Aortic stiffness affects the coronary blood flow response to percutaneous coronary intervention

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Leung, Michael C. H., Ian T. Meredith, and James D. Cameron. Aortic stiffness affects the coronary blood flow response to percutaneous coronary intervention. Am J Physiol Heart Circ Physiol 290: H624–H630, 2006. First published September 2, 2005; doi:10.1152/ajpheart.00380.2005.—We examined the hypothesis that a stiff aorta is associated with reduced coronary blood flow (CBF) and CBF response to percutaneous coronary intervention (PCI). Aortic mechanical properties are thought to affect CBF, with increased stiffness associated with decreased coronary perfusion. Animal studies are conflicting, and human evidence is lacking. Even less is known about the effects of aortic stiffness on the CBF response to successful PCI. In 18 subjects undergoing elective PCI, a Doppler velocity guidewire was positioned proximal to a severe coronary stenosis to measure resting and adenosine-induced hyperemic CBF before and after PCI. Stenosis severity was assessed with Doppler velocity and pressure guidewires. Aortic mechanical indexes measured included central pulse-wave velocity (cPWV) and central pulse pressure (cPP). PCI was successful in all subjects (diameter stenosis: 88 ± 9% to 2 ± 7%; coronary flow velocity reserve: 1.8 ± 0.6 to 3.0 ± 0.8; fractional flow reserve: 0.57 ± 0.19 to 0.92 ± 0.06; all P < 0.001). With the adjustment for age and gender, resting and hyperemic CBF were inversely related to cPWV irrespective of the presence of stenosis (resting: before PCI, r² = 0.452, P < 0.01; after PCI, r² = 0.261, P = 0.043; hyperemic: before PCI r² = 0.503, P = 0.005; after PCI r² = 0.500, P = 0.002), whereas they were related to cPP in absence of stenosis (resting: r² = 0.368, P = 0.022; hyperemic: r² = 0.370, P = 0.016). Hyperemic CBF response (P = 0.005) and hyperemic CBF improvement from PCI (P = 0.025) were less marked in a stiff aorta than in a compliant aorta. A stiff aorta is associated with a reduction in CBF, a lower hyperemic CBF response, and may reduce the improvement in hyperemic CBF after successful PCI.

aorta; elasticity; angioplasty; ischemia

SEVERAL DECADES of epidemiological studies have suggested that systolic and diastolic blood pressures, pulse pressure (2, 10), and more recently, central pulse-wave velocity (cPWV) are strong independent predictors of cardiovascular mortality (13, 16) as well as acute coronary events (4). Aortic stiffness is thought to adversely affect coronary blood flow (CBF). This has been accepted on the basis of an inferred understanding of the hemodynamic relationship between a stiff aorta and CBF. A stiff aorta is thought to result in an early return of the reflected arterial pulse wave with augmentation of the systolic blood pressure and a reduction in diastolic pressure, thus increasing central pulse pressure (cPP). Greater systolic blood pressure thereby increases left ventricular afterload, and the lower diastolic blood pressure reduces coronary perfusion. Human evidence to support this theory, however, is not clear. Experimental studies examining the effect of aortic compliance on CBF have provided conflicting results. Whereas some have shown low aortic compliance is associated with a reduction in CBF (5), particularly subendocardial flow (20, 26), other studies (21, 22) have found an increase in CBF.

Moreover, considering the association between a stiff aorta and the rate of revascularization (4), little is known regarding the influence of aortic stiffness on the CBF response to percutaneous coronary intervention (PCI). We therefore sought to examine the relationship between aortic compliance/stiffness and invasively measured human CBF and its response to PCI.

METHODS

Patient population. Eighteen patients with stable angina pectoris scheduled for elective PCI were recruited. Exclusion criteria included significant left main coronary artery disease, triple vessel disease, prior coronary artery bypass graft surgery, recent acute myocardial infarction (<6 wk), valvular heart disease, atrial fibrillation, or other conduction disturbance or significant peripheral vascular disease. Four subjects with previous history of acute myocardial infarction were included; however, coronary measurements were not performed in the infarct-related artery. All patients gave informed written consent, and the study protocol was approved by the Southern Health Human Research Ethics Committee. No procedure-related complications or ethical problems were encountered.

