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Coronary Flow–Pressure Relationship Distal to Epicardial Stenosis

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To assess the coronary flow velocity–pressure relationship distal to a stenosis, and to evaluate the influence of microvascular abnormalities on this relationship, coronary flow velocity and coronary pressure were measured simultaneously in 38 patients (42 vessels). The instantaneous peak coronary flow velocity was plotted against the simultaneous measured distal coronary pressure, and the slope of the relation in the phase of diastolic flow decrease was calculated as the flow–pressure slope index (FPSI) and the X-intercept of the slope was calculated as zero-flow pressure (Pzf). The slope of the curve increased from 2.0±2.6 to 4.5±4.1 ($p<0.001$) and the X-intercept decreased from 42±16 to 27±13 mmHg ($p<0.001$) after papaverine injection. After successful coronary intervention, Pzf increased from 23±10 to 35±11 ($p<0.01$) and FPSI decreased from 6.8±5.1 to 3.5±1.8 ($p<0.05$). Pzf was higher in patients with an old myocardial infarction. It is feasible to assess the relationship between coronary flow and pressure distal to a stenosis in the clinical setting, and the relationship may provide additional information regarding coronary microcirculation. Microvascular abnormalities may play an important role in the coronary flow–pressure relationship distal to stenosis. (*Circ J* 2003; **67:** 525–529)

Key Words: Coronary flow-pressure relationship; Coronary flow reserve; Fractional flow reserve; Zero-flow pressure

Autoregulation is a characteristic of the coronary circulation. Myocardial oxygen demand is higher than that of other muscles, and the extraction of oxygen by the myocardium is close to maximum. Therefore the coronary circulation can only increase the oxygen supply by increasing blood flow, and the myocardial blood flow is maintained relatively constant by autoregulation[1] which is mediated by changes in the caliber of the resistive vessels.[2] Another characteristic of the coronary circulation is the phasic coronary flow pattern, which is based on diastolic predominance resulting from the influence of cardiac contraction.[3] These characteristics complicate any evaluation of coronary artery resistance or the autoregulatory function.

Analysis of the coronary flow–pressure relationship is one way to evaluate the coronary circulation. In diastole, coronary flow depends on coronary pressure without regard to cardiac contraction, and the diastolic relationship between coronary flow and pressure permits analysis of coronary artery resistance. The slope of the diastolic relationship indicates conductance of the vessels, and the X-intercept of the extrapolated slope indicates zero-flow pressure (Pzf), or back pressure of the myocardium.[4,5]

Development of the Doppler guidewire[6] and the pressure sensor mounted guidewire[7–9] has facilitated measurement of distal coronary flow velocity and pressure in the clinical setting. Several studies on the relation between coronary flow velocity and coronary ostial pressure have been performed,[5,10,11] but no data concerning the relationship between coronary flow velocity and pressure distal to a stenosis have appeared. The relation between distal coronary flow velocity and distal coronary pressure may be affected more by intramyocardial conditions. Therefore we attempted to assess the relationship between coronary flow and pressure distal to a stenosis of the epicardial artery, and to evaluate the influence of microvascular abnormalities on the relation curve.

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Methods

Study Patients

Thirty-eight patients (42 vessels), who underwent coronary angiography for evaluation of coronary stenotic lesions and post-intervention restenosed lesions, took part in this study. Patients with unstable angina, acute myocardial infarction, severe valvular disease or congestive heart failure were excluded. Twenty-one patients had angina pectoris (AP) and 17 patients had an old myocardial infarction (OMI). The mean age was 61±9 years and there were 34 males and 4 females. Coronary risk factors of these patients were hypertension (HT) in 22 patients (58%), diabetes mellitus (DM) in 11 (29%), hyperlipidemia (HL) in 22 (58%) and smoking in 28 patients (74%).

