Interstudy Variability of Coronary Flow Reserve

Influence of Heart Rate, Arterial Pressure, and Ventricular Preload

Andrew L. McGinn, MD, Carl W. White, MD, and Robert F. Wilson, MD

To define the long-term variability of serial coronary flow reserve (CFR) measurements in humans and to evaluate the influence of changes in heart rate, mean arterial pressure, and left ventricular preload on CFR, 45 patients with normal left ventricular function (38 cardiac allograft recipients, five patients with normal coronary arteries, and two patients with minimal coronary artery disease [<50% diameter stenosis]) were studied. CFR (ratio of peak hyperemic [h] to resting [r] coronary blood flow velocity [CBFV]) was measured with a 3F coronary Doppler catheter and intracoronary papaverine. Initial CFR measurements were highly correlated with repeat measurements obtained 11±0.6 months later (r=0.95; mean absolute difference, 0.3±0.1; n=17). Differences in CFR between studies were related to changes in heart rate (r=0.61, p=0.01) but not to changes in mean arterial pressure (r=0.25, p=0.33). To define the effects of rapid changes in heart rate, mean arterial pressure, and preload on CFR, these variables were altered by atrial pacing, handgrip exercise, and volume expansion, respectively. Atrial pacing produced a rate-related increase in rCBFV but did not change hCBFV. Consequently, CFR was significantly reduced as heart rate was increased progressively from 76±2 in sinus rhythm (4.5±0.2) to 100 (3.8±0.2, p<0.05, n=32) to 120 beats/min (3.2±0.1, p<0.05, n=7). Despite a 19±2 mm Hg rise in mean arterial pressure during handgrip exercise, CFR was unchanged from baseline (3.7±0.3 vs. 3.7±0.4, p=NS, n=7) because rCBFV rose proportionally with hCBFV. When pulmonary capillary wedge pressure was increased from 9±1 to 16±1 mm Hg after volume expansion, CFR was significantly decreased (from 3.8±0.2 to 2.9±0.2, p<0.05, n=9) because rCBFV was increased while hCBFV remained unchanged. Hence, serial CFR measurements in humans are highly reproducible in the absence of conditions known to affect resting or hyperemic coronary blood flow. Increases in heart rate or preload reduced CFR because rCBFV was increased while hCBFV was unchanged. In contrast, changes in mean arterial pressure did not alter CFR. Proper interpretation of CFR measurements should take into account the hemodynamic conditions at which they are obtained. (Circulation 1990;81:1319-1330)

The concept of coronary flow reserve, introduced 30 years ago by Coffman and Gregg, provides a method for describing the capacity of the coronary circulation to conduct maximal hyperemic blood flow. The subsequent development of techniques for measuring coronary blood flow in humans (e.g., intracoronary Doppler catheter, digital subtraction angiographic methods, and thermodilution coronary sinus blood flow techniques) has enabled coronary flow reserve to be measured in a variety of disease states (e.g., atherosclerosis, infarction, hypertrophy, Syndrome X, and after cardiac transplantation).2-19 Previous studies have suggested that coronary flow reserve measurements can be used to evaluate coronary microvascular function16-18 and to assess the physiological significance of epicardial coronary stenoses6 and that flow reserve measurements might be useful in assessing the need for revascularization in patients with coronary artery disease of intermediate severity.20,21

In most studies, coronary flow reserve has been measured as a ratio of peak hyperemic coronary...
blood flow (after administration of a maximal coronary vasodilator such as papaverine or dipyridamole) to resting coronary blood flow. It has been hypothesized that changes in hemodynamic conditions, independent of changes in the function of the coronary circulation, might directly influence coronary flow reserve by altering resting or hyperemic blood flow. If human coronary flow reserve is influenced significantly by hemodynamic parameters, then it would be important to adjust the normal limits of coronary flow reserve to particular hemodynamic settings and to consider the effect of differences in hemodynamic conditions between sequential studies. Accordingly, this study was designed to examine the effect of changes in heart rate, arterial pressure, and left ventricular preload on coronary flow reserve and to define the long-term variability of coronary flow reserve measurements.

**Methods**

**Patient Selection**

Four study protocols were used to examine the interstudy variability of coronary flow reserve measurements and the effect of heart rate, arterial pressure, and left ventricular preload on coronary flow reserve. Individuals participating in these protocols were selected from two groups of patients.

