Contribution of Vasodilator Prostanoids and Nitric Oxide to Resting Flow, Metabolic Vasodilation, and Flow-Mediated Dilation in Human Coronary Circulation

Stephen J. Duffy, MB,BS; Sally F. Castle, MA, RN; Richard W. Harper, MB,BS; Ian T. Meredith, MB,BS, PhD

Background—Endothelial dysfunction is associated with atherosclerosis and may contribute to ischemic syndromes. We assessed the contribution of endothelium-derived nitric oxide (NO) and vasodilator prostanoids to resting blood flow, metabolic vasodilation, and flow reserve in the human coronary circulation.

Methods and Results—Coronary hemodynamics were assessed before and after inhibition of vasodilator prostanoids and NO with intracoronary aspirin (acetylsalicylic acid [ASA]) and N\textsuperscript{6}-monomethyl-L-arginine (L-NMMA), respectively. Angiographically smooth or mildly irregular vessels, with normal adenosine-induced coronary flow reserve, were studied in 25 patients undergoing clinically indicated procedures. Coronary blood velocity was measured by Doppler flow wire, and coronary blood flow (CBF) was calculated. ASA reduced resting conduit vessel diameter by 11% (P=0.003) and CBF by 27% (P=0.008) and increased coronary vascular resistance (CVR) by 24% (P<0.0001). ASA attenuated pacing-induced hyperemia by 28% (45.0±4.6 versus 32.6±3.4 mL/min, P=0.005) and increased minimum CVR by 39% (2.8±0.3 versus 3.9±0.5 mm Hg · mL\textsuperscript{-1} · min\textsuperscript{-1}, P=0.007). L-NMMA reduced resting conduit vessel diameter by 9% (P=0.05) and CBF by 20% (P=0.08) and increased CVR by 19% (P=0.03). L-NMMA attenuated pacing-induced hyperemia by 20% (42.4±5.1 versus 34.1±3.4 mL/min, P=0.04) and increased minimum CVR by 33% (2.9±0.4 versus 3.8±0.5 mm Hg · mL\textsuperscript{-1} · min\textsuperscript{-1}, P=0.02). ASA (7.7±2.3% versus −1.6±3.2%, P=0.06) and L-NMMA (12.1±3.9% versus 0.0±2.9%, P=0.02) abolished pacing-induced conduit vessel flow-mediated dilation.

Conclusions—Tonic release of vasodilator prostanoids and NO contributes to resting conduit and resistance vessel tone and to peak functional hyperemia and flow-mediated dilation after metabolic stimulation. This underscores the importance of normal endothelial function for metabolic vasodilation and suggests that it may be a key mechanism for preventing myocardial ischemia in coronary artery disease. (Circulation. 1999;100:1951-1957.)

Key Words: endothelium-derived factors ■ prostaglandins ■ adenosine ■ blood flow ■ vasodilation

Coronary blood flow (CBF) and coronary vascular resistance (CVR) are determined by the complex interaction of systemic and local factors, including mechanical forces, neurohumoral influences, and autoregulation. In working myocardium, local factors, such as vasodilator metabolites, not only stimulate vasodilation but must also offset the systemic neurohumoral activation that occurs in order to maintain or increase blood pressure and heart rate during exercise.\textsuperscript{1,2}

Evidence now indicates that a variety of endothelium-derived factors also controls vascular tone during changes in physiological demand.\textsuperscript{2,3} Vascular endothelium also plays an important role in the prevention of atherosclerosis by inhibiting thrombosis, inflammation, and smooth muscle cell proliferation.\textsuperscript{4} Impaired endothelium-dependent coronary vasodilation has been associated with atherosclerosis and its risk factors.\textsuperscript{5,6} Endothelial dysfunction may occur early in the course of this disease\textsuperscript{6,6} and appears to be reversible.\textsuperscript{7} In conduit and resistance vessels, endothelial dysfunction may contribute to the genesis of myocardial ischemia in patients with coronary artery disease.\textsuperscript{8,9}

