Impact of blood pressure perturbations on arterial stiffness

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ARTERIAL STIFFNESS, PARTICULARLY aortic pulse wave velocity, plays an important role in the pathogenesis of cardiovascular disease (CVD) and is an important independent risk factor for CVD (13, 17). Since changes in arterial stiffness can be detected before the appearance of clinically apparent and overt vascular disease, arterial stiffness can be used as an early marker for subclinical vascular dysfunction (11). There are various techniques used to measure arterial stiffness (16), with each technique measuring a different aspect of arterial stiffness. Thus, these techniques may be affected by behavioral, physiological, and extraneous factors to a different degree. Among these factors, dependence of arterial stiffness on blood pressure (BP) has been a topic of much discussion and debate among investigators working in this field. Indeed, a recent scientific statement from the American Heart Association task force recommended that blood pressure should be recorded at the time of an arterial stiffness measurement and taken into consideration (27).

Arterial stiffness has been implicated as the primary cause of age-related elevation in arterial BP and described as a physiological mechanism underlying hypotensive effects of lifestyle interventions and antihypertensive medications (8, 15). On the other hand, some have questioned the utility of arterial stiffness above and beyond the traditional brachial BP measurement as changes in arterial stiffness are often accompanied by the corresponding changes in BP (10). Most of the available literature focusing on BP dependency on arterial stiffness deal with basal levels of BP or chronic changes with pharmacological or nonpharmacological interventions (19, 20, 29). Currently, it is not clear what extent acute changes in BP are accompanied by corresponding changes in arterial stiffness.

With this information as background, the primary aim of the present study was to determine the effect of acute BP perturbation on various measures of arterial stiffness. There are a number of BP perturbation maneuvers that have been utilized in research settings (18, 25), and these maneuvers use different forms of stress (psychological, physical, and mechanical) to elicit pressor responses. To comprehensively address the stated aim, we used five different BP perturbations. Additionally, we hypothesized that the magnitude of change in arterial stiffness during BP perturbations might be influenced by age (2); therefore, young (20–40 yr) and older (60–80 yr) adults were studied. The working hypotheses were that all measures of arterial stiffness would be dependent on blood pressure and that the magnitude of changes in arterial stiffness parameters induced by acute changes in BP would be variable among various measures of arterial stiffness and widely different age groups.

METHODS

Subjects

A total of 50 subjects were studied. Half of the subjects were young (20–40 yr) and the other half older (60–80 yr). Subjects were recruited from the city of Austin and the surrounding community using flyers and e-mails to various organizations and information sharing. Subjects with overt heart disease, diabetes, or other cardiovascular problems, as assessed by medical history questionnaire, were excluded from study participation. Additional exclusion criteria included pregnancy, chronic smoking, a recent illness or surgery, or any medical intervention in the 12 h before any of the study sessions. Subjects were instructed to abstain from strenuous exercise for 12 h, caffeine consumption for 6 h, and food for 4 h prior to experimental trials. The Institutional Review Board at University of Texas at Austin approved this study. Written informed consent was obtained from all subjects.

Experimental Design

The measurements were performed on two separate visits lasting ~2 h under comfortable laboratory conditions. The two testing ses-
show was composed of two types of slides: (1) congruent color-word slide: equivalent printed color and words of a color (i.e., the word “red” appeared in red font on the slides); and (2) incongruent color-word slide: inequivalent printed color and words of a color (i.e., the word “red” appeared in green font on the slide). To increase the stressfulness of the test, subjects were instructed to comply with the speed of the slide show (one second per slide) and to respond according to the slide type presented. Subjects were provided with a trigger as a method of response in each hand and instructed to respond in their right hands whenever a congruent color-word slide was presented and with the left hand whenever an incongruent color-word slide was presented. The Stroop test proceeded for 2 min, while measurements were obtained. The number of correct answers was not quantified, but the subject was not aware of this during the test.

Isometric handgrip exercise. Subjects performed a 2-min isometric handgrip exercise (HDM-915; Lode Instruments, Groningen, The Netherlands) at 40% of maximal voluntary contraction (MVC). During the test, the force exerted by subjects was shown on a visual display, and the subjects were instructed to hold 40% of their MVC throughout the testing period. Subjects were asked to breathe normally, avoid a Valsalva maneuver (3), and contract only the flexors of the hand to avoid recruiting additional musculature of the upper arm and shoulder.

