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Validation of a Generalized Transfer Function to Noninvasively Derive Central Blood Pressure During Exercise

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Abstract—Exercise brachial blood pressure (BP) predicts mortality, but because of wave reflection, central (ascending aortic) pressure differs from brachial pressure. Exercise central BP may be clinically important, and a noninvasive means to derive it would be useful. The purpose of this study was to test the validity of a noninvasive technique to derive exercise central BP. Ascending aortic pressure waveforms were recorded using a micromanometer-tipped 6F Millar catheter in 30 patients (56±9 years; 21 men) undergoing diagnostic coronary angiography. Simultaneous recordings of the derived central pressure waveform were acquired using servocontrolled radial tonometry at rest and during supine cycling. Pulse wave analysis of the direct and derived pressure signals was performed offline (SphygmoCor 7.01). From rest to exercise, mean arterial pressure and heart rate were increased by 20±10 mm Hg and 15±7 bpm, respectively, and central systolic BP ranged from 77 to 229 mm Hg. There was good agreement and high correlation between invasive and noninvasive techniques with a mean difference (±SD) for central systolic BP of −1.3±3.2 mm Hg at rest and −4.7±3.3 mm Hg at peak exercise (for both r=0.995; P<0.001). Conversely, systolic BP was significantly higher peripherally than centrally at rest (155±33 versus 138±32 mm Hg; mean difference, −16.3±9.4 mm Hg) and during exercise (180±34 versus 164±33 mm Hg; mean difference, −15.5±10.4 mm Hg; for both P<0.001). True myocardial afterload is not reliably estimated by peripheral systolic BP. Radial tonometry and pulse wave analysis is an accurate technique for the noninvasive determination of central BP at rest and during exercise. (Hypertension. 2006;47:1203-1208.)

Key Words: exercise • blood pressure • arteries • blood pressure monitoring • hypertension, arterial

S"Some studies have found that blood pressure (BP) recorded during exercise provides more powerful prognostic information compared with measures taken at rest. An exaggerated brachial systolic BP (SBP) response during an exercise stress test is a marker of cardiovascular disease that predicts the future onset of hypertension,1-3 stroke,4 and cardiovascular mortality.5-7 The physiological mechanisms underlying these findings have not been elucidated but may be related to stiff large arteries augmenting pressure wave reflections and increasing left ventricular afterload during physical activity, even at light intensities, such as those of daily living.

Despite the accumulation of this evidence using peripheral pressure, there are important limitations of brachial cuff sphygmomanometry. In particular, central and brachial SBP may differ widely between individuals (eg, <5 to >20 mm Hg) because of differences in demographic (eg, age, height, and gender) and hemodynamic (eg, arterial stiffness and pattern of left ventricular ejection) factors affecting wave reflection through the arterial tree.8 During exercise, heart rate increases significantly, and the central to peripheral SBP disparity is exacerbated such that pressure differences may exceed 80 mm Hg.9 In addition, recent work has demonstrated important discordance between peripheral and central BP, especially in relation to treatment response.10 Therefore, a noninvasive method to determine central BP during exercise may provide additional information.

The central arterial pressure waveform can be derived noninvasively from the radial pulse using applanation tonometry and application of a generalized transfer function, which corrects for pressure wave amplification in the upper limb.8 Such a device is commercially available, and derived central waveforms have been validated in various hemodynamic settings1-3 but not in the context of aerobic exercise. Because determination of exercise central BP may be of clinical value, we sought to test the validity of its noninvasive measurement using a standard clinical device.

Methods

Subjects
The study population was composed of 30 patients (21 men) undergoing a diagnostic coronary artery angiogram via a femoral...
The study involved acquisition and comparison of resting and exercise pressure waveforms recorded from the ascending aorta: (1) directly by catheter (position fluoroscopically confirmed); (2) derived from radial artery pressure waveforms and pulse wave analysis; and (3) the radial artery directly by applanation tonometry. The transfer function, which converts radial to aortic pressure waveforms, is the ratio in amplitude and phase of radial and aortic pressure harmonics. The generalized transfer function of the pressure waveform, \( H(\omega) = \frac{P_A(\omega)}{P_B(\omega)} \), where site A is the ascending aorta and site B is the radial artery, \( \omega \) is the angular frequency, \( M_A(\omega) \) and \( M_B(\omega) \) are the moduli and \( \varphi_A(\omega) \) and \( \varphi_B(\omega) \) are the phase angles of respective pressure waves.

