Restricted Coronary Flow Reserve in Patients with Mitral Regurgitation Improves After Mitral Reconstructive Surgery

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Objectives. The purpose of this study was to assess coronary flow characteristics in patients with chronic mitral regurgitation (MR).

Background. Coronary flow reserve (CFR) has been reported to be restricted in cases with left ventricular (LV) volume overload caused by aortic regurgitation and increased LV preload.

Methods. The study populations consisted of 31 patients with nonrheumatic chronic MR. Eleven with chest pain and normal coronary arteries served as control subjects. Phasic coronary flow velocities were obtained in the proximal segment of the angiographically normal left anterior descending coronary artery at rest and during hyperemia (0.14 mg/kg/min adenosine infusion intravenously) using a 0.014-in. (0.036 cm), 15-MHz Doppler guide wire. Coronary flow reserve was obtained from the ratio of hyperemic/baseline time-averaged peak velocity (APV). Thirteen cases who underwent mitral valve reconstructive surgery were also studied 1 month after surgery.

Results. Compared with control subjects, CFR was significantly reduced in cases with MR (2.1 ± 0.5 vs. 3.3 ± 0.6, respectively, p < 0.01) because baseline APV was significantly greater (28 ± 8 vs. 19 ± 6 cm/s, respectively, p < 0.01), although maximal hyperemic APV was not significantly different (56 ± 14 vs. 61 ± 16 cm/s, respectively, p = NS). Significant correlations were obtained between CFR and LV end-diastolic pressure (LVEDP) (r = 0.70, p < 0.01), LV mass index (r = 0.42, p < 0.01), LV end-diastolic volume (r = 0.38, p = 0.04) and MR volume (r = 0.39, p = 0.03), and stepwise regression analysis showed LVEDP was the most important determinant of CFR in MR (r^2 = 0.49, p < 0.0001). This restricted CFR improved significantly after mitral valve reconstructive surgery (2.1 ± 0.5 vs. 3.1 ± 0.6, respectively, p < 0.01) because of reduction of baseline APV (28 ± 8 vs. 21 ± 8 cm/s, respectively, p < 0.01).

Conclusions. Coronary flow reserve is limited in cases with MR because of elevation of baseline resting flow velocity. This reduction of CFR correlates well with increase in LV preload, mass and volume overload, especially with increase in LV preload, and this restricted CFR improves after mitral valve surgery.

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It has been reported that coronary flow reserve (CFR) is restricted in patients with left ventricular (LV) hypertrophy secondary to volume overload caused by aortic regurgitation (1–3). Increase in absolute baseline resting coronary flow or diminution in indexed hyperemic coronary flow by LV mass has been demonstrated to be a main mechanism of this restriction of CFR (1,2). However, there has been no report of CFR in cases with LV volume overload caused by mitral regurgitation (MR) in humans. LV hypertrophy secondary to volume overload would also be seen in patients with MR, and reduced CFR could also be expected in this diseased status. Furthermore, increase in LV preload, which has been also described to reduce CFR by increasing resting coronary flow (4), would be observed in cases with MR, and marked restriction of CFR should be expected in patients with MR even with normal LV performance. These limited CFRs, furthermore, would improve after successful operation because of reduction in LV preload, LV mechanical work and LV mass after disappearance of MR.

A recently developed Doppler guide wire has been used for the measurement of phasic spectral flow velocity in human coronary artery with ease and safety (5,6). Using this method, coronary flow velocity and CFR could be easily assessed without any flow disturbance in cases with normal coronary artery (5). This study sought to assess the coronary flow dynamics in patients with chronic MR.

Methods

Study patients. The study populations consisted of 31 patients (15 male and 16 female) with chronic MR secondary to mitral valve prolapse and normal coronary arteries. Patient
Selective coronary angiography was carried out by the Judkins’ technique using a 5-F coronary angiography catheter (Selecon, Clinical Supply, Inc.) after intravenous injection of 3 mg of isosorbide dinitrate, and was immediately analyzed visually by two observers to exclude patients with coronary stenosis. To assess the diameters of the left anterior descending coronary artery at the position corresponding to the tip of the Doppler guide wire where flow velocity was recorded, coronary angiography in end-diastole was analyzed quantitatively with the use of off-line edge detection method with a commercially available system (CMS, Medical Imaging Systems, Inc.) in the same manner as previously reported (16,17). MR volume was calculated from the difference of LV total stroke volume obtained from left ventriculography and right ventricular forward stroke volume determined by thermodilution method, and regurgitant fraction was determined by the ratio of the regurgitant volume/LV stroke volume.