Cold pressor test. Each subject submerged one foot in ice water (2–5°C) for 2 min (4). The foot was selected, rather than the hand, to stimulate maximum hemodynamic and sympathetic responses (18). Subjects were instructed to breathe normally, avoid a Valsalva maneuver (3), and maintain relaxation.

Measurements

The following arterial stiffness indices were measured in the present study.

Cardio-ankle vascular index. Unilateral brachial BP, ankle BP, and heart rate were measured simultaneously by using oscillometric pressure sensor cuffs, electrocardiograms, and phonocardiograms (VaSera VS-1000, Fukuda Denshi, Tokyo, Japan). Cardio-ankle vascular index (CAVI) was calculated by incorporating the stiffness parameter $\beta$, which is known to be a BP-independent measure of arterial stiffness, into an equation (23). The equation to calculate CAVI was $\text{CAVI} = \frac{\ln(\text{systolic BP}/\text{diastolic BP})}{\text{PWV}^2} + b$, where $a$ and $b$ are scale conversion constants to match CAVI values with aortic PWV, $p$ is blood density, and PWV is pulse wave velocity from the aortic valve to the ankle.

CAVI is a relatively new measure, and its reliability has not been well established. Accordingly, the measurements of CAVI were taken 3 times each by two different investigators at the beginning of each testing day to obtain interobserver and intraobserver reliability.

Pulse wave velocity. Both carotid-femoral pulse wave velocity (cPWV) and brachial-ankle pulse wave velocity (baPWV) were simultaneously measured by the vascular testing device (VP-2000, Omron Healthcare, Kyoto, Japan). Arterial examination tonometry sensors incorporating an array of 12 micropiezoresistive transducers were placed on the carotid and femoral arteries to acquire pulse pressure waves (1). In addition, oscillometric pressure sensor cuffs were placed unilaterally on arm and ankle, electrocardiogram sensors were attached to both wrists, and a phonocardiogram was placed above the sternum. baPWV was obtained from the oscillometric pressure sensor cuffs. cPWV was obtained from distance divided by the time delay of the pulse wave. Distance traveled by pulse waves for cPWV was determined by the measurement of body surface distance from the site of transducer placement on the carotid and femoral arteries with a segmenter specifically constructed for pulse wave velocity (PWV) studies. For baPWV, pulse wave travel distance was calculated automatically on the basis of one’s height.

Carotid artery compliance. The simultaneous measurement of ultrasound imaging of the common carotid artery and application tonometrically obtained arterial pressure waveforms from the contralateral carotid artery allows noninvasive determination of arterial compliance (26). Common carotid artery diameter was measured from the images derived from an ultrasound machine equipped with a high-resolution linear array transducer (Philips iE33 Ultrasound System).

Table 2. Intra- and inter-observer reliability tests of cardio-ankle vascular index

| Test as a method of response in each hand and instructed to respond in their right hands whenever a congruent color-word slide was presented | 95% Confidence Interval |
|---|---|---|
| CV | ICC | Minimum | Maximum |
| Intra-observer reliability | 3.4% | 0.99* | 0.98 | 0.99 |
| Inter-observer reliability | 2.4% | 0.98* | 0.98 | 0.99 |
Fig. 1. Changes in mean blood pressure (BP) during vascular reactivity tests. Data are expressed as Δ means ± SE. HUT, head-up tilt; HDT, head-down tilt; MS, mental stress; IHG, isometric hand grip; CPT, cold pressor test. *P < 0.05 vs. HUT, †P < 0.05 vs. HDT, ‡P < 0.05 vs. MS.

Table 3. Relations between changes in arterial stiffness and mean blood pressure during vascular reactivity tests

<table>
<thead>
<tr>
<th></th>
<th>Δ Mean Blood Pressure, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Head-Up Tilt</td>
</tr>
<tr>
<td>Δ CAVI</td>
<td>NS</td>
</tr>
<tr>
<td>Δ cfPWV</td>
<td>NS</td>
</tr>
<tr>
<td>Δ baPWV</td>
<td>0.32*</td>
</tr>
<tr>
<td>Δ Arterial compliance</td>
<td>NS</td>
</tr>
<tr>
<td>Δ Elastic modulus</td>
<td>NS</td>
</tr>
<tr>
<td>Δ Arterial distensibility</td>
<td>NS</td>
</tr>
<tr>
<td>Δ β-stiffness index</td>
<td>0.32*</td>
</tr>
<tr>
<td>Δ Young’s modulus</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are Pearson correlation coefficients. *P < 0.05. CAVI, cardio-ankle vascular index; cfPWV, carotid-femoral pulse wave velocity; baPWV, brachial-ankle pulse wave velocity; NS, not significant.