Cardiac catheterization procedure. All oral medications, with the exception of β-adrenoreceptor antagonist, were continued until the cardiac catheterization; the latter was withheld for 48 h. The procedure was performed via a femoral artery approach. Heparin bolus was administered (80 IU/kg) at the beginning of the procedure. Nitroglycerine (0.1 mg ic) was administered after the insertion of the Doppler velocity wire before coronary angioplasty and stent procedure and also after the stent procedure to reduce the effect of coronary vasospasm on coronary hemodynamic measurements.

Coronary hemodynamic measurements. Aortic pressure was obtained from a 6-Fr guiding catheter positioned at the ostium of the study artery. A 0.014-in. Doppler guidewire (FloWire, Cardiometrics, EndoSonics; Rancho Cordova, CA) was advanced into the study artery through the guiding catheter and positioned with its tip at a distance >10 mm proximal to the stenosis to avoid flow turbulence where the flow profile was sampled. The position of the wire and the stenosis were imaged (Toshiba Medical Systems, Otawara, Japan) during injection of intracoronary contrast for subsequent off-line quantitative coronary angiographic analysis by using an automated edge-detection program (Toshiba proprietary QCA software) to derive volume flow and stenosis severity (percentage diameter).

Aortic pressure, instantaneous peak velocity proximal to the stenosis/stent, and ECG data were digitized on-line by using an eight-
channel analog-to-digital converter (MacLab/8s System, ADInstruments, Castle Hill, NSW, Australia) and recorded at 200 Hz on a computerized chart recorder and analyzed off-line (Chart for Windows version 4.2, ADInstruments, Castle Hill, NSW, Australia).

All signals were measured simultaneously at rest and during hyperemia induced by intracoronary bolus of adenosine at doses of 24 µg into the left coronary artery and 18 µg into the right coronary artery. These doses have previously been shown to produce maximal pharmacological hyperemia (29) and were previously used in our catheterization laboratory (9). After successful PCI, these measurements were repeated at the same location in the stented artery.

For analysis, a maximum of 10 simultaneously recorded instantaneous peak velocity waveforms at rest and three to five waveforms during hyperemia were averaged by using a purpose-written computer program, providing averaged peak velocities for these conditions. Mean CBF was calculated by the formula $\pi \times \text{average peak velocity} \times 0.125 \times \text{diameter}$. Coronary diameter was measured at 5 mm distal to the tip of the Doppler velocity wire by quantitative coronary angiography (Toshiba proprietary QCA software). CBF in the stented artery was taken to represent flow without the effect of a coronary stenosis. In two subjects, the quality of the Doppler velocity signal measured during hyperemic response before PCI was suboptimal and not included in analysis. The resting and hyperemic data after PCI was complete for all 18 subjects.

Before PCI, the hemodynamic significance of the epicardial lesion was assessed with a Doppler velocity wire and a 0.014-in. pressure guidewire (Pressure Wire, RADI Medical Systems, Uppsala, Sweden) placed distal to the lesion during adenosine-induced hyperemia to derive coronary flow velocity reserve (CFVR), myocardial fractional flow reserve (FFR), and translesional pressure gradient (TPG). After PCI, CFVR, FFR, and TPG were measured distal to the stent. Quantitative coronary angiography was used to assess the percentage diameter stenosis of the lesion and the residual diameter stenosis after PCI.

Reproducibility of intracoronary measurements were assessed in seven subjects. Biological variability over 10 cardiac cycles under resting conditions and over 5 cycles under hyperemic conditions demonstrated a coefficient of variation (%CV) below 3.5% for both CBF and coronary blood pressure. Interobserver variability (%CV) was <2.2%.