**Pressure Waveform Acquisition**

A Millar model SSD-1008, 6F micromanometer-tipped luminal catheter (Millar Instruments) with a 0.025-in guide wire was used for all of the procedures. For each study, catheter pressure signals were calibrated to 0 and 100 mm Hg using a Millar transducer control unit (models TC-510 or TCB-500, Millar Instruments). Radial pressure waveforms were acquired by servocontrolled applanation tonometry (Colin CBM-7000, Colin Corp). Pulse wave analysis was used to synthesize an ascending aortic pressure waveform from the radial pulse using customized software (SphygmoCor 7.01, AtCor Medical) with a previously validated generalized transfer function. All of the waveforms were digitized at 200 Hz (ML785 PowerLab/8SP, ADInstruments) and saved using Chart 5 for Windows software (ADInstruments) for offline analysis. For each of the 3 waveforms, a simultaneous 12-s period at rest and during exercise was ensemble averaged and analyzed at 128 Hz using the SphygmoCor 7.01 software.

The radial pressure waveform was calibrated using the catheter mean arterial pressure (MAP) and diastolic BP (DBP). The MAP was derived by integration of the central pressure waveform from the ensemble averaged data. Pulse pressure (PP) was calculated as SBP–DBP. On the central pressure waveform, the subendocardial viability ratio was calculated by the ratio of diastolic to systolic pressure-time integral, which is a measure of subendocardial perfusion capacity. Because differences between central and peripheral BP may have clinical significance, we also assessed PP amplification by the ratio of radial:catheter central PP.

**Generalized Transfer Function**

Using Fourier frequency analysis, each pressure waveform consists of series of harmonic (sinusoidal) waves at multiples of heart rate frequency. The transfer function, which converts radial to aortic pressure waveform, is the ratio in amplitude and phase of radial and aortic pressure harmonics. The generalized transfer function of the pressure pulse between sites A (eg, aorta) and B (eg, radial artery) is defined by Karamanoglu et al as follows:

\[
H_A(\omega) = \frac{P_A(\omega)}{P_B(\omega)}
\]

where \( P_A(\omega) \) and \( P_B(\omega) \) represent the frequency domain of the pressure wave at sites A and B, respectively [ie, \( P_A(\omega) = M_A(\omega) e^{j\varphi_A(\omega)} \) and \( P_B(\omega) = M_B(\omega) e^{j\varphi_B(\omega)} \)], where site A is the ascending aorta and site B is the radial artery, \( \omega \) is the angular frequency, \( M_A(\omega) \) and \( M_B(\omega) \) are the moduli and \( \varphi_A(\omega) \) and \( \varphi_B(\omega) \) are the phase angles.

**Statistics**

Data were analyzed using SPSS software version 11.0 (SPSS Inc). Pearson product–moment correlation coefficient (\( r \)) was used to determine associations between variables. Bland–Altman plots were used to assess agreement between methods. Dependent t tests were used to compare means. Data were expressed as mean±SD, and \( P<0.05 \) was considered significant.

**Results**

Baseline and exercise data are presented in Table 2. From rest to exercise, there was a significant increase in central SBP, central PP, and heart rate (\( P<0.001 \) for all), which were raised by an average of 26±14 mm Hg (total range, 77 to 229 mm Hg), 12±9 mm Hg (total range, 34 to 110 mm Hg), 20±10 mm Hg (total range, 50 to 179 mm Hg), and 15±7 bpm (total range, 48 to 102 bpm), respectively. Radial SBP and PP were also significantly elevated during exercise compared with rest (\( P<0.001 \) for both).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD or n, Range in Brackets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56±9 (37 to 76)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170±8 (146 to 185)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84±16 (53 to 134)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>155±33 (95 to 214)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>77±27 (31 to 134)</td>
</tr>
<tr>
<td>Angiogram result, normal/single/double/triple vessel disease</td>
<td>15/7/2/6</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.0±1.0</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.2±1.3</td>
</tr>
<tr>
<td>Medications</td>
<td>β-Blocker 25, ACE inhibitor 14, Calcium channel blocker 3, Statin 26</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Hypertension 14, Obesity, body mass index &gt;30 kg/m² 6, Cigarette smoking, never/current/former 9/8/13, Hyperlipidemia 20, Type 2 diabetes mellitus 4</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme. Coronary artery disease was denoted by >70% stenosis. Patients were regarded as a current cigarette smoker if they had stopped in the preceding 12 months. BP data were recorded supine from the radial artery waveform at the time of angiogram.
Patients exercised at a heart rate that was equal to 48±7% (range, 37% to 71%) of maximal age-predicted heart rate (220−age). The rate pressure product (heart rate×radial SBP) was increased from resting values by 69% (9924±2965 to 14325±3873; \( P<0.001 \)). After the angiogram procedure and before the start of exercise, 18 patients were hypertensive (radial BP >140/90 mm Hg), and 10 patients had a hypertensive response to exercise (radial BP ≥220/105 mm Hg for men and 195/105 mm Hg for women).