**Coronary flow velocity recordings.** Phasic coronary flow velocity patterns were recorded at rest and during hyperemia induced by 0.14 mg/kg/min of adenosine (Adenocard, Fujisawa USA, Inc.) infusion intravenously in the proximal portion of the left anterior descending coronary artery using a 0.014-in. (0.036 cm), 15-MHz Doppler guide wire (FloWire, Cardiometrics, Inc.) and a velocimeter (FloMap, Cardiometrics, Inc.) (5,6) following selective coronary angiography after isosorbide dinitrate injection intravenously. Pulse repetition frequency of the Doppler flowmeter was variable from 12 to 96 kHz within the velocity range selected.

The Doppler guide wire was advanced into the proximal left anterior descending coronary artery through a 5-F coronary angiography catheter. An optimal Doppler signal was obtained by moving the guide wire slightly within the vessel lumen and adjusting the range gate control. The final position of the Doppler guide wire was confirmed by contrast injection. During the Doppler study, a 12-lead surface electrocardiogram and pressure waveform at the tip of the guiding catheter were monitored continuously.

Frequency analysis of the Doppler signals was carried out in real time by fast Fourier transform using a velocimeter (FloMap, Cardiometrics, Inc.) (5). Five minutes after injection of contrast medium and isosorbide dinitrate, Doppler signals were recorded at rest and during hyperemia on videotape and by a videoprinter at a sweep speed of 100 mm/s along with an electrocardiogram and aortic pressure tracing. Systolic and diastolic peak velocities, and the time average of the instantaneous spectral peak velocity (time-averaged peak velocity; APV) were measured from the phasic coronary flow velocity recordings in the same manner as previously reported (5,6). Coronary flow reserve was obtained from the ratio of maximal coronary flow velocity (time-averaged peak velocity; APV) where

$$Q_{\text{max}} = \pi \times (D/2)^2 \times (0.5 \times \text{APV})$$

Coronary flow reserve was defined as the ratio of maximal coronary flow velocity to resting peak velocity.

**Echocardiographic examination.** Two-dimensional and M-mode echocardiography was performed within a week before cardiac catheterization. Left ventricular wall thickness and dimensions were measured from the M-mode echocardiograms, and LV mass was calculated from two-dimensional echocardiograms by use of the same algorithm as previously described (13–15).

**Cardiac catheterization and angiography.** All medications were terminated at least 24 h before cardiac catheterization, and any drugs likely to affect coronary hemodynamics (including nitroglycerine) were not used during the catheterization procedure prior to selective coronary angiography. After sedation with 5 mg of diazepam administered orally, patients were taken to the cardiac catheterization laboratory.

Cardiac catheterization was performed by the femoral approach after local anesthesia with 0.5% lidocaine. The left ventricle was approached in a retrograde manner. Left and right heart pressure data were recorded after intravenous injection of 4,000 U of heparin using a fluid-filled catheter-transducer system before selective coronary angiography. Cardiac output was measured by the thermodilution method.

**Abbreviations and Acronyms**

- ANOVA = analysis of variance
- APV = time average of the instantaneous spectral peak velocity (time-averaged peak velocity)
- CFR = coronary flow reserve
- LV = left ventricular
- MR = mitral regurgitation
- PCWP = pulmonary capillary wedge pressure