**Aortic mechanics measurements.** Pulse-wave velocity (PWV) and brachial pulse pressure were measured before cardiac catheterization, and cPP was measured during the procedure. Patients were rested in a supine position for 10 min in a temperature-controlled room (21°C) before measurements. Simultaneous ECG and applanation tonometry signals were measured by a noninvasive Millar Mikro-Tip pressure transducer (model SPT-301, Millar Instruments, Houston, TX) obtained from two arterial sites were recorded at 2,000 Hz on a computerized chart recorder for subsequent off-line analysis. Transit time of the pulse wave was measured from the R wave (lead II) of the ECG to the foot of the waveform obtained at the right carotid, femoral, and dorsalis pedis arteries. Sternal-carotid, sternal-femoral, and sternal-dorsalis pedis distances were measured directly from the sternal notch to the applanation sites. Central PWV [(sternal-femoral minus sternal-carotid distance)/(sternal-femoral transit time)] represents the PWV of the aortic segment from the aortic arch to the femoral artery as previously described (6). Peripheral PWV [(sternal-dorsalis pedis minus sternal-femoral distance)/(dorsalis pedis minus femoral transit time)] represents the PWV of the muscular femoral artery to the dorsalis pedis segment.

Reproducibility of cPWV was assessed in seven subjects. Biological variability (over 10 cardiac cycles) and interobserver variability (two observers selecting 10 cardiac cycles for analysis) had %CV <8%.

**Statistical analysis.** Values are expressed as means ± SD unless stated otherwise. Comparisons of mean values between groups were by paired t-test or by two-way ANOVA. The relationship between two continuous variables (e.g., cPWV and CBF) was determined by simple linear regression, and adjustment for age, gender, and rate-pressure product (RPP) was by partial correlation. Analysis of covariance was used when both continuous and categorical variables were present. cPWV and cPP were also dichotomized by their mean values, and the relationship between CBF and aortic stiffness was by independent t-test. A P value of <0.05 was considered significant. Statistical analyses were performed using SPSS for Windows version 11.0.0 (SPSS, Chicago, IL).

## RESULTS

Subject clinical characteristics are summarized in Table 1. Hypercholesterolemia was the most prevalent risk factor, followed by hypertension and a current or previous history of smoking. Two subjects had diabetes. Left ventricular function was within normal range in the study group except for one subject with mild and another subject with moderate impairment.

Coronary Doppler velocity was recorded in eight left anterior descending, three left circumflex, and seven dominant right coronary arteries. Studied lesions were angiographically and physiologically significant (mean diameter stenosis 88 ± 9%, CFVR 1.8 ± 0.6, FFR 0.57 ± 0.19, TPG 29 ± 24 mmHg). Angioplasty and the stent procedure were successful in all cases resulting in a residual diameter stenosis of 2 ± 7%, CFVR of 3.0 ± 0.8, FFR of 0.92 ± 0.61, and TPG of 2 ± 3 mmHg (all P < 0.001).

### Relationship between the aortic function parameters. The indexes of arterial stiffness are shown in Table 2. cPP measured...
once the stenosis was removed was resting CBF inversely
significant relationships between hyperemic CBF and aortic mecha-
only after PCI (Table 4). Hyperemic CBF was not related to
peripheral PWV (pPWV). After adjustment for age and gender, the same signif-
Arterial mechanical indexes

<table>
<thead>
<tr>
<th></th>
<th>Pre-PCI</th>
<th>Hyperemic</th>
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<tbody>
<tr>
<td>Central pulse wave velocity, m/s</td>
<td>7.3±2.6</td>
<td></td>
</tr>
<tr>
<td>Peripheral pulse wave velocity, m/s</td>
<td>9.6±1.8</td>
<td></td>
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<tr>
<td>Brachial pulse pressure, mmHg</td>
<td>60±17</td>
<td></td>
</tr>
<tr>
<td>Brachial SBP, mmHg</td>
<td>127±21</td>
<td></td>
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<tr>
<td>Brachial DBP, mmHg</td>
<td>67±9</td>
<td></td>
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<tr>
<td>Brachial MAP, mmHg</td>
<td>92±15</td>
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Data are means ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

sured at rest before PCI was compared with other aortic function parameters. cPWV was proportional to cPP (P = 0.04) and to brachial pulse pressure (P < 0.001). cPP and brachial pulse pressure were closely and linearly related (P = 0.004). Peripheral PWV (pPWV) was not related to cPWV, cPP, or brachial pulse pressure.