Comparison of Invasive and Noninvasive Central Pressure Measurements
As shown in Table 2, at rest and during exercise there was high correlation and excellent agreement between directly recorded and transfer function–derived aortic SBP, DBP, end systolic pressure, subendocardial viability ratio, and ejection duration. During exercise, the mean difference between direct and derived measures of central PP was marginally higher because of the combination of slight overestimation for DBP and underestimation of SBP. However, the correlation between methods for central PP remained high. Subgroup analysis of resting and exercise central SBP in patients receiving β-blocker (n=25) or angiotensin-converting enzyme inhibitor (n=14) medication showed similar mean results (ie, <1 mm Hg) to the total population.

Figure 1 depicts the relationship between catheter and transfer function–derived central SBP for resting and exercise conditions. These data are also represented by Bland–Altman plot in Figure 2. Example recordings of the direct and transfer function–derived pressure waveforms in a female patient at rest and before the start of exercise are depicted in Figure 3. For this waveform series, the average catheter and derived SBP was 151±4 and 147±5 mm Hg, respectively, at rest (mean difference, −5±2 mm Hg) and 197±4 and 196±6 mm Hg, respectively, during exercise (mean difference, −1±4 mm Hg).

![Figure 1. Relationship between catheter and synthesized central (ascending aortic) SBP at rest (●) and during exercise (○): \( y=0.966x+2.191; R^2=0.990; P<0.001 \). The dotted line is the line of identity.](image_url)
Correlation of Central and Peripheral Pressure Measurements

There was discordance between central and peripheral BP measures at rest and during exercise. At baseline, radial SBP was significantly higher than catheter central SBP (155±33 versus 138±32 mm Hg), and radial PP was significantly higher than catheter central PP (78±18 versus 61±18 mm Hg; for both, P<0.001 and mean difference, −16.3±9.4 mm Hg). Similarly, during exercise, radial SBP and PP were significantly higher than catheter central SBP (180±34 versus 164±33 mm Hg; P<0.001) and central PP (89±21 versus 74±18 mm Hg; P<0.001; for both, P<0.001 and mean difference, −15.5±10.4 mm Hg), respectively.

Although central and radial PP increased during exercise, there was a significantly greater percentage increase in central compared with radial SBP (20±12% versus 17±12%; P<0.05). Overall, there was a significant decrease in the PP amplification ratio from rest (1.30±0.2) to exercise (1.22±0.15; P<0.01). However, there was considerable variation in the PP amplification response to exercise, with a drop occurring in 20 patients (mean, −10±8%) and an increase evident in the remaining 10 patients (mean, 4±4%; total range, −29% to 11%).

Discussion

In this study of patients undergoing diagnostic coronary angiography, central waveforms derived by application of transfer function to radial tonometry correlated closely with those obtained invasively by high-fidelity micromanometer-tipped catheter at rest and during supine cycling. The tonometric technique was able to provide an accurate reproduction of central BP across a broad range of heart rates and MAPs in patients of different age, gender, height, and disease states. In contrast, the central BP changes were unlike the pressure changes recorded at the radial artery during exercise, indicating that the peripheral BP response is not a good reflection of the actual pressure load at the heart.