Table 2 illustrates the reliability of CAVI measurements. Coefficients of variation of intraobserver and interobserver reliability were 3.4 and 2.4%. The intraobserver and interobserver reliability test showed that intraclass correlation coefficients were 0.99 and 0.98.

Figure 1 shows changes in mean BP to various BP perturbation tests. As shown in Table 3, changes in CAVI, cfPWV, baPWV, and elastic modulus were significantly associated with changes in mean BP in the pooled conditions. Changes in arterial compliance, elastic modulus, arterial distensibility, β-stiffness index, and Young’s modulus were not significantly related to changes in mean BP. When each index of arterial stiffness was plotted with mean blood pressure, all of the arterial stiffness indices, including CAVI (r = 0.50), cfPWV (r = 0.51), baPWV (r = 0.61), arterial compliance (r = −0.42), elastic modulus (r = 0.52), arterial distensibility (r = −0.32), β-stiffness index (r = 0.19), and Young’s modulus (r = 0.35) were related to mean BP (r < 0.01) (Fig. 2). Because heart rate is known to modulate parameters of arterial stiffness, we performed partial correlational analyses after partialing out the changes in heart rate. In general, many of the correlations between arterial stiffness measures and blood pressure remained statistically significant (Table 4).

To determine whether the associations between blood pressure and arterial stiffness indices are modulated by age and sex, we stratified the data by age and sex and presented the data in Table 5. In general, the strengths of associations were generally greater in males than in females. For CAVI, cfPWV, and baPWV, young subjects had stronger association with changes in mean BP than in older subjects.

DISCUSSION

The most salient finding of the present study is that all of the arterial stiffness indices examined had some degree of BP dependency to various forms of pressor tasks. This was true for
indices of arterial stiffness that are thought to be BP independent, the β-stiffness index, and CAVI.

One of the strengths of the present study is the use of various types of pressor tests employed. These maneuvers use different forms of stress to elicit BP responses. For instance, mental stress is psychological, cold pressor test is physical, and isometric handgrip is mechanical. A total of five different BP maneuvers were utilized to comprehensively evaluate the effects of acute changes in BP on arterial stiffness. Each test produced different magnitudes of pressor responses, with the most profound increases in BP observed during the cold pressor test. In conjunction with the BP changes, we also observed corresponding changes in most of the arterial stiffness indices during each maneuver.

When various levels of BP induced by pressor tests were plotted against arterial stiffness, all of the arterial stiffness

![Graphs showing relationships between arterial stiffness indices and mean BP](image)

Fig. 2. Relationship between arterial stiffness indices and mean BP. CAVI, cardio-ankle vascular index; cfPWV, carotid-femoral pulse wave velocity; baPWV, brachial-ankle pulse wave velocity.
indices examined in the present study demonstrated significant associations with BP. The strongest association was obtained with baPWV (r = 0.61), and the lowest association was obtained with β-stiffness index (r = 0.19). When the data were analyzed by plotting changes in BP and the corresponding changes in arterial stiffness, CAVI, cPWV, baPWV, and elastic modulus showed significant associations with changes in BP in the pooled population, whereas no such relations were observed for arterial compliance, arterial distensibility, β-stiffness index, and Young’s modulus. These results suggest that some measures of arterial stiffness are more affected by acute changes in BP than others and that the magnitude of BP dependency varies widely among various measures of arterial stiffness.

CAVI has been proposed as an arterial stiffness indicator that is independent of BP (20). The original study from Japan has reported no association between CAVI and BP (r = 0.01–18), whereas baPWV was significantly associated with BP (r = 0.34–0.46) (20). Since then, a number of investigators have confirmed the observation that CAVI was less dependent on BP compared with other arterial stiffness indices (7, 9, 24). CAVI was originally developed by incorporating β-stiffness index, which is thought to be a BP-independent measurement of arterial stiffness (24). Indeed, in a recent study, the incorporation of β-stiffness index substantially reduced the BP dependency on PWV (29). In marked contrast to these previous studies, the present study demonstrated that CAVI was dependent on mean BP whether it is expressed as absolute levels of BP or changes in BP. It should be noted that the previous studies utilized chronic or basal BP, whereas the present study used BP that was changed with acute BP perturbations.