Target vessels were the left anterior descending artery (LAD) in 29, the left circumflex artery (LCx) in 6 and the right coronary artery (RCA) in 7 patients. The % diameter stenosis of the lesions ranged from 5% to 87% (mean 48±26%). Twelve patients underwent percutaneous coronary intervention (PCI), with measurements performed before and after PCI. All procedures were approved by the ethics committee of Tokyo Medical University, and written

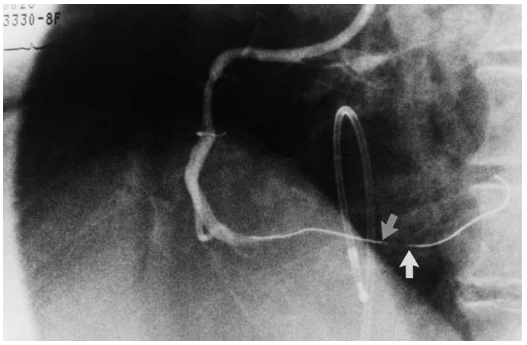

Fig 1. Both the Doppler guidewire and the pressure guidewire were placed distal to the stenosis. The sample volume of the Doppler guidewire was located 5 mm distal from the tip of the wire (closed arrow). The transducer of the pressure guidewire (open arrow) was placed at the same position as the Doppler sample volume.

informed consent was obtained from all patients.

Coronary Angiography

Coronary angiography was performed in a routine manner using the right femoral approach with 8Fr guiding catheters. All patients received 8,000 to 10,000 U of intravenous heparin before the flow and pressure guidewires were introduced and measurements were performed.

Coronary Flow Velocity and Pressure Measurements

Both the pressure guidewire and Doppler guidewire were advanced into the coronary artery through a guiding catheter and positioned across the stenosis (Fig 1). Coronary flow velocity was measured with a Doppler angioplasty guidewire (FloWire™, Cardiometrics Inc), which is a flexible, steerable guide wire, 175-cm long and 0.014-inch in diameter with a 12-MHz piezoelectric ultrasound transducer integrated into the tip. Quadrant Doppler audio signals are processed by a real-time spectrum analyzer using on-line fast Fourier transformation. Coronary pressure was measured with a pressure-monitoring guide wire (Pressure-guide™, Radi Medical), which is a flexible guidewire, 175-cm long and 0.014-inch in diameter with a fiber-optic or piezoelectric (new type) high-fidelity pressure sensor at the transition of the radiopaque floppy tip. Simultaneous acquisition of the instantaneous peak coronary flow velocity and distal coronary pressure at baseline and during hyperemia following intracoronary injection of papaverine hydrochloride (12 mg for left corobary artery and 8 mg for RCA) was performed. Data were recorded on a digital audiotape (DAT recorder, SONY) for off-line analysis of the flow–pressure relationship.

Coronary Flow Reserve and Fractional Flow Reserve

The coronary flow reserve (CFR) derived from coronary flow velocity and the fractional flow reserve (FFR) derived from coronary pressure was calculated for physiological assessment of the epicardial stenoses. CFR was calculated as the ratio of hyperemic coronary flow velocity to baseline and FFR was calculated as the ratio of hyperemic mean distal coronary pressure to mean aortic pressure. According to this physiological assessment of stenosis severity, patients were divided into 2 groups: significant stenosis (group S, FFR <0.75, n=20) and no stenosis (group NS, FFR ≥0.75, n=22).

Coronary Flow Velocity–Pressure Curve Analysis

A DAT recorder connected to a personal computer (Macintosh Power PC 8500, Apple Computer Inc) was used. With commercially available software (AcqKnowledge, BIOPAC Systems Inc), the acquired signals, instantaneous peak coronary flow velocity and distal coronary pressure were displayed in an X-Y scatter plot, so that 3 consecutive cardiac cycles without recording artifacts could be selected at baseline and peak hyperemia (Fig 2). The diastolic interval to be analyzed was selected from the maximal diastolic velocity point to the beginning of the phase of rapid decrease of flow velocity induced by ventricular contraction. Linear regression was used to calculate the slope of the curve in diastole (flow–pressure slope index: FPSI) and the X-intercept of the extrapolated curve (Pzf).