Endothelium-derived nitric oxide (NO) and vasodilator prostanoids (PGs) are important in the control of resting blood flow and metabolic vasodilation in human skeletal muscle vasculature.\textsuperscript{3} Recently, a similar role has been demonstrated for NO in the regulation of resting blood flow, pacing-induced hyperemia, and flow-mediated dilation in the coronary circulation,\textsuperscript{10–13} although some studies have differed in their findings,\textsuperscript{14,15} possibly because of the effect that risk factors have on NO bioavailability.\textsuperscript{12,16}

Previous studies have shown that cyclooxygenase inhibition with indomethacin reduces resting CBF in patients with coronary artery disease.\textsuperscript{17} Although it has been confirmed by...
TABLE 1. Clinical Characteristics for Study Groups

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Reproducibility (n=9)</th>
<th>ASA (n=14)</th>
<th>L-NMMA (n=7)</th>
<th>All Patients (n=25)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.0±9.3</td>
<td>57.0±7.5</td>
<td>56.7±5.5</td>
<td>56.5±7.1</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>4/5</td>
<td>3/11</td>
<td>4/3</td>
<td>10/15</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.1±0.8</td>
<td>4.8±1.0</td>
<td>5.4±0.8</td>
<td>5.1±0.9</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>7 (78%)</td>
<td>11 (79%)</td>
<td>5 (71%)</td>
<td>19 (76%)</td>
</tr>
<tr>
<td>Family history of IHD</td>
<td>5 (56%)</td>
<td>5 (36%)</td>
<td>6 (86%)</td>
<td>15 (60%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (44%)</td>
<td>6 (43%)</td>
<td>1 (14%)</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (11%)</td>
<td>1 (7%)</td>
<td>1 (14%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Exsmoker†</td>
<td>3 (33%)</td>
<td>6 (43%)</td>
<td>0</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Number of risk factors/patient‡</td>
<td>3.2±1.3</td>
<td>3.1±1.2</td>
<td>2.6±0.8</td>
<td>2.9±1.1</td>
</tr>
</tbody>
</table>

Data are mean±SD or number (%) of patients with the risk factor. IHD indicates ischemic heart disease.

*Five reproducibility patients also participated in the ASA study.
†Indicates current or recent (<1 year) exsmoker.
‡Includes the 5 indicated risk factors, male sex, and age >60 years.

Methods

Study Population
Clinically stable patients scheduled for percutaneous intervention or diagnostic study for investigation of chest pain were screened. Twenty-five patients (mean±SD 56.5±7.1 years) were recruited between July 1996 and July 1998 in the following order of study: reproducibility (vehicle infusion), aspirin (acetylsalicylic acid [ASA]), and N\(^{\circ}\)-monomethyl-L-arginine (L-NMMA) protocols; 5 reproducibility patients also participated in the ASA protocol. Clinical characteristics are shown in Table 1. Angiographically smooth or mildly irregular coronary arteries were studied. In single-vessel disease, the study was performed in an adjacent vessel after the percutaneous intervention, as previously described. Twelve patients had diagnostic angiography only. Thirteen had successful single-vessel intervention (all in the ASA study).

The left anterior descending coronary artery was studied in 14 patients; the circumflex or major branch artery, in 10; and the right coronary artery, in 1. The vessel subtended viable myocardium, as defined by no Q waves on ECG and no hypokinesis, akinesis, or dyskinesis on resting echocardiogram or left ventriculography. Exclusion criteria included unstable angina, significant left ventricular impairment or valvular disease, left main stem, double-vessel, or triple-vessel coronary disease, and abnormal adenosine-induced CFVR. The Monash Medical Center Human Research Ethics Committee approved the study. All patients provided written informed consent.

Study Design
Vasoactive medications were withheld for ≥24 hours. Maintenance ASA (150 mg/day) was continued in 21 patients (including all ASA study patients). Heparin (10 000 IU) was given and supplemented as necessary. A Doppler flow wire (Cardiometrics) was advanced to a straight midvessel segment that provided adequate images and stable Doppler signals. A 2.8F infusion catheter (Tracker, Target Therapeutics) was used for subselective infusion into the proximal segment.

