laloux, and M. E. Safar. Arterial response during cold pressor test in borderline hypertension. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H409–H415, 1998.—We observed previously that sympathetic activation produced by lower body negative pressure increases pulse-pressure amplification with little change in mean pressure. Whether the cold pressor test (CPT) might produce a similar hemodynamic pattern has been ignored. Ten subjects with borderline hypertension and ten age- and sex-matched normotensive controls were compared to investigate carotid-brachial pulse-pressure amplification (applanation tonometry) and changes in brachial and carotid distensibility (echotracking technique) before and during CPT. The maneuver markedly increased blood pressure without a change in heart rate. Pulse-pressure amplification tended to disappear as a consequence of a larger increase in carotid than in brachial pulse pressure, due to an earlier return of wave reflections at the carotid site. CPT caused a significant decrease in carotid and brachial distensibility. Both results were more pronounced in controls than in borderline hypertensives. Thus CPT reduces pulse-pressure amplification. In humans, this change may greatly influence the calculation of arterial distensibility, although this point is usually minimized in animal experiments. Furthermore, in young subjects, sympathetic stimulus may induce different arterial responses, depending on the mechanism involved: reflex or global nonspecific stimulus.

pulsatile arterial hemodynamics; wave reflection

The blood pressure curve may be divided into two components: a steady component, mean arterial pressure, and a pulsatile component, pulse pressure, which is the difference between peak systolic and end-diastolic blood pressure (29). Whereas mean arterial pressure remains almost constant along the arterial tree, pulse pressure increases markedly from central to peripheral arteries (15, 29). This is due to the changing pattern in the timing of wave reflections when the blood pressure propagates along arterial conduits with a progressive decrease in lumen diameter and an increase in vascular rigidity. We have previously shown (31) that the activation of the autonomic nervous system produced by lower body negative pressure (LBNP) is able not only to cause a slight decrease in mean arterial pressure and a significant increase in heart rate but also to enhance pulse-pressure amplification as a consequence of a substantial decrease in central (carotid) pulse pressure with minimal changes in peripheral (brachial) pulse pressure. However, whether other maneuvers that activate the sympathetic nervous system may cause similar changes in pulse-pressure amplification has never been investigated.

The cold pressor test (CPT) is known to cause a global sympathetic activation in subjects with different levels of baseline sympathetic tone, such as a group of normal subjects and patients with borderline hypertension (23, 36). CPT results in a significant arteriolar vasconstriction, with a subsequent increase in blood pressure and a slight increase in plasma catecholamines but with no change in heart rate (1, 5, 8, 32, 37). Associated changes in the rigidity of large arterial vessels have been observed (10), but, in normal volunteers, major discrepancies have been noted at the site of the radial artery (3, 12). In particular, decreased or increased values of distensibility and compliance have been obtained depending on the intensity of the stimulus and the number of pulse-pressure measurements. Because distensibility is the ratio between pulsatile diameter and pulsatile pressure, it is important to determine whether the sympathetic activation produced by CPT is able to substantially modify pulse pressure and greatly modify pulse-pressure amplification.

In the present report, we investigated a population of subjects with borderline hypertension in comparison with a group of age- and sex-matched normotensive controls. The goal of the study was twofold: 1) to evaluate whether pulse-pressure amplification is modified by CPT, and 2) to determine the changes in arterial diameter and distensibility at the site of two different arteries, a peripheral, medium-sized muscular artery, the brachial artery, and a central elastic artery, the common carotid artery (9). In both cases, distensibility was measured from local pulse pressure and pulsatile diameter using a high-resolution echotracking technique.

METHODS

Patients. Ten Caucasian borderline hypertensive patients (8 males, 2 females) ages 21–58 yr (33 ± 13 yr, mean ± SD) and 10 normotensive subjects (7 males and 3 females) ages 28–45 yr (35 ± 6 yr) were studied in the morning after they had consumed a light, standardized breakfast in a temperature-controlled room (22 ± 2°C). Normotension was defined as auscultatory blood pressure <140/90 mmHg measured at three different times over a 2-wk period. Borderline hypertension (BHT) was defined as two casual blood pressure recordings with a diastolic blood pressure (DBP) ≥90 mmHg during the previous 12 mo, plus at least two measurements with a DBP <90 mmHg (34). No patients had cardiovascular complications or other diseases. None of them had been previously treated with cardiovascular agents. The principal clinical characteristics of the subjects are given in Table 1. All of them gave informed consent, and the study was approved by the Ethical Committee of Broussais Hospital.