**Thirty-eight cardiac allograft recipients.** Each heart transplant recipient underwent a routine annual invasive cardiac evaluation (coronary angiography, pulmonary artery catheterization, and right ventricular endomyocardial biopsy) for the purpose of screening for subacute-chronic allograft rejection. Posttransplantation immunosuppression was achieved in each patient with cyclosporine, azathioprine, and prednisone. None of the patients evaluated had an episode of acute rejection at any time after transplantation, and all had normal coronary arteries at angiography. Cross-sectional and M-mode echocardiographic evaluations of left ventricular systolic performance, obtained 1 day before catheterization, were normal in each subject. Four patients had left ventricular hypertrophy, defined as diastolic septal or posterior wall thickness greater than 11 mm.

**Five patients with normal coronary arteries and two with minimal coronary artery disease (<50% diameter stenosis by quantitative coronary angiography with the Brown et al. method).** Each patient underwent coronary angiography for the diagnosis of a chest pain syndrome. Left ventricular function, as assessed by contrast or equilibrium radionuclide ventriculography, was normal (left ventricular ejection fraction greater than 50% with no focal wall motion abnormality).

None of the patients from either group had the following conditions that might have affected the vasodilator capacity of the coronary vasculature: 1) historical or electrocardiographic evidence of myocardial infarction, defined by either clinical history of infarction associated with total serum creatine kinase elevation, increased creatine kinase–MB fraction, and classic evolutionary electrocardiographic changes (with or without the development of Q waves) or an electrocardiogram showing pathological Q waves of more than 0.04 seconds in duration and a focal wall motion abnormality demonstrated by contrast or equilibrium radionuclide ventriculography; 2) valvular heart disease; 3) historical or clinical observations consistent with variant angina pectoris or recent ergonovine maleate administration (within 6 hours); or 4) anemia (hemoglobin level less than 10.0 g/dl).

Informed consent was obtained from each patient. All studies were approved by the institutional review board of the University of Minnesota.

**Cardiac Catheterization and Measurement of Coronary Flow Reserve**

Patients came to the cardiac catheterization laboratory after having fasted overnight. Medications with cardiac or vasoactive properties (i.e., nitrates, calcium channel or β-adrenergic receptor blocking agents, and arterial vasodilators) were discontinued at least 12 hours before the procedure in all patients except six individuals who took a β-adrenergic blocking agent or vasodilator 4 hours or less before catheterization. Nineteen of the 38 transplant patients received long-term regimens of long-acting β-adrenergic receptor antagonist agents (atenolol or metoprolol). All of the patients were premedicated with diazepam (10 mg p.o. or i.v.). No patient received narcotic analgesia or atropine.

After routine diagnostic coronary angiography was performed, maximal epicardial coronary artery vasodilation was produced with intracoronary nitroglycerin (300–600 μg). Heparin sodium (5–10,000 U i.v.) was administered to increase the activated clotting time to at least twice the control level. A 3F 20-mHz coronary Doppler catheter (NuMed, Hopkinton, New York) was then advanced through an 8F large lumen coronary guiding catheter into the proximal segment of a coronary artery. The catheter position and Doppler range gate were adjusted to obtain a high-quality tracing of phasic coronary blood flow velocity. Mean and phasic signals of coronary blood flow velocity (kilohertz shift), arterial pressure obtained through the guiding catheter, heart rate, and electrocardiogram were recorded continuously on a multichannel direct-writing recorder (Gould, Oxnard, California). This technique has been previously described. Because the arterial waveform obtained from the guiding catheter was damped by the coronary Doppler catheter, only mean arterial pressure could be accurately monitored.

Before any intervention, baseline measurements of resting coronary blood flow velocity were obtained. To determine coronary flow reserve during resting hemodynamic conditions, 8–14 mg papaverine hydrochloride (2 mg/ml 0.9% saline) was injected through the guiding catheter into the coronary ostium, and the resultant increase in coronary blood flow velocity was recorded. To confirm that maximal hyperemia was produced in each patient, progressively larger
doses of papaverine (increases of 2–4 mg/injection) were administered until coronary blood flow velocity was maximal. Blood flow velocity was allowed to return to baseline levels between doses of papaverine. We have previously demonstrated that, administered in this fashion, intracoronary papaverine produces maximal coronary hyperemia equal in magnitude to that caused by intravenous diprydamole infusion.26 The papaverine dose required to produce maximal increases in coronary blood flow velocity was subsequently used for measurement of coronary flow reserve during the interventions.