Baseline Doppler velocity and angiography were recorded after 5 minutes of vehicle infusion (isotonic glucose 0.8 mL/min). Adenosine-induced CFVR was assessed 3 times, with ≥2 minutes between measures. Patients with abnormal CFVR (<2.0)\(^2\) were excluded. Baseline CBF was reestablished, and metabolic vasodilation was induced by 2 minutes of ventricular pacing. Ventricular pacing was used as during the preliminary atrial pacing reproducibility studies.

TABLE 2. Pacing Reproducibility

<table>
<thead>
<tr>
<th>Response</th>
<th>Baseline 1</th>
<th>Maximal Pacing</th>
<th>Baseline 2</th>
<th>Maximal Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>APV, cm/s</td>
<td>21.1±2.6</td>
<td>26.6±2.7</td>
<td>20.7±2.7</td>
<td>25.8±2.5</td>
</tr>
<tr>
<td></td>
<td>0.56</td>
<td>0.56</td>
<td>0.66</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>0.29</td>
<td>0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary diameter, mm</td>
<td>2.4±0.2</td>
<td>2.5±0.2</td>
<td>2.3±0.2</td>
<td>2.4±0.2</td>
</tr>
<tr>
<td>CBF, mL/min</td>
<td>26.6±3.3</td>
<td>36.8±5.5</td>
<td>24.8±3.0</td>
<td>34.3±5.1</td>
</tr>
<tr>
<td>CVR, mm Hg · mL⁻¹ · min⁻¹</td>
<td>4.2±0.4</td>
<td>3.6±0.5</td>
<td>4.8±0.7</td>
<td>3.9±0.5</td>
</tr>
<tr>
<td>RPP, mm Hg · bpm</td>
<td>9346±700</td>
<td>18 530±810</td>
<td>9715±517</td>
<td>18 964±745</td>
</tr>
</tbody>
</table>

Data are mean±SE. RPP indicates rate-pressure product.

*Comparison between pacing episodes.
several patients developed Wenckebach phenomena. Ventricular pacing in 9 patients induced reproducible functional hyperemia (Table 2). After 5 minutes of rest, baseline data were recorded. Either ASA or L-NMMA was then infused for 10 minutes, followed by repeat measurements. Pacing was repeated with continuous infusion of study medication, and functional hyperemia was recorded. After 5 minutes of rest, CFVR was repeated. Pacing responses were available in 24 patients. Resting data were available for the other subject (ASA protocol) and are included in analyses.

Study Medications
CFVR was measured in response to bolus doses of adenosine (Sanofi Winthrop) given via the guiding catheter. 12 μg in the right and 18 μg in the left coronary artery.24 ASA (Aspisol, Bayer), an irreversible acetylator of cyclooxygenase and inhibitor of PG production, was infused at 20 mg/min. Dosage was calculated to achieve a local plasma concentration of ~500 μg/mL. We anticipated that this dose would reduce net coronary prostacyclin production (and other PGs) at rest by ~80%.25 L-NMMA (Cinalfa AG) inhibits NO by competing with L-arginine for NO synthase and was infused at 6 mg/min (32 μmol/min).11-12 Drugs were diluted in isotonic glucose and infused at 0.8 mL/min by syringe pump (Terumo Corp).

Estimation of Coronary Diameter and Blood Flow
Coronary flow velocity was measured continuously. To calculate CBF, coronary diameter was measured by angiography at baseline and after each intervention. Nonionic contrast (9 mL, Ultravist, Shering AG) was given by automated pump at 7 mL/s. Images were digitized on-line (Toshiba) and stored on compact disks for subsequent analysis. Diameter was measured over a 0.5-cm segment beginning 0.25 cm distal to the Doppler flow wire. Quantitative coronary angiography was performed by use of a validated commercially available edge-detection algorithm (CMS, MEDIS Medical Imaging Systems); a contrast-filled distal guiding catheter was used for calibration by an operator blinded to the study design.

For resting hemodynamics (average peak velocity [APV], blood pressure, and heart rate), the means of 30 seconds of stable recordings were analyzed. Adenosine-induced CFVR was calculated as the ratio of maximal hyperemic APV to baseline APV, and was defined as normal.23 CFVR reproducibility was documented in 23 CFVR reproducibility was documented in 24 patients. Resting data were available for the other subject (ASA protocol) and are included in analyses.