Age ranged from 27 to 73 years with a mean age of 58 ± 10 years. Of these cases, 29 underwent mitral reconstructive surgery, and 13 (7 male and 6 female) out of these 29 patients were studied again 1 month after surgery (60 ± 9 years, range from 31 to 72 years). The remaining two cases were treated medically without surgery. The subjects who had history or electrocardiographic findings of old myocardial infarction, other valvular heart disease, primary cardiomyopathy, hypertension (more than 160/95 mm Hg), atrial fibrillation and miscellaneous electrocardiographic abnormalities were excluded from this study. The patients with diabetes mellitus (7–9), hypercholesterolemia (10) and coronary vasospasm (11,12), which has been reported to have some influences on CFR, were also excluded from this study. Eleven cases (5 male and 6 female) with angiographically normal coronary arteries and without valvular heart disease, who were referred to cardiac catheterization laboratory for the final evaluation of chest pain, served as control subjects. The age of the control subjects ranged from 49 to 73 years with a mean age of 62 ± 8 years. After written informed consent was obtained, cardiac catheterization, coronary angiography and the subsequent coronary flow velocity recordings were carried out as part of diagnostic procedure.

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Table 1. Clinical Characteristics and Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>Mitral Regurgitation (n = 31)</th>
<th>Mitral Valve Plasty (n = 13) Before Operation</th>
<th>After Operation</th>
<th>Control Subjects (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 ± 10</td>
<td>60 ± 9</td>
<td>62 ± 8</td>
<td></td>
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<tr>
<td>Male/female</td>
<td>15/16</td>
<td>7/6</td>
<td>5/6</td>
<td></td>
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<tr>
<td>Hemoglobin concentration (mg/dl)</td>
<td>13.2 ± 1.3</td>
<td>13.1 ± 1.4</td>
<td>12.4 ± 1.2</td>
<td>13.3 ± 1.3</td>
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<tr>
<td>Left atrial dimension (cm)</td>
<td>5.7 ± 0.7*†</td>
<td>5.4 ± 0.7*†</td>
<td>4.1 ± 0.5*</td>
<td>4.9 ± 0.4</td>
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<tr>
<td>LVESVI (ml/m²)</td>
<td>14 ± 18*†</td>
<td>41 ± 14*†</td>
<td>31 ± 8</td>
<td>29 ± 3</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>190 ± 32*†</td>
<td>180 ± 33*†</td>
<td>138 ± 31</td>
<td>124 ± 26</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75 ± 14</td>
<td>74 ± 16</td>
<td>82 ± 17</td>
<td>68 ± 4</td>
</tr>
<tr>
<td>Cardiac index (ml/min/m²)</td>
<td>5 ± 0.6</td>
<td>2 ± 0.7</td>
<td>2 ± 0.6</td>
<td>2 ± 0.5</td>
</tr>
<tr>
<td>LVDD (cm)</td>
<td>132 ± 53*†</td>
<td>133 ± 49*†</td>
<td>72 ± 18</td>
<td>78 ± 15</td>
</tr>
<tr>
<td>LVESDI (ml/m²)</td>
<td>48 ± 14*†</td>
<td>41 ± 14*†</td>
<td>31 ± 8</td>
<td>29 ± 3</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>67 ± 6*†</td>
<td>69 ± 6†</td>
<td>56 ± 6*</td>
<td>62 ± 8</td>
</tr>
<tr>
<td>SVR (mm Hg)</td>
<td>91 ± 14</td>
<td>94 ± 14</td>
<td>96 ± 12</td>
<td>98 ± 13</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>13 ± 7*†</td>
<td>14 ± 8*†</td>
<td>6 ± 3</td>
<td>7 ± 3</td>
</tr>
<tr>
<td>Regurgitant volume (ml)</td>
<td>81 ± 53*</td>
<td>84 ± 46*†</td>
<td>6 ± 7</td>
<td>2 ± 5</td>
</tr>
<tr>
<td>Coronary diameter (mm)</td>
<td>2.9 ± 0.6</td>
<td>2.7 ± 0.6</td>
<td>2.7 ± 0.6</td>
<td>2.6 ± 0.3</td>
</tr>
</tbody>
</table>

*p < 0.01 versus control subjects, †p < 0.01 versus mitral valve plasty after operation. LVDD = left ventricular end-diastolic dimension; LVESDI = left ventricular end-systolic dimension; SVR = systemic vascular resistance; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; LVMI = left ventricular mass index; PCWP = pulmonary capillary wedge pressure; %FS = percent fractional shortening.