Angiographic Data Analysis

Quantitative angiography of the lesion was performed by the caliper method. In lesions where orthogonal views could not be obtained, the view showing the most severe diameter narrowing was used.

Statistical Analysis

The difference of FPSI and Pzf between the conditions before and after PCI, and the difference between these indexes at baseline and hyperemia were compared using the paired Student's t test. The difference between the indexes with and without OMI, DM, HL and smoking were compared using the unpaired Student's t test. The comparison of the incremental ratio of FPSI among the number of coronary risk factors were made by ANOVA. Statistical significance was defined as $p<0.05$. All data were expressed as mean ± SD.

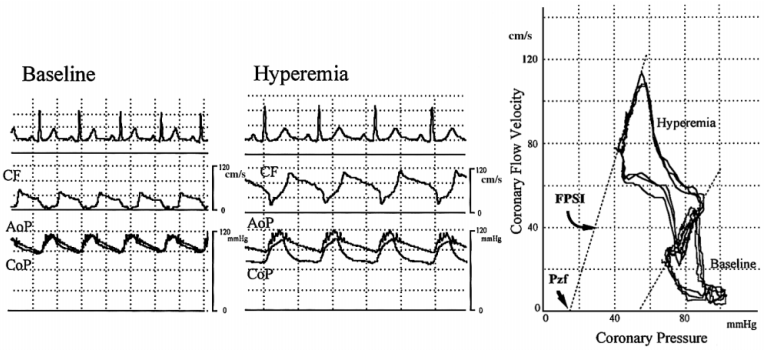

Fig 2. Representative tracings of the simultaneous recording of coronary flow velocity (CF), aortic pressure (AoP) and distal coronary pressure (CoP) are shown (Left panel). The instantaneous peak coronary flow velocity was plotted against the simultaneous measured distal coronary pressure (Right panel), and the slope of the flow–pressure relation in the diastolic flow decrease phase was calculated as the flow–pressure slope index (FPSI) and the X-intercept of the slope was calculated as the zero-flow pressure (Pzf).

Table 1 Changes in Pzf and FPSI During Maximal Hyperemia

	Baseline	*Hyperemia*	*p value*
Pzf	*42±16*	*27±13*	*<0.001*
FPSI	*2.0±2.6*	*4.5±4.1*	*<0.001*

Pzf, pressure at zero flow; FPSI, flow pressure slope index.

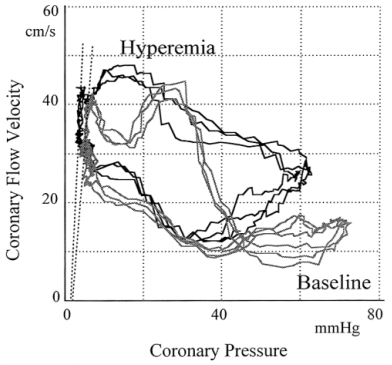

Fig 3. Relation curve between coronary flow velocity and pressure in patients with severe stenosis. The slope of the curve in diastole was steeper even at baseline, and the slope did not change during maximal hyperemia.

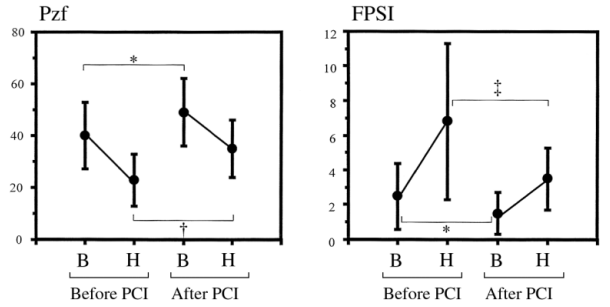

Fig 4. Changes in Pzf and FPSI after PCI. The X-intercept and the slope of the curve in diastole were measured at baseline (B) and maximal hyperemia (H). Pzf increased and FPSI decreased after PCI, although no significant changes in the X-intercept and the slope of the curve in diastole at baseline were seen. *p=NS, †p<0.01, ‡p<0.05.