Results
Effect of ASA on Coronary Tone
ASA infusion reduced resting coronary artery diameter by 11% (from 2.6±0.2 to 2.3±0.1 mm, P=0.003; Figure 1). APV was similar before and after ASA (20.5±1.6 versus 19.4±1.5 cm/s). ASA reduced resting CBF by 27% (from 31.8±4.2 to 23.3±2.5 mL/min, P=0.008) and increased CVR by 24% (from 4.2±0.6 to 5.2±0.6 mm Hg · mL⁻¹ · min⁻¹, P=0.0001). There were no changes in heart rate (64±3 versus 66±3 bpm) or MABP (106±3 versus 104±3 mm Hg). Thus, the rate-pressure product was unchanged by ASA (9421±508 versus 9438±561 mm Hg · bpm).

Adenosine-induced CFVR was marginally higher with ASA (3.00±0.2 versus 3.24±0.2, P=0.09). Baseline APV before CFVR assessment was similar with vehicle or ASA infusion (17.3±1.1 versus 17.9±1.2 cm/s). Thus, the increased CFVR was due to augmentation of maximum adenosine-induced APV with ASA (30.8±3.6 versus 57.5±5.6 cm/s, P=0.036). However, estimated maximal adenosine-induced CBF was similar during vehicle or ASA infusion (76.7±12.1 versus 67.8±10.7 mL/min) because of the reduction of coronary diameter with ASA (2.4±0.2 versus 2.2±0.1 mm, P=0.095). Thus, estimated adenosine-induced coronary flow reserve was similar before and after ASA (3.0±0.2 versus 3.2±0.2, P=0.16).

Pacing increased the coronary artery diameter from 2.36±0.1 to 2.54±0.2 mm (P=0.01), but this increase was abolished by ASA (2.23±0.1 versus 2.19±0.1 mm). Maximum pacing-induced APV was similar before and after ASA (29.7±1.8 versus 30.0±2.4 cm/s). Pacing increased CBF by 78% (from 25.2±2.6 to 45.0±4.6 mL/min, P=0.0002) during vehicle infusion, but ASA attenuated the pacing-induced hyperemia to a 42% increase (from 22.9±2.6 to 32.6±3.4 mL/min, P=0.03 compared with before ASA, 2-way repeated measures ANOVA; Figure 2). Maximum pacing-induced hyperemia was 28% less with ASA (P=0.005). Pacing reduced CVR by 40% (from 4.8±0.6 to 2.8±0.3 mm Hg · mL⁻¹ · min⁻¹) during vehicle infusion (P=0.006). With ASA, CVR decreased with pacing by 27% (from 5.3±0.6 to 3.9±0.5 mm Hg · mL⁻¹ · min⁻¹). Thus, minimum CVR after pacing was 39% greater with ASA (P=0.007). Maximal rate-pressure product during pacing was similar before and after ASA (19 327±866 versus 19 525±912 mm Hg · bpm),
3.48 ± 0.3 (P = 0.023) because of a slightly lower baseline APV (27.2 ± 6.6 cm/s). Estimated CBF with L-NMMA was similar before and after L-NMMA (16.7 ± 2.6 versus 16.5 ± 2.6 cm/s). L-NMMA reduced resting CBF by 20% (from 26.7 ± 5.2 to 21.3 ± 3.0 mL/min, P = 0.08) and increased CVR by 19% (from 4.7 ± 0.9 to 5.6 ± 0.9 mm Hg · mL⁻¹ · min⁻¹, P = 0.03). L-NMMA increased MABP (from 103 ± 4 to 106 ± 4 mm Hg, P = 0.04) and reduced resting heart rate (from 73 ± 4 to 70 ± 3 bpm, P < 0.01). Thus, rate-pressure product was unchanged (10115 ± 751 versus 10065 ± 734 mm Hg · bpm).