Statistical analysis. All data are expressed as mean values ± SD. One-way analysis of variance (ANOVA) was used to compare the three groups for clinical characteristics, hemodynamic data and coronary flow data. A Fisher protected least significant difference (PLSD) test was carried out if the ANOVA showed significant differences. Within cases with mitral reconstructive surgery, a paired two-tailed t testing was performed to compare the data between before and after surgery. The relations between CFR and other hemodynamic parameters were assessed by linear regression analysis. A probability value <0.05 was considered significant. Stepwise regression analysis was also performed to estimate the most important determinant of CFR among hemodynamic parameters.

Results

Clinical characteristics and hemodynamic data. As indicated in Table 1, among patients with MR, cases after mitral reconstructive surgery and control subjects, there were no significant differences in patients’ age, cardiac index, mean aortic pressure, heart rate and hemoglobin concentration. In cases with MR, LV end-diastolic and end-systolic volume indexes, MR volume and fraction, LV mass index, LV end-diastolic pressure and mean pulmonary capillary wedge pressure (PCWP) were significantly greater than those in cases after mitral reconstructive surgery and control subjects, although they were not significantly different between cases after mitral valve surgery and control subjects. In cases after mitral reconstructive surgery, no or trivial MR was demonstrated by echocardiography and left ventriculography, and calculated MR volume and fraction were not significantly different from those in control subjects. Left ventricular ejection fraction was significantly decreased in cases after mitral valve surgery compared with that in patients with MR and control subjects. Mitral regurgitation volume was 81 ± 53 ml and regurgitant fraction was 55 ± 19% in patients with MR, although trivial regurgitant volume and fraction were obtained in cases after mitral reconstructive surgery and even in control subjects as described in Table 1. Within 13 cases with MR, who were examined before and after mitral reconstructive surgery, there were no significant differences between before and after mitral reconstructive surgery in cardiac index, mean aortic pressure, heart rate and hemoglobin concentration, although LV end-diastolic and end-systolic volume indexes, LV ejection fraction, MR volume and fraction, LV mass index, LV end-diastolic pressure and mean PCWP were significantly greater before mitral reconstructive surgery compared with those after surgery (Table 1).

Coronary flow velocity data. In each subjects’ group, there were no significant differences in mean aortic pressure and heart rate during hyperemia compared with those at baseline.
Coronary flow reserve 2.1
Maximal hyperemia
LVMI
Regurgitant volume
Regurgitant fraction
LVEDP
Mean aortic pressure
LVEF
LVESVI
Cardiac index
Heart rate
Maximal APV
Hemodynamic Parameters
Regression Analyses Between Coronary Flow Reserve and

Table 3. Regression Analyses Between Coronary Flow Reserve and Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>p Value</th>
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<tr>
<td>Baseline APV</td>
<td>0.59</td>
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<tr>
<td>Maximal APV</td>
<td>0.27</td>
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<tr>
<td>Heart rate</td>
<td>0.46</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.04</td>
</tr>
<tr>
<td>LVEDVI</td>
<td>0.38</td>
</tr>
<tr>
<td>LVESVI</td>
<td>0.39</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean aortic pressure</td>
<td>0.26</td>
</tr>
<tr>
<td>LVEDP</td>
<td>0.70</td>
</tr>
<tr>
<td>PCWP</td>
<td>0.40</td>
</tr>
<tr>
<td>Regurgitant fraction</td>
<td>0.53</td>
</tr>
<tr>
<td>Regurgitant volume</td>
<td>0.39</td>
</tr>
<tr>
<td>LVMI</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*p < 0.01 versus control subjects. †p < 0.01. ‡p = 0.01 versus mitral valve plasty after operation. APV = time-averaged peak velocity.

condition. At baseline resting condition, as described in Table 2, APV was significantly greater in patients with MR compared with that in cases after mitral reconstructive surgery and control subjects, although there were no significant differences in maximal hyperemic APV among them. Similarly, baseline flow rate was significantly greater in patients with MR compared with that in cases after mitral reconstructive surgery and control subjects, although there were no significant differences in maximal hyperemic flow rate among them. As a result, CFR was significantly smaller in patients with MR compared with cases after mitral reconstructive surgery and control subjects. In patients with MR, as demonstrated in Table 3 and Figure 1, a significant correlation with substantial scatter was observed between CFR and baseline APV. Furthermore, as indicated in Table 3 and Figure 2, significant correlations with considerable scatter were also observed between CFR and LV end-diastolic pressure, PCWP, LV mass index, LV end-diastolic volume index and MR volume in cases with MR. Stepwise regression analysis showed LV end-diastolic pressure was the most important determinant of CFR in MR among hemodynamic parameters ($r^2 = 0.49, p < 0.0001$).