**Study Protocols**

**Interstudy variability in coronary flow reserve.** To examine the long-term reproducibility of coronary flow reserve measurements, a second measurement was obtained in 15 patients (12 cardiac allograft recipients and three patients with no or minimal coronary artery disease) 11±0.6 months (range, 6–13 months) after the first study. In each patient, coronary flow reserve was measured in the same coronary artery or arteries (nine left anterior descending, five left circumflex, and three right coronary arteries). One transplant patient had left ventricular hypertrophy (diastolic left ventricular posterior wall thickness [LVPWd]=12 mm), which was unchanged according to echocardiography between the two studies.

**Effect of heart rate on coronary flow reserve.** To examine the influence of heart rate on coronary flow reserve, we increased the heart rate in 32 cardiac allograft recipients by right atrial pacing with a 6F temporary transvenous bipolar pacing electrode (USCI, Billerica, Massachusetts) placed percutaneously through the femoral or internal jugular vein. While phasic and mean coronary blood flow velocities, aortic and coronary blood pressures, heart rate, and the electrocardiogram were continuously recorded, maximal coronary flow reserve was measured during sinus rhythm and 3–5 minutes later during atrial pacing at 100 beats/min after hemodynamic parameters had reached a new steady state (19 left anterior descending, 11 left circumflex, one right coronary, and one intermediate coronary arteries). Three of these patients had left ventricular hypertrophy (LVPWd=12 mm). In seven patients with normal left ventricular wall thickness, coronary flow reserve also was measured during steady-state atrial pacing at 120 beats/min.

**Effect of arterial pressure on coronary flow reserve.** To examine the effect of increased arterial pressure on coronary flow reserve, mean aortic blood pressure was increased in six cardiac allograft recipients by isometric handgrip exercise. One patient had left ventricular hypertrophy (LVPWd=12 mm). In three patients, heart rate was held constant at 100 beats/min by pacing the donor right atrium. In the remaining three patients pacing was not used because the heart rate in sinus rhythm was nearly 100 beats/min and changed 3% or less during handgrip exercise. After the initial coronary flow reserve measurement was obtained (four left anterior descending, two left circumflex, and one right coronary arteries), each patient performed isometric exercise by squeezing a hand-held dynamometer at approximately one third of maximal effort for 2 minutes or until mean aortic pressure rose by 20 mm Hg. At peak exercise, coronary flow reserve again was measured. Cardiac allograft recipients were chosen to avoid neurally mediated changes in coronary vascular tone that might accompany reflex sympathetic activation by handgrip exercise.27 To evaluate whether handgrip exercise was associated with significant humoral release of catecholamines, which also might affect coronary blood flow velocity through coronary vasoconstriction, supine arterial plasma norepinephrine concentration was measured at rest and at peak handgrip exercise in two of these patients and in 10 other transplant recipients (during similar handgrip exercise) with a previously validated radioenzymatic method28 (CAT-A-KIT Assay System, Amersham, Zurich, Switzerland).

**Effect of left ventricular preload on coronary flow reserve.** The effect of ventricular preload on coronary flow reserve was studied in nine patients (seven heart transplant recipients and two normal subjects). Heart rate was held constant in six subjects by right atrial pacing at 100 beats/min. In the remaining three patients, heart rate in sinus rhythm was nearly 100 beats/min and changed 2% or less after left ventricular preload was increased. Phasic and mean coronary blood flow velocity, mean aortic and coronary pressures, heart rate, electrocardiogram, and pulmonary capillary wedge pressure were continuously monitored. After baseline coronary flow reserve was measured (five left anterior descending and four left circumflex coronary arteries), intravascular volume was expanded by rapid administration of warmed normal saline (600–1,000 ml/10 min i.v.). After intravascular volume expansion, maximal coronary flow reserve measurements were repeated.

**Data Analysis**

Coronary flow reserve was determined as the quotient of the peak blood flow velocity (maximal kilohertz shift after papaverine administration) and resting blood flow velocity. To characterize the change in coronary vascular resistance at maximal hyperemia, an index of minimum coronary vascular resistance was calculated as the quotient of (mean aortic blood pressure at peak flow velocity [mm Hg]/peak blood flow velocity [kHz shift]) and (mean aortic blood pressure at resting flow velocity/resting blood flow velocity).