Effect of L-NMMA on Coronary Tone
L-NMMA reduced resting coronary artery diameter by 9% (from 2.6 ± 0.1 to 2.4 ± 0.1 mm, P = 0.051; Figure 3). APV was similar before and after L-NMMA (16.7 ± 2.6 versus 16.5 ± 2.6 cm/s). L-NMMA reduced resting CBF by 20% (from 26.7 ± 5.2 to 21.3 ± 3.0 mL/min, P = 0.08) and increased CVR by 19% (from 4.7 ± 0.9 to 5.6 ± 0.9 mm Hg · mL⁻¹ · min⁻¹, P = 0.03). L-NMMA increased MABP (from 103 ± 4 to 106 ± 4 mm Hg, P = 0.04) and reduced resting heart rate (from 73 ± 4 to 70 ± 3 bpm, P < 0.01). Thus, rate-pressure product was unchanged (10115 ± 751 versus 10065 ± 734 mm Hg · bpm).

CFVR before and after L-NMMA was available in 5 patients. L-NMMA increased CFVR from 2.56 ± 0.2 to 3.48 ± 0.3 (P = 0.023) because of a slightly lower baseline APV (27.2 ± 0.8 versus 19.3 ± 3.3 cm/s, P = 0.11). Maximal adenosine-induced APV was similar before and after L-NMMA (70.0 ± 5.2 versus 64.2 ± 7.9 cm/s). Estimated CBF was consistent with APV data. Baseline CBF with vehicle was 35.8 ± 4.8 versus 24.4 ± 2.6 mL/min with L-NMMA (P = 0.036). Maximal adenosine-induced CBF was similar with vehicle or L-NMMA (88.9 ± 10.7 versus 81.9 ± 3.1 mL/min). Thus, estimated coronary flow reserve increased with L-NMMA (from 2.56 ± 0.2 to 3.51 ± 0.3, P = 0.024).

Pacing increased coronary artery diameter (from 2.32 ± 0.1 to 2.60 ± 0.1 mm, P = 0.02), but this increase was abolished by L-NMMA (2.38 ± 0.1 versus 2.38 ± 0.1 mm). Maximum pacing-induced APV was similar before and after L-NMMA (26.5 ± 2.5 versus 26.2 ± 3.1 cm/s). Pacing increased CBF by 60% (from 26.6 ± 4.4 to 42.4 ± 5.1 mL/min, P = 0.0016) during vehicle infusion. With L-NMMA, pacing increased CBF to a similar extent (by 60%, from 21.3 ± 3.0 to 34.1 ± 3.4 mL/min; Figure 4), although maximum pacing-induced hyperemia was 20% less with L-NMMA (P = 0.038). Thus, although the percent increase in CBF was similar after L-NMMA, the maximum CBF achieved was less. Baseline CBF just before pacing with L-NMMA was also less (P = 0.05). Thus, the change in maximal CBF with L-NMMA did not reach significance by 2-way repeated-measures ANOVA. Pacing reduced CVR by 39% (from 4.7 ± 1.0 to 2.9 ± 0.4 mm Hg · mL⁻¹ · min⁻¹, P = 0.07) during vehicle infusion. With L-NMMA, CVR also decreased with pacing (by 32%, from 5.6 ± 0.9 to 3.8 ± 0.5 mm Hg · mL⁻¹ · min⁻¹; P = 0.09). Thus, minimum CVR after pacing was 33% greater with L-NMMA (P = 0.018). Baseline CVR just before pacing with L-NMMA was also higher (P = 0.05). Maximal rate-pressure product with pacing was similar before and during L-NMMA infusion (19.278 ± 961 versus 19.641 ± 807 mm Hg · bpm), as were heart rate (151 ± 1 versus 150 ± 1 bpm) and MABP (100 ± 6 versus 104 ± 5 mm Hg).
Effect of ASA and L-NMMA on Flow-Mediated Dilation

ASA abolished pacing-induced conduit vessel flow–mediated coronary artery dilation. Flow-mediated dilation with vehicle infusion was 7.7 ± 2.3%, whereas with ASA there was modest flow-mediated vasoconstriction of −1.6 ± 3.2% ($P=0.06$, Figure 5). L-NMMA also abolished pacing-induced conduit vessel flow–mediated coronary artery dilation. Flow-mediated dilation with vehicle infusion was 12.1 ± 3.9%, whereas with L-NMMA there was no flow-mediated vasodilation (0.0 ± 2.9%, $P=0.017$).