Results

Changes in the Coronary Flow Velocity–Pressure Relationship During Hyperemia

The slope of the curve in diastole and the X-intercept of the slope changed significantly during maximal hyperemia induced by papaverine administration (Table 1). During maximal hyperemia the slope became steeper, and the X-intercept decreased compared with baseline. In patients with severe stenosis, the slope of the curve in diastole was steeper even at baseline, and the value did not change after papaverine injection (Fig 3).

Changes in the Coronary Flow Velocity–Pressure Relationship After PCI

After successful PCI, Pzf increased from 23±10 to 35±11 ($p<0.01$) and FPSI decreased from 6.8±5.1 to 3.5±1.8 ($p<0.05$) at maximal hyperemic conditions, although the X-intercept and the slope of the curve in diastole at baseline showed no significant change before or after PCI (Fig 4).

Table 2 Influence of Old Myocardial Infarction (OMI) and Angina Pectoris (AP) on Pzf, FPSI and Flow Reserve

	AP	*OMI*	*p value*
Group NS (no stenosis)			
Pzf	*29±6*	*38±17*	*<0.05*
FPSI	*3.2±2.4*	*4.4±4.1*	*NS*
CFR	*3.0±1.1*	*2.9±0.4*	*NS*
FFR	*0.87±0.07*	*0.84±0.06*	*NS*
Group S (stenosis)			
Pzf	*19±10*	*24±9*	*0.1*
FPSI	*5.4±4.8*	*5.5±5.1*	*NS*
CFR	*1.8±0.6*	*1.7±0.8*	*NS*
FFR	*0.52±0.16*	*0.56±0.09*	*NS*

CFR, coronary flow reserve; FFR, fractional flow reserve; FPSI, flow-pressure slope index; Pzf, zero-flow pressure.

Table 3 Influence of Coronary Risk Factors on Pzf and FPSI

	Present	*Absent*	*p value*
Group S			
Pzf			
HT (n=14)	*18±10*	*27±5*	*<0.05*
HL (n=9)	*22±11*	*20±9*	*NS*
DM (n=9)	*21±10*	*21±9*	*NS*
Smoking (n=13)	*23±10*	*17±9*	*NS*
FPSI			
HT	*4.0±3.6*	*8.8±5.9*	*<0.05*
HL	*4.9±4.2*	*5.8±5.4*	*NS*
DM	*5.6±5.4*	*5.3±4.5*	*NS*
Smoking	*6.1±4.9*	*4.3±4.9*	*NS*
Group NS			
Pzf			
HT (n=11)	*29±12*	*36±13*	*NS*
HL (n=15)	*32±12*	*34±15*	*NS*
DM (n=4)	*27±2*	*34±14*	*NS*
Smoking (n=19)	*34±13*	*24±5*	*NS*
FPSI			
HT	*2.9±3.3*	*4.5±3.2*	*NS*
HL	*3.2±2.3*	*4.8±4.8*	*NS*
DM	*1.8±1.6*	*4.1±3.4*	*NS*
Smoking	*4.0±3.4*	*1.9±1.3*	*NS*

DM, diabetes mellitus; HL, hyperlipidemia; HT, hypertension; other abbreviations, see Table 2.

Influence of MI

In group NS, patients with an OMI had higher Pzf values than patients without an OMI. However, in group S, Pzf of the OMI patients tended to be higher, but the influence of MI was not so apparent as that seen in group NS (Table 2). On the other hand there was no significant difference in the FPSI value between AP and OMI in groups NS and S. The differences in CFR and FFR between AP and OMI were not significant.

Influence of Coronary Risk Factors

Because the Pzf and FPSI values depend on the presence of stenotic lesions, we analyzed the influence of coronary risk factors on the values in each group separately (Table 3). In group S patients with HT, the FPSI and Pzf were lower than in patients without HT. FPSI in group NS patients with coronary risk factors (HT, HL or DM) tended to be lower.