**Statistical Analysis**

Differences between group means were analyzed by analysis of variance (Statview II, Statworks). Correlation coefficients were calculated with the least-squares linear regression method. Except where noted, all values are expressed as mean±SEM. Statistical significance was defined by a p value less than 0.05.
TABLE 1. Interstudy Variability in Coronary Flow Reserve

<table>
<thead>
<tr>
<th></th>
<th>Mean absolute HR (beats/min)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Mean absolute Δ MAP (mm Hg)</th>
<th>Coronary flow reserve</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>76±4</td>
<td>90±3</td>
<td>5.0±0.3</td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>75±3*</td>
<td>93±3*</td>
<td>11±2</td>
<td>5.2±0.3</td>
</tr>
</tbody>
</table>

Values are mean±SEM. HR, heart rate; MAP, mean arterial pressure. *p=NS vs. first study.

Results

Interstudy Variability in Coronary Flow Reserve

Coronary flow reserve measured during the first study was almost identical to the coronary flow reserve measured during the second study (n=17, Table 1). As shown in Figure 1, the initial measurements were highly correlated with subsequent measurements [second measurement=0.956(first measurement)+0.409; r=0.95; mean absolute difference, 0.3±0.1]. Differences in coronary flow reserve between measurements were significantly related to changes in heart rate (r=0.61, p=0.01) but not to changes in mean arterial pressure (r=0.25, p=0.33).

Effect of Increased Heart Rate on Coronary Flow Reserve

To examine further the relation between heart rate and coronary flow reserve, hemodynamic and coronary blood flow velocity measurements were obtained during normal sinus rhythm and right atrial pacing at 100 beats/min in 32 patients (Table 2). As expected, when the heart rate was increased from sinus rhythm (76±2 beats/min) to 100 beats/min, coronary blood flow velocity increased significantly. Hyperemic coronary blood flow velocity, however, did not significantly change (Table 2, Figure 2). Consequently, coronary flow reserve measured during normal sinus rhythm (4.5±0.2) was significantly greater than flow reserve at a heart rate of 100 beats/min (3.8±0.2, p<0.05, Figure 3).

In seven of these patients, in whom serial flow reserve measurements were obtained during normal sinus rhythm and right atrial pacing at 100 and 120 beats/min, coronary flow reserve progressively decreased as heart rate was increased from sinus rhythm to 100 beats/min and from 100 to 120 beats/min (Table 2). Although there was a trend for hyperemic coronary blood flow velocity to decrease with progressively higher heart rates, it was not statistically significant.

Figure 4 displays the relation between the magnitude of change in coronary flow reserve and the change in heart rate for all patients studied. Small changes in heart rate between studies were associated with small changes in coronary flow reserve, whereas large changes in heart rate were associated with large changes in coronary flow reserve.

Mean arterial pressure was lower during sinus rhythm (104±3 mm Hg) than during atrial pacing at 100 beats/min (109±3 mm Hg; mean difference, 5±1 mm Hg; p<0.05, n=32). To evaluate whether pacing-induced changes in coronary driving pressure might have resulted in the observed reduction in coronary flow reserve associated with increased heart rate, we analyzed a subgroup of 16 patients who had less than a 5-mm Hg change in mean arterial pressure when the heart rate was increased from sinus rhythm to 100 beats/min during pacing. In these patients, resting coronary blood flow velocity increased significantly during atrial pacing at 100 beats/min (from 1.9±0.2 to 2.4±0.2 kHz shift; p<0.05), whereas hyperemic coronary blood flow velocity remained unchanged (8.0±0.6 in sinus rhythm vs. 7.8±0.6 during atrial pacing, p=NS). Hence, increases in heart rate produced rate-related increases in resting coronary blood flow velocity, independent of changes in arterial blood pressure.

Figure 1. Plot of interstudy variability of coronary flow reserve measurements. Initial coronary flow reserve determinations correlated highly with repeat measurements obtained 11±0.6 months later (r=0.95; second measurement=0.956(first measurement)+0.409; n=17). ◆, Left anterior descending; ●, left circumflex; ▲, right coronary artery; CBFV, coronary blood flow velocity.
pressure. Because hyperemic coronary blood flow velocity remained constant, coronary flow reserve was reduced by tachycardia. Consequently, measurements of coronary flow reserve were heart rate dependent.