Discussion

The present study has demonstrated that in patients with atherosclerosis or coronary risk factors, vasodilator PGs are important in the maintenance of resting conduit and resistance vessel tone and contribute to metabolic vasodilation and flow-mediated dilation in response to rapid cardiac pacing. The present study also shows that NO regulates resting coronary tone and flow-mediated dilation after pacing. Although NO appeared to contribute to metabolic vasodilation and coronary flow reserve, these occurrences may be influenced by the effects of NO blockade on resting hemodynamics. These results emphasize the importance of local vascular regulation of CBF and suggest that risk factors that impair bioactivity of these paracrine factors may alter physiological responses and potentially contribute to myocardial ischemia.

Vasodilator PGs

Although experimental studies have not demonstrated a reduction of resting CBF after cyclooxygenase inhibition,20 in models of coronary artery disease, PG inhibition significantly decreased coronary diameter and CBF.26,27 In humans with atherosclerosis, indomethacin has been shown to reduce resting CBF and increase CVR17–19; these effects are associated with increased MABP, estimated myocardial oxygen demand, and arteriovenous oxygen extraction.17,19 Although estimated myocardial workload did not increase in the present study, our findings are otherwise consistent with these previous investigations.

Published studies of cyclooxygenase inhibition and coronary metabolic vasodilation have been inconsistent. Pacold et al.19 found a moderate reduction in maximum hyperemia with indomethacin, but several other investigations using indomethacin,18 ASA,21 and ibuprofen22 have not shown any effect. Our results, however, indicate that PGs are important regulators of metabolic vasodilation in patients with atherosclerosis. Differences in study design may explain these disparities. Previously, CBF was measured by coronary sinus thermodilution; cyclooxygenase inhibitors were given orally; and in patients with atherosclerosis (3 of the 4 studies), the metabolic stimulus induced myocardial ischemia. We were careful to avoid myocardial ischemia. In addition, one study22 included only healthy humans.

Previous data suggest that patients with atherosclerosis have increased prostacyclin production.28 Thus, PGs may contribute more to CBF in patients with atherosclerosis than in those without atherosclerosis. Local production of PGs in atherosclerosis may be upregulated by platelet activation,28 increased shear stress,29 endothelial damage,27 or impaired NO production related to risk factors.12,30 In support of this concept, pacing-induced coronary adenosine production is upregulated when NO production is diminished in patients with risk factors.16

Nitric Oxide

Several human studies10,11,14,15 have demonstrated that NO inhibition with L-NMMA reduces resting conduit vessel caliber and CBF; these studies are consistent with the present report. L-NMMA also increases arteriovenous oxygen extraction, whereas the rate-pressure product is unchanged.11 Although we found that L-NMMA attenuated maximum pacing-induced hyperemia and increased minimum CVR, when changes in basal coronary hemodynamics were accounted for, the effects on pacing hemodynamics were no longer significant. This implies that the principal effect of NO inhibition is on resting coronary conduit and resistance vessel tone and concurs with several previous studies.14,15 However, this may still be of critical importance in patients with reduced NO bioavailability, particularly if there are coexistent conduit vessel stenoses.9,12 This is emphasized by recent data that demonstrate impaired NO-mediated metabolic vasodilation in patients with risk factors for atherosclerosis.12,16

Because PG and NO inhibition did not eliminate metabolic vasodilation, other factors may be involved. Myocardial metabolites, especially adenosine, are likely to be important. Myogenic autoregulation also contributes to the hyperemic response.1,2 Recent experimental evidence suggests that stimulation of ATP-sensitive K+ channels is critical in coronary metabolic vasodilation.31 Their importance in humans is of considerable interest and will require further investigation.