In 13 cases who underwent mitral reconstructive surgery, as indicated in Table 2 and Figures 3 and 4, baseline APV and coronary flow rate were significantly greater before surgery compared with those after surgery, although there were no significant differences in maximal hyperemic APV and coronary flow rate between before and after reconstructive surgery. As a result, CFR before mitral reconstructive surgery was significantly smaller than that after surgery.

**Discussion**

The present study demonstrates CFR is limited in patients with MR because of increase in baseline coronary flow and flow velocity, and this restriction of CFR improves after successful mitral reconstructive surgery because of reduction in baseline coronary flow and flow velocity with reductions of LV preload, LV volume and LV hypertrophy. This restriction of CFR correlates significantly with baseline resting coronary flow velocity, LV preload, which was demonstrated by LV end-diastolic pressure, LV end-diastolic volume index, MR volume and LV mass index. Thus, increase in baseline resting coronary blood flow caused by increase in LV preload, LV volume overload and LV hypertrophy due to MR might be main mechanisms of restricted CFR in patients with MR, and especially, LV preload proves to be the most important determinant of CFR in MR among various hemodynamic parameters.

**Coronary flow reserve and left ventricular preload.** It has been reported that increase in heart rate and LV preload reduce CFR because of increase in baseline resting blood flow velocity without any change in maximal hyperemic blood flow velocity (4). In the present study, there were no significant differences in heart rate among three patients groups, and this might not be the cause of restricted CFR in cases with MR. Furthermore, in 13 cases who underwent mitral reconstructive surgery, CFR improved after surgery because of reduction in baseline flow velocity, although there was no significant difference in heart rate between before and after surgery. This might
also support that heart rate is not the cause of restricted CFR in cases with MR. Left ventricular preload, which was determined by LV end-diastolic pressure, was significantly greater in cases with MR in the present study compared with that in control subjects and cases after mitral valve reconstructive surgery. Furthermore, a significant correlation was observed between CFR and LV end-diastolic pressure in cases with MR, although there was substantial scatter. Thus, increase in LV preload might be one cause of increase in baseline resting coronary flow velocity resulting in restriction in CFR, and this might be the most important determinant of CFR in MR as demonstrated by stepwise regression analysis. After reduction in LV preload and LV mechanical work after successful mitral reconstructive surgery, baseline resting flow velocity uniformly decreased, with uniform increase in CFR. Changes in heart rate and maximal hyperemic flow velocity were observed in individual cases after mitral valve surgery, and these might influence CFR in some degree. Substantial scatter in correlations between CFR and LV end-diastolic pressure in cases with MR might be related to these individual factors and the other mechanisms described below.

A significant and weak correlation was also obtained be-

Figure 1. Scatterplot of coronary flow reserve and baseline time-averaged peak velocity (APV). Significant linear correlations between coronary flow reserve and baseline coronary flow velocity are observed with substantial scatter. Dotted line indicates 90% confidence bands.

Figure 2. Scatterplots of coronary flow reserve and left ventricular end-diastolic pressure (LVEDP), left ventricular end-diastolic volume index, left ventricular mass index (LVEDVI) and mitral regurgitant volume. Significant linear correlations between coronary flow reserve and LVEDP, LVEDVI, LVMI and mitral regurgitant volume are observed with substantial scatter. Dotted lines indicate 90% confidence bands.