**Effect of Increased Arterial Pressure on Coronary Flow Reserve**

Hemodynamic and coronary flow reserve measurements obtained before and during isometric handgrip exercise are shown in Table 3 and Figure 5. Heart rate (99 ± 4 beats/min) did not change significantly with handgrip exercise (100 ± 5 beats/min; mean percent change, 0.5). Mean arterial pressure, however, increased significantly (mean change, 19 ± 2 mm Hg; 15 ± 2% of resting mean arterial pressure).

Associated with the rise in arterial pressure during sustained handgrip, both resting and hyperemic coronary blood flow velocity also increased (Table 3, Figure 6). Importantly, hyperemic and resting coronary blood flow velocities increased proportionally during handgrip so that their ratio, coronary flow reserve, was unchanged (3.7 ± 0.3 at rest vs. 3.7 ± 0.4 during handgrip, p = NS, Figure 6). Similarly, minimum coronary vascular resistance during handgrip also was not significantly different from baseline. Hence, maximal coronary flow reserve and an index of minimum coronary vascular resistance remained constant despite an average increase in mean arterial pressure of 19 ± 2 mm Hg.

In response to isometric handgrip exercise, supine plasma arterial norepinephrine concentration was unchanged (235 ± 35 at rest vs. 256 ± 26 pg/ml at maximum handgrip, p = NS, n = 12), suggesting that changes in humoral norepinephrine concentration could not have altered microcirculatory function.

![Figure 2](http://circ.ahajournals.org/)

**TABLE 2. Effect of Heart Rate on Coronary Flow Reserve**

<table>
<thead>
<tr>
<th>Patients</th>
<th>HR (beats/min)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Coronary blood flow velocity (kHz shift)</th>
<th>Coronary flow reserve</th>
<th>mCVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>76±2</td>
<td>104±3 93±3</td>
<td>1.8±0.1 7.7±0.4</td>
<td>4.5±0.2</td>
<td>0.21±0.01</td>
</tr>
<tr>
<td>Paced</td>
<td>100</td>
<td>109±3* 99±2*</td>
<td>2.2±0.1* 7.8±0.4</td>
<td>3.8±0.2*</td>
<td>0.25±0.01*</td>
</tr>
<tr>
<td>Serial atrial pacing (n=7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>75±3</td>
<td>93±5 82±5</td>
<td>1.7±0.3 7.5±0.8</td>
<td>4.6±0.4</td>
<td>0.20±0.02</td>
</tr>
<tr>
<td>Paced</td>
<td>100</td>
<td>95±5 91±4‡</td>
<td>2.0±0.2§ 7.1±0.7¶</td>
<td>3.6±0.2**</td>
<td>0.26±0.01**</td>
</tr>
<tr>
<td>Paced</td>
<td>120</td>
<td>100±4‡ 90±4</td>
<td>2.2±0.3† 7.1±0.7]</td>
<td>3.2±0.1†‖</td>
<td>0.28±0.02**</td>
</tr>
</tbody>
</table>

Values are mean±SEM. HR, heart rate; mCVR, minimum coronary vascular resistance; sr, sinus rhythm.

*p<0.05 vs. sr; ‡p<0.05 vs. sr; §p<0.05 vs. sr; ¶p<0.05 vs. sr; ‥p=0.06 vs. sr; †p<0.05 vs. paced 100; ‡‡p<0.05 vs. sr; ‌p<0.05 vs. paced 100.
Effect of Increased Preload on Coronary Flow Reserve

Pulmonary capillary wedge pressure increased from 9±1 to 16±1 mm Hg (p<0.05) after intravascular volume expansion (844±42 ml normal saline i.v.). In response to increased left ventricular preload, resting coronary blood flow velocity rose 15±7%, whereas hyperemic coronary blood flow velocity was unchanged (Table 4, Figures 7 and 8). Consequently, a rapid increase in left ventricular preload reduced maximal coronary flow reserve (3.8±0.2 at baseline vs. 2.9±0.2 after fluid administration, p<0.02).

Although heart rate and mean arterial pressure at peak hyperemia did not change in response to increased preload, mean arterial pressure at rest increased a small but significant amount (96±3 vs. 101±4 mm Hg; range, −2 to +11 mm Hg; p<0.05). The magnitude of the increase in resting arterial pressure did not correlate with the rise in resting coronary blood flow velocity (r=0.24) or with change in coronary flow reserve (r=0.11) after volume expansion. Moreover, when patients with less than a 5 mm Hg rise in arterial pressure after volume expansion were studied (n=5, Table 4), similar results were found. Hence, rapid increases in ventricular preload significantly increased resting coronary blood flow velocity, did not significantly alter peak hyperemic coronary blood flow velocity, and, consequently, reduced coronary flow reserve.