Flow-Mediated Vasodilation

Pacing-induced flow-mediated epicardial vasodilation was abolished by NO or PG inhibition. This finding is consistent with previous investigations12–14 and confirms a role for NO in this process. Although experimental studies have not demonstrated a role for PG in coronary flow–mediated dilation,32 our results suggest that patients with atherosclerosis may become dependent on PG for flow-mediated dilation, particularly when NO bioavailability is reduced.30 Although the dependence of flow-mediated dilation on both NO and PG may appear contradictory, a combination of NO and PG inhibition may have resulted in flow-mediated vasoconstriction. Exercise-induced paradoxical vasoconstriction has been previously documented in patients with extensive atherosclerosis.5

Response to Adenosine

Recent evidence suggests that adenosine-induced vasodilation is partly NO dependent.33,34 However, we did not detect any diminution of coronary flow reserve with L-NMMA. CBF estimation was based on the assumption that adenosine does not significantly affect conduit vessel dimensions within the 15 to 20 seconds taken for maximum vasodilation.24 Augmentation of CVFR and coronary flow reserve with L-NMMA appeared to be due to decreased resting coronary APV and dimensions associated with L-NMMA.

ASA tended to increase CFVR because of augmentation of the maximum APV in response to adenosine. However, the
estimated maximal CBF before and after ASA was not significantly different and is consistent with previous experimental data. To achieve the same hyperemia with adenosine, although with a smaller resting coronary diameter with ASA, the velocity response was higher. These findings demonstrate a limitation of using velocity ratios to determine vascular function and suggest that endothelial function may modulate the CFVR in response to adenosine.

**Study Limitations**

These data apply to a small patient group with risk factors and established, albeit mild, atherosclerosis. Comparison with people free of atherosclerosis and risk factors may have provided different results.\(^1\)\(^2\)\(^\text{a}\)\(^\text{b}\)\(^\text{c}\)\(^\text{d}\) We measured regional CBF and CVR and could not determine whether there was heterogeneity in resistance vessel responses. In experimental studies, small coronary arteries (>100 µm) are the principal site of NO-mediated metabolic vasodilation, and autoregulation occurs in arterioles (<100 µm) with NO inhibition.\(^3\) Thus, in human studies, autoregulatory changes in segments of the microcirculation will be overlooked, and the contribution of NO or PG may be underestimated.

Most patients were on low-dose ASA, which may have inhibited vascular wall prostacyclin production. However, previous investigations have shown that this would be unlikely to affect our results.\(^2\)\(^1\) Anti-inflammatory doses are required to inhibit vascular prostacyclin production completely.\(^2\)\(^5\) Indeed, the effect that intracoronary ASA had on coronary tone suggests that maintenance ASA had no significant impact on coronary PG production.

**Clinical Implications**

Patients with atherosclerosis or risk factors may have endothelial dysfunction in response to pharmacological agonists, but less is known about responses to physiological stimuli.\(^5\)\(^6\) The present data suggest that anti-inflammatory doses of cyclooxygenase inhibitors in patients with atherosclerosis may affect exercise responses, particularly if there are coexisting conduit vessel stenoses. These findings also suggest that treatment strategies that enhance PG or NO bioavailability in patients with coronary artery disease may improve CBF and reduce symptoms, particularly in response to metabolic demand.\(^4\) Evidence of improved endothelial function and decreased myocardial ischemia with cholesterol lowering\(^7\)\(^,\)\(^8\) is consistent with this hypothesis.

**Conclusions**

Our findings indicate that both endothelium-derived NO and vasodilator PGs contribute to resting CBF, metabolic vasodilation, and flow-mediated coronary artery dilation in response to pacing. Our results also suggest that these 2 paracrine factors may influence adenosine-induced vasodilation. This indicates that coronary metabolic vasodilation may be influenced by diseases that affect NO and vasodilator PGs, such as atherosclerosis and its risk factors.

**Acknowledgments**

This study was supported by a medical research project grant (No. 960048). Dr Duffy was supported by a medical postgraduate research scholarship (No. 958123) from the National Health and Medical Research Council of Australia. ASA was generously supplied by Bayer, Leverkusen, Germany. We are grateful to Lynette G. Williams, RN, Rachel A. Dowling, BSc, and Karen L. Berry, BSc, for technical assistance. We are indebted to the patients who participated, the nursing and technical staff of the catheterization laboratory, and Monash Medical Center cardiologists for allowing us to recruit their patients.

**References**