Resting CBF and aortic function. CBF in the study artery before and after PCI are shown in Table 3. Resting CBF increased from 31 ± 3 to 45 ± 4 ml/min after PCI (P = 0.038) without significant change in heart rate, mean arterial pressure (MAP), and RPP. Resting CBF was inversely related to cPWV irrespective of the presence of the stenosis (before PCI: r² = 0.398, after PCI: r² = 0.359; both P < 0.01) (Table 4). Only once the stenosis was removed was resting CBF inversely related to cPP (r² = 0.536; P < 0.01). Resting CBF was not related to pPWV. After adjustment for age, gender, and RPP, the relationships between resting CBF and aortic mechanical indexes remained intact (all P < 0.05).

Hyperemic CBF and aortic function. CBF was assessed during administration of intracoronary adenosine in the presence and absence of a significant coronary stenosis. Adenosine-induced hyperemic CBF before and after PCI is shown in Table 3. Hyperemic CBF increased from 66 ± 8 to 122 ± 11 ml/min after PCI (P = 0.04), without a significant change in heart rate, MAP, and RPP.

Hyperemic CBF was inversely related to cPWV irrespective of the presence of a significant coronary stenosis (before PCI: r² = 0.334, P = 0.019; after PCI: r² = 0.570, P < 0.001), whereas cPP was inversely related (r² = 0.493, P = 0.002) only after PCI (Table 4). Hyperemic CBF was not related to pPWV. After adjustment for age and gender, the same significant relationships between hyperemic CBF and aortic mechanical indexes remained intact.

cPWV adjusted for MAP. MAP was related to all aortic stiffness indexes (cPWV: P = 0.003; r² = 0.394, cPP: P = 0.021; r² = 0.291). Before PCI, when cPWV was adjusted for MAP, cPWV was not associated with CBF. After PCI, adjusted cPWV was related to hyperemic CBF (P = 0.014, r² = 0.341), with a trend to be related to resting CBF (P = 0.066; r² = 0.195).

Effect of aortic stiffness on the magnitude of the hyperemic response to adenosine. Figure 1, A and B, shows the relationship between resting and hyperemic CBF after the stent procedure and cPWV and cPP, respectively, in the index artery. There was a significant (P < 0.01) difference in the slopes such that the curves converge as cPWV and cPP increases. Those with a higher cPWV or cPP showed a smaller hyperemic response than those with a lower cPWV or cPP.

Resting and hyperemic CBF against cPWV obtained before the stent procedure is shown in Fig. 2. The slopes of the resting and hyperemic curves were not different (P = 0.151).

Effect of aortic stiffness on the improvement in CBF from PCI. Hyperemic CBF improved to a greater extent compared with resting CBF as a result of PCI (Table 3). The effect of aortic stiffness on this improvement in CBF (resting and hyperemic) is shown in Fig. 3, A and B. The change in CBF from PCI was plotted against aortic stiffness, which was categorized into compliant or stiff using the mean value of cPWV (7.3 m/s) (Fig. 3A) and cPP (73 mmHg) (Fig. 3B). PCI

Table 2. Arterial mechanical indexes

<table>
<thead>
<tr>
<th></th>
<th>Before PCI</th>
<th>After PCI</th>
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<tbody>
<tr>
<td>Central pulse wave velocity, m/s</td>
<td>7.3±2.6</td>
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<tr>
<td>Peripheral pulse wave velocity, m/s</td>
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<td>Brachial pulse pressure, mmHg</td>
<td>60±17</td>
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<tr>
<td>Brachial SBP, mmHg</td>
<td>127±21</td>
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<tr>
<td>Brachial DBP, mmHg</td>
<td>67±9</td>
<td></td>
</tr>
<tr>
<td>Brachial MAP, mmHg</td>
<td>92±15</td>
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Table 3. Central and coronary hemodynamics

<table>
<thead>
<tr>
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<th>Pre-PCI</th>
<th>Hyperemic</th>
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<tbody>
<tr>
<td>CBF, ml/min</td>
<td>31±3</td>
<td>66±8*</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>67±4</td>
<td>67±4</td>
</tr>
<tr>
<td>Central SBP, mmHg</td>
<td>139±6</td>
<td>132±6*</td>
</tr>
<tr>
<td>Central DBP, mmHg</td>
<td>72±3</td>
<td>68±3*</td>
</tr>
<tr>
<td>Central MAP, mmHg</td>
<td>94±3</td>
<td>90±3*</td>
</tr>
<tr>
<td>Central PP, mmHg</td>
<td>66±6</td>
<td>63±6</td>
</tr>
<tr>
<td>RPP, beats/min/mmHg</td>
<td>9,132±617</td>
<td>8,824±579</td>
</tr>
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Data are means ± SE. CBF, coronary blood flow; HR, heart rate; Central PP, central pulse pressure; RPP, rate pressure product. *Hyperemic parameter significantly different from resting parameter (P < 0.05); †Post-PCI parameter significantly different from Pre-PCI parameter (P < 0.05).