Discussion

These data demonstrate that coronary flow reserve, measured as the ratio of peak hyperemic to resting
coronary blood flow velocity, is dependent on heart rate and left ventricular preload but not on arterial pressure. Moreover, although serial coronary flow reserve measurements are highly reproducible, differences in serial coronary flow reserve measurements are related significantly to differences in heart rate but not to differences in mean arterial pressure. Hence, interpretation of coronary flow reserve measurements should take into account the heart rate and left ventricular preload at which they are obtained.

**Potential Methodological Limitations**

Several potential methodological limitations must be considered when interpreting these data. First, measurements of coronary flow reserve obtained with the Doppler catheter might be affected by changes in the caliber of the coronary vessel containing the catheter, obstruction of hyperemic blood flow by the guiding catheter, and altered velocity profiles. These potential problems have been discussed in detail elsewhere.² Importantly, to preserve the linear relation between coronary blood flow and coronary blood flow velocity, we produced maximal epicardial coronary vasodilation with nitroglycerin before measuring flow reserve.

Second, this investigation examined the effects of rapid changes in heart rate, systemic arterial pressure, and ventricular preload on coronary flow reserve. It is possible that long-term alterations in these parameters might be associated with effects different from what we observed in this study. A prolonged period of hypertension, for example, might cause a true decrease in microvascular conductance and, consequently, reduce coronary flow reserve.²⁹

Third, only patients with normal coronary arteries were studied. In patients with significant coronary artery or myocardial disease, maximal hyperemic coronary blood flow velocity should be blunted at any given heart rate, arterial pressure, or left ventricular preload. Consequently, a smaller absolute change in coronary flow reserve would be expected in these.

**TABLE 3. Effect of Arterial Pressure on Coronary Flow Reserve**

<table>
<thead>
<tr>
<th>Patients (n=7)</th>
<th>HR (beats/min)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Coronary blood flow velocity (kHz shift)</th>
<th>Coronary flow reserve</th>
<th>mCVR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100±5</td>
<td>108±5</td>
<td>97±4</td>
<td>2.1±0.2</td>
<td>3.7±0.3</td>
</tr>
<tr>
<td></td>
<td>Handgrip</td>
<td>128±4*</td>
<td>122±4*</td>
<td>2.5±0.3*</td>
<td>3.7±0.4</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
HR, heart rate; mCVR, minimum coronary vascular resistance.
*p<0.05 vs. baseline; tp=0.07 vs. baseline.

**FIGURE 5. Tracings of effect of arterial pressure on coronary flow reserve (CFR).** Simultaneous recordings of phasic and mean left anterior descending coronary blood flow velocity (CBFV), phasic aortic pressure, coronary pressure, heart rate, mean aortic pressure, and electrocardiogram (EKG) from a cardiac allograft recipient. As heart rate remained constant at 100 beats/min, isometric handgrip exercise increased mean aortic pressure from 104 to 124 mm Hg. Despite this 20-mm Hg increase in mean arterial pressure, coronary flow reserve was unchanged from baseline because resting coronary blood flow velocity changed proportionally with hyperemic coronary blood flow velocity.
patients. The fractional change in coronary flow reserve, however, should be the same in the absence of mechanical or reflex changes that alter stenosis severity. This study in patients with normal coronary arteries and left ventricular systolic function, therefore, probably describes the maximal effect of changes in heart rate, arterial pressure, and preload on coronary flow reserve.

Fourth, although changes in heart rate and ventricular preload significantly affected coronary flow reserve, moderate elevation of systemic arterial pressure did not. It is possible that coronary flow reserve might be altered significantly by changes in systemic arterial pressure of greater magnitude, particularly if arterial pressure exceeded the bounds of coronary autoregulation. Such a change in arterial pressure in humans, however, would be extreme.

Fifth, we evaluated the effect of increased arterial pressure on coronary flow reserve only in patients with presumed cardiac denervation. In these patients, plasma arterial norepinephrine levels did not rise significantly with handgrip exercise. In individuals with intact autonomic cardiac innervation, however, changes in autonomic coronary tone induced by changes in hemodynamic conditions might alter microvascular function and oxygen demand, thereby changing resting or hyperemic blood flow.