Relationship Between FPSI and CFR

The incremental ratio of the slope of the curve in diastole from baseline to hyperemia (FPSI ratio) was significantly

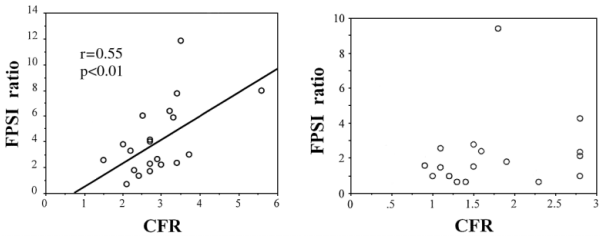

Fig 5. Relation between FPSI ratio (incremental ratio of the slope of the curve in diastole from baseline to hyperemia) and CFR. A significant relation was noted in group NS (Left), but no relation was seen in group S (Right).

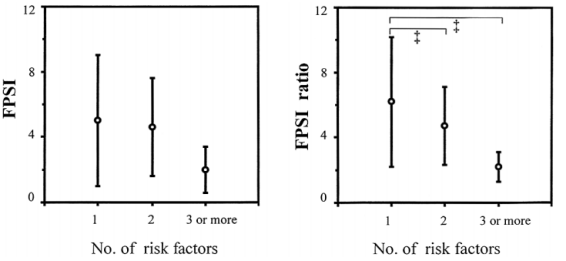

Fig 6. Relation between FPSI, FPSI ratio and the number of coronary risk factors. An increase in the number of coronary risk factors caused a decrease in the FPSI ratio. ‡p<0.05.

related to CFR in group NS (Fig 5). The incremental ratio also showed a significant relation with the number of coronary risk factors (Fig 6). An increase in the number of coronary risk factors caused a decrease in the FPSI ratio.

On the other hand, FPSI ratio in group S had no significant relation with CFR or the number of coronary risk factors.

Discussion

One of the characteristics of coronary circulation is the diastolic predominance of blood flow, because of myocardial contraction. During systole, the myocardial contraction phase, the blood flow into the myocardium is impeded, and during diastole blood enters the myocardium. To determine the status of coronary perfusion to the myocardium, we have to analyze the diastolic properties of coronary flow and pressure. Our analytical method permits assessment of the coronary flow–pressure relation during diastole. The status of perfusion impedance can be expressed only by the diastolic part of the relation curve. Some clinical studies on the relation between aortic pressure and distal coronary flow have been reported,[5,10,11] but in those studies, although the data showed the influence of coronary stenosis on the relation, they did not assess the microvascular status. We sampled both coronary pressure and flow data distal to the stenosis, which distal pressure indicated the perfusion pressure for the distal flow, so that the relation curve directly reflected the microvascular conditions.

The other characteristic of coronary circulation is the autoregulatory system. The presence of an epicardial artery stenosis causes dilation of the resistance vessels, so that coronary blood flow can be maintained. The autoregulatory system makes evaluation of coronary circulation more complex. At baseline, the resistance vessels show some degree of constriction; the diastolic slope of the coronary flow–pressure relation curve is lower and the X-intercept is higher. Papaverine causes maximum dilatation of the resistance vessels, so the diastolic slope of the curve becomes steeper and the X-intercept lower after papaverine administration. These changes show relaxation of the resistance vessels, caused by papaverine, but not by nitrates.

Pzf indicates static or dynamic back pressure to flow. These back pressures are closely related to the vascular waterfall theory,[12] vascular compliance,[13] or both mechanisms combined. On the other hand, FPSI indicates coronary vascular resistance. An increase in the slope indicates a decrease in vascular resistance. After successful PCI, the slope of the relation curve in diastole decreased and the X-intercept of the slope increased at baseline and also during hyperemia. Relief of the epicardial stenosis by PCI caused a decrease in total coronary resistance, and it appeared that constriction of autoregulatory vessels might develop at baseline. Elevation of Pzf in hyperemic conditions after PCI might be influenced by elevation of left ventricular end diastolic pressure after the procedure[14] or by methodological problems. Hypothetically, measurement of Pzf requires a long diastolic phase, because the coronary flow–pressure relation is not linear at the low end of the relation when the aortic pressure is close to zero.[15] Therefore, the estimated Pzf will be higher than the true Pzf, even in patients in whom the measurements could be performed reliably as shown in Figs 2 and 3. Although a long diastolic phase permits analysis of the relation,[16] it can be difficult to achieve such a long diastolic phase in the clinical setting. In patients with severe stenosis, distal coronary pressure was low, and we were able to assess the pressure–flow relation at the lower driving pressure.