Table 4. Correlation between aortic mechanical parameters and CBF before and after adjustment for age, gender, and rate-pressure product

<table>
<thead>
<tr>
<th></th>
<th>Before PCI</th>
<th>After PCI</th>
</tr>
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<tbody>
<tr>
<td>cPWV r</td>
<td>−0.631 (0.005)</td>
<td>−0.362 (0.140)</td>
</tr>
<tr>
<td>Hyperemic CBF</td>
<td>−0.578 (0.019)</td>
<td>−0.290 (0.277)</td>
</tr>
<tr>
<td>pPWV r</td>
<td>−0.000 (0.800)</td>
<td>0.157 (0.535)</td>
</tr>
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</table>

Table values.

r, Pearson correlation coefficient; Numbers in parentheses are P values. Bolded text, statistically significant. cPWV, central pulse wave velocity; pPWV, peripheral pulse-wave velocity. *Relationship adjusted for age, gender, and rate-pressure product; †relationship adjusted for age and gender.

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resulted in a significant improvement in resting and hyperemic CBF in the compliant aorta (resting: 35.2 ± 15.4 ml/min, P = 0.001; hyperemic: 75.5 ± 35.2 vs. 140.8 ± 34.6 ml/min, P < 0.001) but only for hyperemic CBF in the stiff aorta (resting: 17.5 ± 4.6 vs. 26.2 ± 3.7 ml/min, P = 0.103; hyperemic: 40.4 ± 14.1 vs. 57.9 ± 14.0 ml/min, P = 0.02) as defined by cPWV. PCI resulted in a significant improvement in resting and hyperemic CBF in the compliant (resting: 33.9 ± 15.8 vs. 55.5 ± 14.7 ml/min, P = 0.003; hyperemic: 71.0 ± 39.8 vs. 146.9 ± 32.6 ml/min, P = 0.002) and the stiff aorta (resting: 27.8 ± 13.7 vs. 36.8 ± 16.5, P = 0.024; hyperemic: 61.9 ± 31.1 vs. 94.1 ± 47.7, P = 0.015) as defined by cPP. The change in resting CBF from PCI was not related to cPWV or cPP. The improvement in hyperemic CBF from PCI was greater in the compliant than the stiff aorta (cPWV: 65.3 vs. 17.6 ml/min; P = 0.002, cPP: 75.9 vs. 32.2 ml/min; P = 0.03). This relationship remained after adjusting for angiographic stenosis severity (cPWV: P = 0.025, cPP: P = 0.039) and CFVR (cPWV: P = 0.046) but only tended to be related to cPP after adjusting for CFVR (P = 0.083).

**DISCUSSION**

**Indexes of aortic stiffness as predictors of CBF.** In this study, we observed that both resting and hyperemic CBF were related to aortic stiffness, as measured by cPWV and cPP, after successful PCI. These relationships remained after adjusting for age, gender [both known to influence aortic stiffness indexes (23)], and RPP [a surrogate of myocardial work known to influence resting CBF (17)], suggesting that aortic stiffness is an important factor governing CBF. Furthermore, as cPWV increased, resting and hyperemic CBF decreased irrespective of the presence of a significant flow-limiting stenosis.

**Previous studies on aortic stiffness and CBF.** Aortic stiffening is the consequence of changes in the properties of the arterial wall that accompany aging and disease. These changes include medial hypertrophy and fragmentation of elastin and accumulation of collagen in the arterial wall (1). Atherosclerosis and its risk factors are believed to accelerate this process (3). In a stiff aorta with high PWV, not only is the forward propagating pulse wave traveling faster, but the reflected pulse wave returns earlier resulting in summation in systole rather than in diastole. Correspondingly, the cPP will be higher. The effect of a stiff aorta on CBF may be explained hemodynamically by its reduced capacity to function as an elastic reservoir resulting in a greater peripheral runoff of stroke volume during systole. Together with the reduced elastic recoil, the diastolic blood pressure and hence CBF is decreased.