Description of study and CPT. Baseline conditions were recorded after 20 min of rest in the supine position. Investiga-
two different waveform components on the recorded pressure: a forward, or incident, wave and a backward, or reflected, wave. The mid-to-late systolic peak is interpreted as the result of the reflected wave coming back from peripheral sites of reflection and is responsible for a late increase in PP and SBP due to the reflected wave. Finally, the ratio of (P_k - P_i) to PP (as a percentage), expressed conventionally as a negative value, is considered a rough indicator of the relative contribution of the reflected pressure wave to the systolic pressure in central arteries, particularly the ascending aorta. On the other hand, the delay from the foot of the pressure wave to the P_i (D_{Pi}) has been interpreted as representing the travel time for the incident wave to reach the peripheral reflecting sites and return (16, 28). Left ventricular ejection time (LVET) was measured from the foot of the pressure wave to the diastolic incisure. Murgto et al. (28) classified the aortic pressure waveform, depending on age and hypertensive status, into three subgroups according to its shape: type A, in which P_i occurs in late systole after a well-defined P_k; and (P_k - P_i)/PP > 0.12; type C, in which P_k occurs in early systole, P_i < P_k, and (P_k - P_i)/PP < 0.12; and type B, which is the same as type A except that 0.0 < (P_k - P_i)/PP < 0.12. Typically, type A is observed in older subjects and hypertensive patients, and type C is observed in normotensive subjects and younger subjects. SBP and PP may increase significantly from central to peripheral arteries. This contrasts with drops in DBP and mean blood pressure (MBP) from the ascending aorta to the radial artery that do not exceed 1–2 mmHg (15, 29). Therefore, carotid SBP and PP were estimated from the carotid pressure waveform, with the assumption that brachial and carotid DBP and MBP were equal, with the use of the HP Sketch Pro Tablet Digitizer connected to a PC. Carotid MBP was computed from a carotid pressure tracing from the area of the carotid pressure waveform, determined from the Carotid Digitizer, and was set equal to brachial MBP (21). Repeatability of measurements has been previously reported (31).

Pressurization was performed with a sphygmomanometer. NS, not significant.

<table>
<thead>
<tr>
<th>Weight, kg</th>
<th>Height, cm</th>
<th>Age, yr</th>
<th>SBP, mmHg</th>
<th>DBP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>72 ± 8</td>
<td>175 ± 11</td>
<td>35 ± 6</td>
<td>118 ± 11</td>
<td>72 ± 9</td>
</tr>
</tbody>
</table>

Values are means ± SD for normal and borderline hypertensive (BHT) subjects. Systolic (SBP) and diastolic blood pressure (DBP) were measured with a sphygmomanometer. NS, not significant.

<table>
<thead>
<tr>
<th>Table 1. Clinical characteristics</th>
<th>Normal</th>
<th>BHT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>72 ± 8</td>
<td>77 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175 ± 11</td>
<td>175 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Age, yr</td>
<td>35 ± 6</td>
<td>33 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>118 ± 11</td>
<td>146 ± 7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>72 ± 9</td>
<td>84 ± 7</td>
<td>&lt;0.01</td>
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</table>
and heart rate minute by minute throughout the CPT using a two-way ANOVA for repeated measures (group, time). In case of significant variations in the time factor, with no group-time interaction, we subsequently performed a t-test at each minute in comparison with the baseline value in each group of patients. A two-way ANOVA for repeated measures (group, test) was performed to analyze the changes in parameters throughout the study. A group-test interaction was the indicator of the difference in behavior between the two groups. Finally, a three-way ANOVA (group, test, arterial site; data not shown) was performed to compare behavior during CPT depending on the measured artery (carotid or brachial). A P value < 0.05 was considered significant.