Influence of Myocardial Infarction

In patients with an OMI, high values of Pzf were observed. Pzf is influenced mainly by back pressure from the myocardium and the resistance of the microvasculature. The higher left ventricular diastolic pressure in OMI patients caused higher back pressure, and interstitial fibrosis in the infarcted myocardium may impede blood flow to the myocardium, thus causing a higher Pzf. On the other hand, there was no significant difference in FPSI between in patients with and without OMI, which indicated that the resistance of the residual microvasculature was maintained even though the volume of microvasculature in the infarcted area is decreased in OMI patients. Therefore Pzf may have more impact on coronary circulation in patients with OMI than FPSI.

Influence of Coronary Risk Factors

In group S patients, the degree of stenosis markedly affected the FPSI value. If the patient had a severe stenosis, the distal coronary pressure wave showed a left ventricular pressure-like waveform, the mid diastolic pressure was almost horizontal and FPSI became very steep (Fig 6). In these patients analysis of the influence of coronary risk factors on FPSI values was difficult.

In group NS patients, FPSI reflects conductance of the microvasculature; that is, low FPSI values indicate impairment of the microvasculature. FPSI in patients with HT, HL and DM tended to be lower, which may indicate a tendency for the microvascular function to decrease. The number of coronary risk factors was related to the incremental ratio of the slope of the curve in diastole (FPSI ratio). The FPSI ratio showed a significant relation with CFR in group NS (Fig 5), indicating that CFR is affected by

not only maximal flow (indicated by FPSI), but also by the response of the microvasculature to vasodilatory mediators. A decrease in the FPSI ratio indicates impairment of the microvascular response to vasodilatory mediators or vasodilatation present at baseline.

Comparison With Other Indexes

Thallium scintigraphy and CFR are already recognized indexes for the evaluation of microvascular dysfunction. Thallium scintigraphy is able to detect the microvascular dysfunction noninvasively, but it is a relative evaluation between each area. Therefore, if microvascular dysfunction occurs in the whole heart, evaluation becomes impossible. On the other hand, CFR reflects the microcirculation subtly in each area, but it can be influenced by epicardial stenosis and hemodynamics (blood pressure, heart rate, contractility and so on), which would then make it difficult to use CFR only as an index for microvascular dysfunction. Future examination will be necessary to ascertain whether the new indexes used in this study reflect only the microcirculation.

Study Limitations

Absolute coronary blood volume was required for these analyses, but we could determine only coronary flow velocity. Coronary blood volume was calculated from coronary flow velocity and coronary artery diameter. If the diameter was constant, the flow volume–pressure relation was the same as the flow velocity–pressure relation, but when the coronary distal pressure decreases, it appears that the coronary diameter will be smaller.

In this study we inserted 2 guide wires into the distal part of coronary artery for simultaneous recordings. Thus the maneuver became complicated and it would be difficult to use as an ordinary examination. In addition, the 2 guide wire technique may be affected by the degree of stenosis. If a new guide wire that can carry both sensors of Doppler flow and pressure is developed, then this measurement and the new indexes can be utilised more easily.

The analysis of the coronary flow pressure loop was complex, as it mainly depends on high-quality velocity measurements, which was difficult in some cases. Also, the interpretation of the data had some ambiguity, so more study will be needed.

In conclusion, it is feasible to assess the relationship between coronary flow and pressure distal to a stenosis in the clinical setting, and the relationship may provide additional information regarding the coronary microcirculation. Microvascular abnormalities may play an important role in the coronary flow–pressure relationship distal to the stenosis.

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