Sixth, assessment of the interstudy variability of coronary flow reserve measurements was performed primarily in cardiac allograft recipients, whose heart rate changed little between studies (mean absolute difference, 8 ± 1 beats/min), likely related to cardiac autonomic denervation. Because coronary flow

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**TABLE 4. Effect of Ventricular Preload on Coronary Flow Reserve**

<table>
<thead>
<tr>
<th>Patients</th>
<th>HR (beats/min)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Coronary flow velocity (kHz shift)</th>
<th>Coronary flow reserve</th>
<th>mCVR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Resting</td>
<td>Hyperemia</td>
<td>Resting</td>
<td>Hyperemia</td>
</tr>
<tr>
<td>All (n = 9)</td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>97±4</td>
<td>96±3</td>
<td>88±2</td>
<td>9±1</td>
<td>1.9±0.2</td>
</tr>
<tr>
<td>After fluid</td>
<td>97±4</td>
<td>101±4*</td>
<td>92±3</td>
<td>16±1*</td>
<td>2.5±0.5*</td>
</tr>
<tr>
<td>With &lt;5 mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ΔMAP (n = 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>98±7</td>
<td>94±3</td>
<td>87±3</td>
<td>9±1</td>
<td>1.9±0.3</td>
</tr>
<tr>
<td>After fluid</td>
<td>99±6</td>
<td>95±4</td>
<td>87±4</td>
<td>16±2†</td>
<td>2.3±0.3†</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

HR, heart rate; mCVR, minimum coronary vascular resistance; PCWP, pulmonary capillary wedge pressure.

*p < 0.05 vs. baseline; †p < 0.05 vs. baseline.
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Left Anterior Descending Coronary Artery

Phasic CBFV (kHz shift)

Mean CBFV (kHz shift)

Aortic Pressure (mmHg)

Mean Pulmonary Capillary Wedge Pressure (mmHg)

Mean Aortic Pressure (mmHg)

Mean PCWP (mmHg)

FIGURE 7. Tracings of effect of left ventricular preload on coronary flow reserve (CFR). Simultaneous recording of phasic and mean left anterior descending coronary blood flow velocity (CBFV), phasic aortic pressure, phasic pulmonary capillary wedge pressure (PCWP), measured mean aortic and mean pulmonary capillary wedge pressures, and electrocardiogram (EKG) from a cardiac allograft recipient. Heart rate was held constant by right atrial pacing at 100 beats/min. When mean pulmonary capillary wedge pressure was increased from 10 to 18 mm Hg, resting coronary blood flow velocity increased by 80%. Because hyperemic coronary blood flow velocity remained essentially unchanged, coronary flow reserve at increased left ventricular preload was significantly reduced.

reserve is significantly heart rate dependent, the exceptional long-term reproducibility of flow reserve measurements in these patients might have been related, in part, to the absence of significant changes in heart rate between studies.

Seventh, the interstudy variability of coronary flow reserve measurements also might have been influenced by pharmacological alterations of resting or maximal hyperemic coronary blood flow. Although medications with cardiac or vasoactive properties were discontinued at least 4 hours before the study, nine of the 17 patients in this protocol received long-term treatment for hypertension with calcium channel or β-adrenergic receptor antagonists that

FIGURE 8. Bar graphs of effect of increased preload on resting and hyperemic coronary blood flow velocities (CBFV) and coronary flow reserve. Panel A: Change in resting and hyperemic coronary blood flow velocities in response to increased preload. After fluid administration, resting coronary blood flow velocity increased significantly, whereas hyperemic coronary blood flow velocity remained unchanged. Panel B: Effect of increased preload on coronary flow reserve. Coronary flow reserve was reduced significantly after fluid administration.
can have a relatively long duration of action. The effect of any residual drug should have been similar during both measurements of flow reserve, however, because medications and dosages did not change between studies.

Last, in this study, coronary flow reserve was measured as a ratio of peak hyperemic to resting coronary blood flow velocity. Consequently, coronary flow reserve can be altered by changes in either resting or hyperemic coronary blood flow. In contrast to animals, in which minimum coronary vascular resistance can be measured in absolute terms (i.e., dyne·sec/cm$^5$) with microspheres or perivascular flow probes, no currently available technique can accurately measure absolute regional peak hyperemic blood flow in human myocardium. The development of such methods will enhance studies of the human coronary circulation by removing the reliance on measurements of the ratio between peak hyperemic and resting coronary blood flow velocity to assess the maximal coronary flow reserve. Preliminary reports of methods developed in animals for determining coronary flow reserve that are independent of hemodynamic conditions might become applicable to humans.