RESULTS

Table 1 shows the clinical characteristics of both groups of patients. Whereas body weight, height, and age did not differ, the blood pressure measured with a mercury sphygmomanometer significantly differed, although the mean value for DBP was only slightly increased in subjects with borderline hypertension. Table 2 shows the changes in mean values of blood pressure and heart rate (automatically recorded with Dinamap) during the CPT. All the variables of blood pressure (SBP, DBP, MBP, and PP) were significantly higher in patients with BHT (group factor: P < 0.001, P < 0.001, P < 0.001, and P < 0.01, respectively). The basal level of heart rate was higher in patients with BHT than in normotensive subjects (P < 0.01). The CPT increased all variables of blood pressure in both groups (P < 0.001, P < 0.01, P < 0.001, and P < 0.01, respectively), but heart rate did not change during CPT. However, no group-time interaction was observed. Figure 1 shows the SBP, DBP, PP, and heart rate evolution during the CPT minute by minute. The group factor was significantly different for blood pressure but not for heart rate. The latter remained unchanged throughout the test, whereas SBP increased from the first minute until the end of the test. The same finding was observed for PP, but only in normal subjects. DBP also increased from the beginning of the stimulus but returned to baseline after the 3rd minute. There was no group-time interaction, suggesting a similar behavior between groups.

Table 3 shows the hemodynamic changes observed for the carotid artery. Between-group differences were observed for local SBP, DBP, and PP (higher in patients with BHT; P < 0.001, P < 0.01, and P < 0.01, respectively) as well as CSC and DC (P < 0.05 and P < 0.01, respectively). CPT increased local SBP, DBP, PP, (P_k − P_l), and (P_k − P_l)/PP and decreased the transit time of the reflection wave (D tp), the relative stroke change in diameter [(D s − D d)/D d], CSC, and DC. Although CSC seemed to decrease less in patients with BHT (due to differences in diameter behavior), a group-test interaction was only observed for carotid artery D s and D d, which decreased in patients with BHT but increased in normal controls (P < 0.05). The augmentation index [(P_k − P_l)/PP] increased more in normal subjects (interaction: P < 0.05) from a negative value to a positive amplification, suggesting a different hemodynamic behavior between groups at the central artery level.

![Fig. 1. Kinetics of systolic (SBP) and diastolic blood pressure (DBP), pulse pressure (PP), and heart rate during cold pressor test (CPT) compared with baseline in normal subjects (○) and borderline hypertensive (BHT) patients (●). NS, not significant. *P < 0.05; **P < 0.01 vs. baseline. For each variable, interaction is not significant.](http://ajpheart.physiology.org/Downloadedfrom/10.22032/458.png)
Table 3. Carotid artery changes in local pressure, diameter, compliance, distensibility, and reflection wave

<table>
<thead>
<tr>
<th></th>
<th>Normal Baseline</th>
<th>Normal CPT</th>
<th>BHT Baseline</th>
<th>BHT CPT</th>
<th>Group factor</th>
<th>CPT factor</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>D0, mm</td>
<td>6.28 ± 0.48</td>
<td>6.60 ± 0.58</td>
<td>6.51 ± 0.54</td>
<td>6.34 ± 0.63</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>D0, mm</td>
<td>6.74 ± 0.53</td>
<td>7.02 ± 0.60</td>
<td>6.90 ± 0.52</td>
<td>6.69 ± 0.67</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(D0 – D0)/D0, %</td>
<td>7.33 ± 2.45</td>
<td>6.36 ± 2.00</td>
<td>6.13 ± 2.28</td>
<td>5.45 ± 2.62</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>103 ± 8</td>
<td>122 ± 11</td>
<td>133 ± 10</td>
<td>149 ± 8</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>68 ± 6</td>
<td>73 ± 7</td>
<td>84 ± 7</td>
<td>88 ± 9</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>35 ± 4</td>
<td>50 ± 8</td>
<td>48 ± 13</td>
<td>61 ± 11</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>CAC, 10^-2 mm²/mm²</td>
<td>13.04 ± 4.9</td>
<td>8.45 ± 3.05</td>
<td>5.51 ± 2.4</td>
<td>5.86 ± 4.84</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>DC, 10^-3 mm^-1</td>
<td>4.21 ± 1.62</td>
<td>2.65 ± 1.00</td>
<td>2.53 ± 0.75</td>
<td>1.73 ± 0.70</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Pp – Pi, mmHg</td>
<td>-1.61 ± 5.9</td>
<td>6.46 ± 5.74</td>
<td>1.07 ± 8.01</td>
<td>4.81 ± 7.78</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(Pp – Pi)/PP, %</td>
<td>-5.22 ± 16.00</td>
<td>12.12 ± 11.45</td>
<td>3.83 ± 13.72</td>
<td>8.79 ± 12.60</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Dtp, mm</td>
<td>171 ± 25</td>
<td>148 ± 24</td>
<td>149 ± 24</td>
<td>137 ± 22</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LVET, ms</td>
<td>305 ± 19</td>
<td>307 ± 16</td>
<td>293 ± 29</td>
<td>290 ± 31</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>D0/LVET, %</td>
<td>0.56 ± 0.08</td>
<td>0.48 ± 0.07</td>
<td>0.51 ± 0.08</td>
<td>0.48 ± 0.08</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Values are means ± SD. D0 and D0, diastolic and systolic diameter, respectively; CAC, cross-sectional compliance; DC, distensibility coefficient; Pp, maximal peak in blood pressure curve; Pi, inflection point in pressure wave; Dtp, delay to Pi representing transit time of wave reflection; LVET, left ventricular ejection time.