Figure 3. Examples of coronary flow velocity recordings in the proximal left anterior descending coronary artery at baseline (left panels) and during hyperemia (right panels) in a case with mitral regurgitation before (upper panels; Pre-op) and after (lower panels; Post-op) mitral reconstructive surgery. Baseline flow velocity decreases and coronary flow reserve increases after mitral reconstructive surgery compared with those before surgery. APV = time-averaged peak velocity; FR = coronary flow reserve.
tween CFR and PCWP. In cases without MR, PCWP may correlate well with LV end-diastolic pressure and reflect LV preload. However, in cases with MR, PCWP would depend not only on LV end-diastolic pressure but also on MR volume and the size and distensibility of the left atrium. This might be a cause of the weak correlation between CFR and PCWP in cases with MR.

As described below, a significant and weak correlation was obtained between CFR and LV end-diastolic volume. In chronic volume overload by MR, LV end-diastolic volume may represent LV preload in some degree; many factors including LV afterload, LV contractility and MR volume might also influence LV end-diastolic volume, and this might be a weak correlation between them.

**Coronary flow reserve and left ventricular hypertrophy.**

Left ventricular hypertrophy has been reported to increase baseline resting coronary flow resulting in reducing CFR in cases with aortic regurgitation (1–3), hypertension (18), hypertrophic cardiomyopathy (19) and aortic stenosis (20,21). It has been reported that patients with LV hypertrophy usually have normal coronary blood flow per unit mass of left ventricle at rest (1,2,22), and total baseline flow may increase in proportion to increase in LV mass, although the precise mechanism of limited CFR has not yet been determined in cases with LV hypertrophy (22). In the present study, although there was substantial scatter, a significant correlation was also demonstrated between LV mass index and CFR in cases with MR. Thus, LV hypertrophy might have some influence on increase in baseline resting coronary flow velocity and restriction in CFR, because LV hypertrophy was significantly reduced after successful mitral valve surgery, and baseline coronary blood flow and flow velocity were also decreased significantly and CFR improved significantly after surgery. However, in cases with chronic MR, the increased mechanical work might be the common determinant of the LV dilatation, the myocardial hypertrophy and the coronary blood flow, and significant correlations would be expected between CFR and the indexes of LV volume overload and LV hypertrophy. Thus, LV hypertrophy might not be a cause of increase in basal coronary flow in MR, but simply a variable similar to elevation of the basal coronary flow, which is related to chronic volume overload by MR.

**Coronary flow reserve and degree of mitral regurgitation.**

A significant correlation with substantial scatter was observed between CFR and degree of MR, which was demonstrated by LV end-diastolic volume index or MR volume, in cases with MR in the present study. There were many indexes to speculate the severity of MR, such as LV end-diastolic volume, PCWP, MR volume, regurgitant fraction and so on. In the present study, most of the subjects with MR might be ideal cases for mitral reconstructive surgery, and there were no cases with markedly deteriorated LV function. Therefore, CFR and indexes of MR showed significant correlations to one another as indicated in Table 3. In patients with markedly deteriorated LV function, marked increase in LV volume may increase in baseline coronary flow, and the deterioration of LV function may reduce myocardial oxygen demand leading to reduction of baseline coronary flow. Further study is necessary in this regard.

Although MR volume might be an important index to diagnose severity of MR, afterload may have some influence on MR volume. This might be related to a weak correlation between CFR and MR volume. A weak correlation was also obtained between CFR and MR fraction, although MR fraction is also affected by afterload and LV volume. As described above, markedly deteriorated LV function was not seen in the subjects with MR, and most of them might be ideal cases for mitral reconstructive surgery in the present study. This might be a cause of a significant correlation between CFR and MR fraction in the present study.

**Comparison with previous studies.** Carabello et al. (23) have reported that no significant differences can be demonstrated in baseline resting and maximal hyperemic coronary blood flow and CFR in experimental dogs after 3 months of MR compared with control dogs. The results were completely different from the present study in humans. This might be related to differences in species, method of coronary flow measurement and length of illness. Left ventricular hypertrophy was demonstrated in these experimental dogs (23), and increase in LV preload should also be expected in the experimental study. As discussed above, increase in baseline resting coronary flow and decrease in CFR have been reported in human cases with various types of LV hypertrophy (1–3,18–21) and increase in LV preload (4), and similar results would be
expected in cases with chronic MR as demonstrated in the present study. A main difference between their experimental study and the present study might be study subjects. Coronary circulation in dog might be somewhat different from coronary circulation in humans, and microvascular angiogenesis, which could preserve CFR, might be expected in this species. Furthermore, the experimental study measures coronary flow in dogs with MR with contractile dysfunction, which is normally associated with decrease in myocardial oxygen demand resulting in reduction in baseline coronary blood flow. This might be related to length of illness as they discussed in the limitations in their report. Preservation of LV contractility would be expected in some degree in humans with chronic MR.