**Previous Studies**

In conscious humans and dogs, tachycardia produced by cardiac pacing is associated with elevated myocardial oxygen demand and increased coronary blood flow. In awake dogs, maximal hyperemic coronary blood flow (produced by intravenous adenosine), however, remained constant as heart rate was increased to 200 beats/min and decreased significantly only at a heart rate of 250 beats/min. Consequently, coronary flow reserve was reduced during tachycardia primarily because of elevated resting coronary blood flow, although at very rapid heart rates, coronary arterial compressive forces accompanying mechanical ventricular systole and shortened diastolic coronary perfusion time might have significantly reduced hyperemic coronary blood flow. These studies parallel our observations in humans. Although there was a trend for hyperemic coronary blood flow velocity to be reduced at higher heart rates, it was not significant.

When the mean arterial pressure of dogs anesthetized with barbiturates was increased from 94±2 to 123±4 mm Hg by constriction of the descending thoracic aorta, resting and peak reactive hyperemic coronary blood flow rose proportionally with the increased coronary driving pressure. Within the zone of coronary autoregulation, coronary flow reserve remained constant, as we observed in humans. When arterial pressure in dogs was increased to levels at which autoregulation of coronary blood flow was lost (138±2 mm Hg), however, coronary flow reserve was reduced because resting coronary blood flow increased more than hyperemic coronary blood flow. Hence, although the results of our study in humans were similar to those performed in animals with an arterial pressure in the zone of coronary autoregulation, elevation of arterial pressure beyond the bounds of autoregulation might reduce maximal coronary reserve.

In an open-chest, open-pericardium, anesthetized dog preparation in which coronary autoregulation was abolished with vasodilation (carbochromen or adenosine), increased left ventricular preload produced by volume expansion was associated with a reduction in the ratio of endocardial to epicardial coronary blood flow. Total diastolic left circumflex coronary blood flow was either decreased or did not change. When heart rate and systemic perfusion rate were controlled in anesthetized, open-chest dogs, however, increased left ventricular volume was associated with increased left ventricular wall tension and myocardial oxygen demand. Coronary blood flow increased in response to elevated left ventricular preload. The effect of increased left ventricular preload on total coronary blood flow in the conscious animal has not been studied. Our study suggests, however, that in the conscious human with an intact pericardium, rapid increases in left ventricular preload are associated with significant increases in resting coronary blood flow without a significant change in total peak hyperemic blood flow.

**Implications**

In the absence of significant changes in heart rate or ventricular preload, serial coronary flow reserve measurements (ratio of peak hyperemic to resting coronary blood flow velocity) are highly reproducible in humans. Hence, sequential determinations of coronary flow reserve obtained with a Doppler catheter can be a valuable clinical tool in the longitudinal assessment of the coronary circulation of conscious humans. Proper interpretation of both isolated and serial coronary flow reserve measurements, however, should take into account the hemodynamic conditions at which they are obtained. In our laboratory, we now obtain all coronary flow reserve measurements at a heart rate of 100 beats/min (atrial pacing). In this way, we can compare the results of serial measurements and assess the significance (normal vs. abnormal) of an isolated measurement. In heart transplant patients with normal coronary arteries and myocardium, the mean (±SD) coronary flow reserve at a heart rate of 100 beats/min is 4.0±1.1 (range, 3.0–7.5, n=25).

Many prior clinical studies have investigated the effects of pathological states, physiological stimuli, and coronary revascularization on coronary flow reserve. It is possible that hemodynamic alterations, rather than a process intrinsic to the condition or intervention being studied, caused some of the reported abnormalities of coronary flow reserve. Reduced coronary flow reserve in congestive cardiomyopathy, for example, might have been partly due to the direct effects on resting coronary blood flow of tachycardia and elevated left ventricular preload rather than an anatomic or functional abnormality that reduced maximal hyperemic blood flow in...
the coronary vasculature. The results of these studies and of future investigations should be examined with attention to the effect of heart rate and left ventricular preload on coronary flow reserve measurements.

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References


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