Table 4 shows the hemodynamic changes observed for the brachial artery. Between-group differences were observed for local SBP, DBP, and PP (higher in patients with BHT; P < 0.001, P < 0.001, and P < 0.05, respectively). CPT increased local SBP, DBP, and PP and decreased (D0 – D0), (D0 – D0)/D0, CAC, and DC. For the two latter parameters, there was no group effect. A decrease in arterial distension is also present in normal subjects than in patients with BHT. PP amplification, evaluated from the ratio of brachial to carotid PP, decreased markedly during CPT in both groups and reached similar values during CPT (Fig. 3).

DISCUSSION

CPT is a classic test of sympathetic activity causing arteriolar vasconstriction, resulting in an increase in blood pressure without a change in heart rate. In the present study, we showed that CPT was responsible for a disappearance of pulse pressure amplification as a consequence of an earlier return of carotid wave reflections and an increase in carotid pulse pressure. Arterial distensibility was reduced at the site of the radial and carotid arteries, but a group effect was observed only for the carotid artery. In addition, a lesser response was noted in subjects with BHT than in controls.

CPT and pulse pressure amplification. During the CPT, we have shown that blood pressure increased...
without a significant difference between groups. Although larger increases were found in several studies including borderline hypertensive subjects (18, 24, 25), the present finding has already been shown by other groups (26, 27, 30). Such discrepancies could be explained mainly by methodological aspects, particularly differences in duration of stimulus. However, even when blood pressure was measured minute by minute, we did not observe any difference in responses between groups (see Fig. 1, interaction NS). SBP increased in both groups throughout the stimulus in comparison with baseline, except at the 5th minute of recording in patients with BHT. With regard to DBP, the increase was observed only until the 2nd minute in patients with BHT and the 3rd minute in controls. However, this small difference may be important to consider in terms of calculation of pulse pressure, which increased in normal subjects but not in patients with BHT. In previous studies, differences in intensity of stimulus and in the timing of measurements have been responsible for discrepancies in pulse-pressure calculations and, hence, in compliance determinations of the radial artery (3, 12). In this study, according to average values or minute-by-minute recordings, heart rate did not show any significant variation, as already reported by others (1, 32, 37). Finally, one major limitation of this study is related to the intermediate duration of hemodynamic changes observed during the 5-min CPT. However, even in patients with BHT, the increase in SBP lasted until the beginning of the 5th minute of the test, and our vascular examinations were always finished during the first part of this 5th minute.

One of the major findings of this study is the behavior of the aortic reflection waves during CPT. In normal subjects, as expected (7, 19, 28), the shape of the baseline carotid artery pressure curve was of type C, whereas in patients with BHT, the baseline pressure curve was of type A or B. Expressed in terms of the augmentation index \((\frac{P_k - P_i}{PP})\) and the delay to \(P_i\) (absolute \(D_{tp}\), or relative to LVET), the differences did not reach the statistically significant level. During CPT, all the normal subjects presented a type B or A central pressure curve, and the change in augmentation index was of higher amplitude than in patients with BHT. It is well established that, for a given absorption coefficient of the arterial tree, reflection wave depends on two principal factors: the length of the arterial tree, particularly until the reflection site(s), and the velocity of the wave travel (28, 29). With regard to the length of the arterial tree, the reflection site(s) are considered as the embranchments (particularly at the level of renal arteries) and bifurcation of the aorta (16) and, mostly, the arteriolar network (20, 29), which directly depends on the status of the arteriolar vasconstriction. During CPT, as a consequence of the increase in peripheral resistance, the arteriolar site of reflection becomes closer to the heart and contributes to enhance the impact of the backward wave on central pulse pressure. On the other hand, it is well known that the pulse-wave velocity is influenced not only by the arterial physical properties but also by the level of blood pressure (29). Thus, due to the increase in blood pressure observed during CPT, we can reasonably assume that the pulse-wave velocity increased significantly and contributed to the enhancement of reflection waves. Finally, the global effect of wave reflections in both populations was a significant decrease in \(D_{tp}\) and an increase in \((P_k - P_i)/PP\), indicating an earlier return of the backward pressure wave and causing a higher
carotid systolic peak, which was even more pronounced in normal subjects than in patients with BHT.