It has been described that increase in baseline resting coronary flow results in decrease in CFR in the conditions with increase in LV preload (4), LV mass and volume overload (1,2). In patients with MR, all these conditions would be expected, and CFR could be influenced by each of these factors to some degree. As a result, considerable scatter was demonstrated in correlations between CFR and each factor, including LV preload indicated by LV end-diastolic pressure, LV mass index and degree of volume overload demonstrated by MR volume or LV end-diastolic volume index.

Even in cases with normal epicardial coronary artery, reduction of CFR has been reported without LV hypertrophy in cases with diabetes mellitus (7–9), hypercholesterolemia (10) and coronary vasospasm (11,12). However, these were excluded from the present study.

**Study limitations.** Several limitations to the present study must be considered. Although patients with angiographically normal coronary arteries were included in the present study, it might be difficult to exclude completely cases with diffuse concentric thickening of coronary vessel wall by angiography alone. Recently developed intravascular ultrasound would be more accurate to exclude diseased coronary artery (24,25). Second, as described above, reduced CFR with angiographically normal coronary arteries has been reported in cases with diabetes mellitus (7–9), hypercholesterolemia (10), vasospastic angina (11,12) and LV hypertrophy including hypertension (18), hypertrophic cardiomyopathy (19), aortic stenosis (20,21) and aortic regurgitation (1–3). Therefore, these cases were excluded from this study. It has also been reported that CFR was limited in some cases with chest pain and normal coronary arteries such as syndrome X (26). As in all invasive studies, control subjects in the present study might not be completely normal, because they were being investigated for chest pain. However, normal CFR was demonstrated in the control subjects, and they would be thought to be apparently normal because no abnormalities were confirmed in electrocardiogram, echocardiogram, left ventriculogram and coronary angiograms in all cases. Furthermore, patients after mitral valve surgery demonstrated almost normal coronary flow reserve, and syndrome X might not be included in these cases before operation. Third, flow velocities were analyzed only in the left anterior descending coronary artery and after isosorbide dinitrate injection in the present study. Those in the right and the left circumflex coronary arteries would give us more complete information about coronary circulation in MR. However, variations of the coronary tree might rarely be expected in the left anterior descending coronary artery compared with the left circumflex and right coronary arteries. Isosorbide dinitrate should decrease LV preload and may give some influences in coronary flow velocity measurements. However, these influences might be equal to baseline and hyperemic conditions in each individual, and CFR determined by the ratio of hyperemic/baseline flow velocity might have only small influence. Fourth, MR volume and fraction were calculated from total LV stroke volume obtained from left ventriculography and right ventricular forward stroke volume determined by thermodilution method. A small amount of MR volume and fraction was obtained even in control subjects without any regurgitation, and this was thought to be a limitation of this method. However, this was small and might not influence the present study. Finally, progressive deterioration of LV function has been reported in cases with chronic MR (27–30), and those with marked deterioration of LV function were not included in the present study. Restriction of CFR has been proposed to be a mechanism of the progressive deterioration of LV function in cases with chronic aortic regurgitation (2), and coronary flow analysis in cases with MR and LV dysfunction might give us important information about coronary hemodynamics in MR. Further study should also be addressed in this regard, as described above.

**Conclusions.** Coronary flow reserve is restricted in cases with MR because of elevation of baseline resting coronary flow velocity. This reduction of CFR relates to degree of increase in LV volume overload, LV hypertrophy and particularly LV preload. By the reduction of these factors after mitral valve reconstruction surgery, this restriction of CFR improves significantly with decrease in baseline resting coronary flow velocity.

**References**

8. Nahser PJ, Brown RE, Oskarsson H, Winniford MD, Rossen JD. Maximal...