Although the hypothesis that coronary flow may be influenced by mechanical properties of the aorta was introduced by Bouvraian and Levy in 1981 (5), substantive data are lacking. Chronic experimental studies have shown the balance and distribution of coronary flow shifts away from the subendocardium with increasing aortic stiffness, most noticeable with increased contractility (20) and heart rate (26). Conversely, the acute alteration of aortic compliance in a canine model resulted in an increase in pulse pressure and an increase rather than decrease in mean CBF despite matching workload and MAP (22). Increase in pulsatility enhancing endothelial release of nitric oxide was shown to be partly responsible for the acute
Aortic stiffness affects coronary blood flow

Increase in CBF (21). Chronic reduction in aortic compliance with aging and atherosclerosis associated with endothelial dysfunction may result in a different flow response. To the best of our knowledge, the present study is the first in humans to demonstrate a correlation between direct invasive measurement of CBF and measures of aortic stiffness.

Our findings provide in vivo physiological data to support the epidemiological observations that aortic stiffness is an important and independent prognostic marker. In a cohort of 1,980 hypertensive subjects, cPWV was a strong independent predictor of primary coronary events (4) beyond the prediction provided by Framingham score or classic cardiovascular risk factors. Although pulse pressure is a less direct measure of stiffness than cPWV (2), it has been demonstrated in a longitudinal study (mean followup 19.5 yr) of 19,083 men with low cardiovascular risk that pulse pressure is an important predictor of coronary mortality independent of age and MAP (2).

Other mechanisms for the relationship between CBF and aortic stiffness. Besides the aortocoronary hemodynamic relationship that may explain the lower CBF associated with a stiff aorta, aortic stiffness may be a marker of a more generalized vascular disease process that not only impede CBF but also increase the risk of cardiovascular and specifically coronary events. The link between aortic and coronary atherosclerosis has been demonstrated by the correlation between central aortic stiffness and coronary artery plaque volume as measured by intravascular ultrasound (15). Furthermore, the distribution of atherosclerosis leading to resistance to CBF may not necessarily be severe focal conduit stenosis but may result from diffuse atherosclerotic coronary disease causing a graded pressure drop along the length of the vessel (7).

Aortic stiffness may also coexist with microvascular disease. Hypertension and diabetes are associated with increased aortic stiffness (3) and have been documented to cause functional and structural microvascular changes (19, 24, 25, 27). Large artery stiffness itself is influenced by endothelial function via basal release of nitric oxide (28). Aortic stiffness is associated with brachial artery endothelial dysfunction (18). It is conceivable that coronary endothelial dysfunction may coexist with aortic stiffness and may contribute to impaired CBF. Although this study does not specifically address coronary endothelial dysfunction, the direct effect of adenosine on smooth muscle cells to induce maximum hyperemia may reflect a structural rather than a functional (endothelial dysfunction) limitation on CBF. Aortic stiffness may be a surrogate for the presence of structural microvascular disease, including arteriolar and capillary rarefaction and interstitial and periarteriolar fibrosis. This microvascular remodeling may be responsible for impeding CBF as seen in our study.

Effect of cPWV and cPP on the CBF response to PCI. Our data suggests that a compliant aorta, as measured by cPWV and cPP, is associated with a greater improvement in hyperemic CBF from successful PCI than a stiff aorta (Fig. 3, A and B). Even after accounting for stenosis severity as measured angiographically and physiologically, this relationship persisted for cPWV. Relieving an epicardial stenosis improves hyperemic CBF. This improvement may be limited by preexisting microvascular disease or low diastolic CBF associated with a stiff aorta. Improvement appears better with a compliant aorta.

Fig. 3. Change in hyperemic, but not resting CBF, from PCI was related to aortic stiffness indexes. Aortic stiffness, represented by cPWV (A; \( P = 0.002 \)) and cPP (B; \( P = 0.03 \)), was categorized into compliant or stiff by the mean value of cPWV (7.3 m/s) (A) and cPP (73 mmHg) (B). *Significant change in CBF from PCI.