Subsequently, the major finding in both populations of subjects was the disappearance of pulse-pressure amplification during CPT (Fig. 3). This hemodynamic pattern is largely different from that observed during the sympathetic activation produced by LBNP (31). During LBNP, an increase in pulse-pressure amplification occurs because of a decrease in carotid pulse pressure in relation to an acceleration of heart rate and a shortening of LVET. During CPT, such a change was totally absent, because there was no significant change in heart rate.

Changes in compliance and distensibility under CPT. Until recent years, in most studies in the literature, compliance was evaluated in vitro from arterial segments on which a steady pressure was applied to determine the static pressure-diameter curve (29). However, during such studies, when a sinusoidal transmural pressure could be applied acutely, it was possible to determine dynamic compliance at different arbitrary levels of steady transmural pressure (2). In a given large artery, dynamic compliance is known to be constantly lower than the corresponding static compliance because of the frequency dependence of the viscosity of the arterial wall (2). Subsequently, when two arteries were simultaneously studied and compared in vitro, the same sinusoidal transmural pressure was applied to determine the dynamic compliance of each artery. This methodology is totally different from that of the dynamic compliance measurements in clinical studies. In a given subject, when two different arteries are compared, this comparison is obviously done for the same mean arterial pressure (which is constant along the arterial tree) but at different values of pulse pressure, because of the presence of pulse-pressure amplification. Using this procedure, we showed that, both before and during CPT, distensibility was reduced in subjects with BHT, but only at the site of the carotid artery, not at the site of the brachial artery. This finding clearly demonstrates that changes in distensibility in vivo are influenced not only by the level of blood pressure but also by the changes in the intrinsic properties of the arterial wall. In a previous study, we compared in vitro the mechanical properties of the muscular radial artery and the muscular elastic internal mammary artery (6). We showed that under norepinephrine stimulation, the isobaric elastic modulus decreased in the former and was unchanged in the latter, suggesting that the sympathetic response is influenced by the baseline status of vascular structure and function. Other hypotheses may arise taking into account the approach of integrative physiology. It is possible that activation of thermoreceptors in the skin during cold exposure sends afferent impulses to the central nervous system, which, in turn, may cause the radial artery (close to the skin) and the carotid artery (away from the skin) to respond in a significantly different manner, although this suggestion results from study of the arteriolar splanchnic bed (33), not large arteries.

In the case of large arteries studied under physiological conditions, pulse pressure is known to be the mechanical signal producing an increase in pulsatile diameter. Thus it is expected that the higher the pulse pressure, the higher the pulsatile change of diameter. In contrast with this simple logic, we observed that during CPT, the increase in pulse pressure was associated with a significant decrease (and not an increase) in pulsatile diameter. Thus, with the activation of the autonomic nervous system produced by CPT, both a mechanical (increase in pulse pressure) and a nonmechanical (decrease in pulsatile diameter) alteration were obtained. In normal subjects, the two mechanisms contributed to the decrease in distensibility during CPT, particularly for the brachial artery (Fig. 2). In subjects with BHT, only the increase in pulse pressure contributed to the decrease in distensibility, resulting in a smaller change in arterial stiffness.

In conclusion, the present study has shown that the interpretation of the distensibility changes of the large arteries is quite different in situations of in vivo and in vitro experiments. In humans the exact role of blood pressure should be evaluated by taking into account the presence of pulse-pressure amplification. Pulse-pressure amplification tends to disappear during CPT as a consequence of a higher increase in carotid than in brachial pulse pressure. Such changes in normal subjects are different from those in patients with BHT, possibly as a consequence of a higher basal sympathetically tone in the latter.

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REFERENCES