Table 5. Associations between changes in arterial stiffness indices and mean blood pressure stratified by age and sex

<table>
<thead>
<tr>
<th>Δ Mean BP, mmHg</th>
<th>Male</th>
<th>Female</th>
<th>Young (20–40 yr)</th>
<th>Older (60–80 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAVI, AU</td>
<td>0.42*</td>
<td>0.26*</td>
<td>0.45*</td>
<td>0.22*</td>
</tr>
<tr>
<td>cPWV, cm/s</td>
<td>0.44*</td>
<td>0.29*</td>
<td>0.56*</td>
<td>0.23*</td>
</tr>
<tr>
<td>baPWV, cm/s</td>
<td>0.44*</td>
<td>0.26*</td>
<td>0.45*</td>
<td>0.31*</td>
</tr>
<tr>
<td>Arterial compliance, cm/mmHg</td>
<td>NS</td>
<td>NS</td>
<td>0.72*</td>
<td>NS</td>
</tr>
<tr>
<td>Elastic modulus, mmHg</td>
<td>0.30*</td>
<td>NS</td>
<td>0.27*</td>
<td>NS</td>
</tr>
<tr>
<td>Arterial distensibility, mmHg⁻¹</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>β-stiffness index, AU</td>
<td>NS</td>
<td>−0.28*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Young’s modulus, mmHg/cm</td>
<td>NS</td>
<td>NS</td>
<td>0.22*</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are Pearson correlation coefficients. *P < 0.05.

As expected, lowest associations with BP were observed in β-stiffness index, though its BP dependency was evident during several pressor tests. The original assumption involved in the β-stiffness index is a simple exponential relation between the intraluminal pressure and the distension of arteries (6). However, the exponential relation was constructed in a limited BP range obtained in a healthy normal population, and the validity has been questioned as to whether it is applicable to other populations (12). Indeed, highly significant associations between BP and β-stiffness index have previously been reported in a variety of patient populations (12). Interestingly, blood pressure perturbations affected CAVI and β-stiffness index differently, even though CAVI was calculated by incorporating the stiffness parameter β into an equation. However, CAVI differs from the β-stiffness index in a number of ways. For example, the β-stiffness index is a measure of local arterial stiffness determined from the pulsatile changes in arterial diameter and blood pressure. On the other hand, CAVI is a measure of segmental arterial stiffness that is derived from pulse wave velocity. While the β-stiffness index is an index of central arterial stiffness, CAVI may reflect a combination of central and peripheral artery stiffness.

Prevalence of hypertension increases markedly with advancing age in both men and women (5). Men are generally at greater risk for developing hypertension than age-matched women (5). Accordingly, we stratified the data for age (young and older) and sex (men and women) and performed separate statistical analyses. In general, the associations between changes in arterial stiffness and BP appear larger for men than for women and for young than for older in many of the arterial stiffness indices. These results are consistent with previous studies reporting that BP reactivity is modulated by both age and sex (21, 28). Although the exact reasons are not clear, it may be related to a “ceiling effect” due to higher arterial stiffness values at baseline.

The simplest premise of the present study is that any changes in arterial stiffness would be attributed to changes in BP induced by pressor tests. But these changes in arterial stiffness and BP could be independent. For instance, sympathoexcitatory stimuli induced by BP reactivity tests can act on the smooth muscle cells surrounding the large elastic arteries and stiffen arteries (14). The same vasoconstrictor tone can stimulate smooth muscle cells on the peripheral muscular arteries and increase vascular resistance and increase mean BP via the Ohm’s law (14). Thus, it should be noted that changes in...
arterial stiffness may not be epiphenomenon of BP changes induced by various pressor tests.

There were several limitations that should be taken into consideration. First, because only apparently healthy subjects were included in the present study, the results may not be extrapolated to patient populations. Second, vascular reactivity tests were neither measured simultaneously nor randomized in this study. The present protocol provided substantial procedural challenges in placing all of the measurement devices on a given subject. In spite of a number of pilot studies conducted, it was not possible to accommodate everything in one testing session. Additionally, some vascular reactivity tests, such as the cold pressor test, induces a prolonged BP change and had to be placed at the end of the testing session. However, in an attempt to establish the reliability of pressor responses, we performed isometric handgrip or cold pressor test twice in different testing sessions and found that there were no significant differences in pressor responses between the two testing sessions. Furthermore, although vascular reactivity tests were not all randomized in this study, each two sessions of isometric handgrip and cold pressor test was randomized, which eliminates the order effects.

In summary, the results of the present study indicate that BP changes in response to various forms of pressor stimuli were associated with the corresponding changes in arterial stiffness indices examined and that the strengths of associations varied widely depending on which arterial stiffness indices were examined.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


REFERENCES