Consistency of Transfer Function Under Different Hemodynamic Conditions

A number of previous studies have tested the effectiveness of a generalized transfer function to estimate central BP after hemodynamic alterations induced by vasoactive drugs or maneuvers including Valsalva, abdominal compression, and temporary occlusion of the inferior vena cava. Using a fluid-filled manometer system of known frequency response, Pauca et al found excellent agreement between invasive and transfer function–derived central pressures at rest, which were results similar to our own and those of others. Karamanoglu et al conducted a retrospective analysis of pressure waveforms in which the amplitude of transfer function between the ascending aorta and the radial artery was compared between different published data, including those in which aortic and radial intra-arterial pressure waves were recorded in humans during exercise. Despite the exercise-induced cardiovascular changes, the same amplification to that of rest or other hemodynamic transients was reported to ≤6 Hz, with scatter >4 Hz. Considering that most of the power (ie, ≈96%) of the ascending aortic pressure pulse is contained in...
the first 4 harmonics between 0.8 and 4.0 Hz, these data strongly suggested that the transfer function in the upper limb was not appreciably altered during exercise, implying that central BP could be reliably estimated. Our results, which are the first to validate the derivation of central pressure waveforms from tonometry during exercise, are consistent with these reported findings.

**Effects of Exercise on Central and Peripheral BP**

Aerobic exercise elicits a constellation of hemodynamic changes, including increased MAP and cardiac output (because of positive chronotropic and inotropic effects), in addition to idiosyncratic changes in the vascular tone of different vessel beds (eg, upper versus lower limbs). The PP between the ascending aorta and the brachial/radial artery is also greatly amplified because of a higher relative increase in peripheral compared with central SBP. Indeed, the SBP difference may be >80 mm Hg during maximal aerobic activity. However, the relationship between central and peripheral SBP (ie, the degree of amplification) is subject to considerable individual variation and depends on several factors, including the vasodilatory state of upper limb muscular arteries, as well as the intensity and duration of exercise. Therefore, whereas the use of traditional cuff sphygmomanometry during exercise has been shown to provide useful prognostic information, it may give a poor approximation of central systolic loading between individuals. Our results emphasize the potential complimentary role of radial tonometry to acquire closer estimates of true afterload.

**Study Limitations**

Because our aim was to test the validity of the generalized transfer function, we calibrated the radial waveform by invasive recordings of central MAP and DBP rather than brachial auscultatory measures. This recommended methodology, which has been used by others, removes the confounding influence of the less accurate brachial cuff recordings. On the other hand, this approach does not reflect how central pressure would be estimated during exercise. Also, we did not screen patients for the presence of upper extremity obstructive atherosclerosis and cannot rule this out as a possible confounding variable.

During exercise, central DBP was slightly overestimated by the transfer function. A previous invasive intra-arterial study has shown radial DBP to be 7% lower than central DBP during submaximal supine cycling. It is, therefore, likely that the exercise radial waveform has been calibrated with a DBP higher than the actual value in the radial artery (beyond the normal 1- to 3-mm Hg difference at rest). This error...
would have introduced an overestimation of derived central DBP together with an underestimated in the amplitude of the central pressure wave during exercise. Indeed, compared with the catheter, such an effect was observed. Importantly, derived values were still within limits of accepted standards for central SBP and DBP (±5 mm Hg or less and SD 8 mm Hg or less).19 This limitation could be resolved by calibrating the radial waveform with invasive radial recordings, although this was not clinically indicated in our study population and would have exposed participants to unacceptable additional risk.

Perspectives
The lack of concordance between central and brachial SBP and PP is well established, with many studies showing the clinical and prognostic importance of the central pressure waveform (derived by radial or carotid tonometry) beyond BP measured at the upper arm.20–24 In some studies, an excessively high brachial SBP response to exercise seems to hold more predictive value for cardiovascular mortality and morbidity than resting brachial BP.4–7 An elevated brachial BP with exercise may be a consequence of excessive upper limb pressure amplification or increased central BP, with the latter being of more pathophysiological importance. The potential clinical significance of the pressure disparities between the heart and upper arm during exercise was raised >35 years ago16 but has never been followed up with larger-scale studies of exercise central BP. Taken together, these findings draw attention to the need to assess the predictive value of central compared with peripheral BP changes during exercise. The results of this current study confirm the efficacy of radial tonometry and pulse wave analysis as a clinical tool for this purpose.

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