Effect of cPWV and cPP on the CBF response to adenosine: a model of ischemic threshold. Figure 1A provides insight into the relationship between cPWV and the increase in CBF from rest to maximum hyperemia in the absence of coronary stenosis—a measure of coronary flow reserve. A similar result is apparent for cPP (Fig. 1B). The magnitude of CBF response induced by adenosine is less in a stiffer aorta. The presence of a coronary stenosis has an important effect on coronary flow reserve and thus would explain the lack of significant convergence between the two curves in Fig. 2.

With the application of the above to an exercise model, it is conceivable that exercise-induced rise in CBF, related to is-
chastic threshold, could be determined by aortic stiffness. This is supported by the findings of Kingwell et al. (11) who found indexes of arterial stiffness were stronger independent predictors of the exercise-induced ischemic threshold than maximum coronary stenosis assessed angiographically. The restriction in CBF that is associated with a stiff aorta in addition to mild to moderate coronary stenosis may approximate a severe coronary stenosis in the presence of a compliant aorta.

**Relationship between CBF and cPWV after adjusting for MAP.** As the MAP rises, the distended vessel wall becomes less compliant and functionally stiffer (12, 14). Our data are in agreement with this; increasing MAP is associated with a stiffer aorta as measured by cPWV and cPP. To remove the confounding influence of differing operating MAP on cPWV, measured cPWV was adjusted for differences in MAP. This parameter can be taken as a measure of relative intrinsic stiffness of the central aorta.

This was only associated with hyperemic CBF without stenosis and suggests that intrinsic aortic stiffness predicts maximum CBF in the absence of a flow-limiting conduit stenosis. Conduit stenosis and vascular tone appear to confound this relationship.

Functional aortic stiffness, however, is the measured cPWV that takes into account the patient’s operating MAP and is of more practical use. MAP makes an important contribution to the measured cPWV that influences resting and hyperemic CBF with a coronary stenosis and resting CBF after PCI. It is a measure of the patient’s effective aortic stiffness from the combination of intrinsic stiffness and distending MAP. This influences CBF irrespective of the presence of a conduit stenosis or if CBF is resting or hyperemic. Our data suggests that increased functional aortic stiffness predicts lower CBF.

**Limitations.** The present study assessed CBF in a stented artery rather than a “normal” artery to allow the investigation of the effect of aortic stiffness on CBF response to PCI. All study patients had a procedurally successful PCI with minimal residual stenosis and improvement in CFVR to 3.0 ± 0.8 (Table 1), suggesting the stented vessel was angiographically and physiologically close, if not equivalent, to normal.

Potential inaccuracies present in mean coronary velocity or cross-sectional vessel area will be magnified in the calculation of CBF. Careful attention was given to obtain optimal Doppler velocity signals with the wire tip positioned coaxial with the artery. Overall, 8.3% of the coronary data were excluded because of suboptimal Doppler signals. Our group demonstrated good reproducibility (performed in 7 subjects) for mean coronary velocity (CV: at rest, 2.4%, at hyperemia, 3.1% where Doppler wire was withdrawn and repositioned to the same location) and QCA (CV = 4.0% when vessel diameter, 5 mm from wire tip, was measured twice on the same cine run).

Oval vasodilators were not withheld before the study as patients were symptomatic. One-third of our cohort was on three vasodilators, with 44% of subjects on two agents and 22% on one agent. Although the use of these agents may possibly influence CBF measurements, the use of a vasodilator or the number of vasodilators was not associated with aortic stiffness indexes or CBF at rest or during hyperemia with or without epicardial stenosis.

An intracoronary placebo arm was not used because it would lengthen the invasive procedure. Moreover, the hyperemic effect of intracoronary adenosine is well recognized in humans.

In conclusion, a stiff aorta, represented by increased cPWV and cPP, is associated with a reduction in CBF, a lower adenosine-induced hyperemic CBF response, and may reduce the improvement in hyperemic CBF after successful PCI. The mechanism behind these potential limitations (i.e., hemodynamic relationship, surrogate for microvascular disease) requires further investigation.

**GRANTS.**

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**REFERENCES.**


