Coronary Flow Reserve and Ischemic-like Electrocardiogram in Patients with Symptomatic Mitral Valve Prolapse

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SUMMARY

The purpose of the present study was to determine whether coronary microvascular function is impaired in patients with symptomatic mitral valve prolapse (MVP) and whether ischemia-like ECG, if present, is related to coronary microvascular dysfunction.

Twenty chest pain patients with normal coronary angiograms and MVP proven by echocardiogram were included. Both treadmill exercise test (TET) and coronary hemodynamic study were done in each patient. Coronary flow reserve (CFR) was determined by measuring coronary sinus flow (CSF) or great cardiac venous flow (GCVF) both at baseline and after dipyridamole 0.56 mg/kg IV for 4 minutes (maximum). All patients were divided into 2 groups with either negative (TET-) or positive results of TET (TET+). Another 10 subjects with atypical chest pain, normal coronary angiograms, echocardiogram and TET were used as controls.

There were no differences in GCVF, either at baseline or after dipyridamole infusion, among the 3 groups. Calculated CFR using GCVF was similar among the 3 groups. However, baseline CSF was higher in the TET+ group (TET- vs TET+ vs control: 77 ± 24 vs 96 ± 31 vs 75 ± 12 ml/min, $p < 0.05$) and maximum CSF was lower in the TET- group (TET- vs TET+ vs control: 167 ± 25 vs 219 ± 85 vs 238 ± 80 ml/min, $p < 0.05$). Calculated CFR using CSF was significantly reduced in both the TET- (2.26 ± 0.4) and TET+ groups (2.31 ± 0.7) as compared with the control subjects (3.18 ± 0.95 , $p < 0.01$). There were no differences in any of the hemodynamic parameters between the TET- and TET+ groups.

Coronary microvascular function could be impaired in patients with

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symptomatic MVP. Such impairment, when presented, was probably regional and outside the territory of the left anterior descending coronary artery. However, it was irrelevant to the presence of ischemic-like ECG during exercise. (Jpn Heart J 1999; 40: 571–578)

Key words: Mitral valve prolapse, Coronary flow reserve, Myocardial ischemia

MITRAL valve prolapse (MVP) is the most common valvular heart disease and also one of the most frequently seen causes of angina in our daily practice.¹⁾ Chest pain, mostly atypical, is a complaint in 60–70% of patients with MVP.^{2,3)} In 25–75% of these patients, evidence of myocardial ischemia was noted with ischemia-like electrocardiogram (ECG) or Thallium-201 scintigram, either at rest or during exercise.^{2,4)} While coronary angiograms were normal in most of these patients,⁵⁾ the cause of the chest pain as well as ischemia-like ECG was not completely clarified.

Several potential mechanisms have been suggested for both chest pain and myocardial ischemia in patients with MVP. They include coronary artery spasm, inadequate coronary vasodilator reserve with microvascular dysfunction or microembolism, papillary muscle ischemia by excessive chordae stretching, and subendocardial ischemia during sudden tachycardia.¹⁾ Other factors such as increased adrenergic tone, excessive myocardial lactate production, hyperventilation and extracardiac causes may also contribute to the dilemma of ischemia-like symptoms in MVP patients.³⁾ Recently, we⁶⁾ and other investigators⁷⁾ have shown that coronary flow reserve (CFR) could be impaired in patients with anginal chest pain, exercise-induced myocardial ischemia and normal coronary angiograms (syndrome X). Chest pain and ischemic ECG were also noted with myocardial lactate production during rapid atrial pacing in patients with MVP.⁸⁾ However, it is unknown whether this myocardial ischemia resulted from coronary microvascular dysfunction. The purpose of the present study was to determine whether coronary microvascular function is impaired in patients with symptomatic MVP and whether ischemia-like ECG during exercise, if present, resulted from coronary microvascular dysfunction in these patients.

METHODS

Patients: A series of patients with chest pain, MVP proven by both auscultation and 2-dimensional echocardiogram, and normal coronary angiogram were included. Patients with established hypertension (blood pressure > 160/95 mmHg), diabetes mellitus, collagen disease, previous myocardial infarction, congestive heart failure, cardiomyopathy, left ventricular hypertrophy, unstable angina,

variant angina, significant valvular heart disease other than MVP and other major systemic disease were excluded. The study was approved by the Human Research Committee of our hospital and written informed consent was obtained from each patient.

Treadmill exercise test (TET): All patients underwent TET with modified Bruce protocol.^{6,9} Cardiac medications, except sublingual nitroglycerin, were prohibited for 3 days before the test. A result was taken as positive if there was ≥ 1 mm horizontal or down-sloping depression of ST segment 80 ms after the J point in ≥ 2 leads. The symptoms during exercise were also recorded.

Coronary hemodynamic study: Within 2 days of the treadmill exercise test, all patients underwent cardiac catheterization. The protocol of the coronary hemodynamic study has been described in detailed elsewhere previously.^{6,9} In brief, immediately after normal coronary angiograms were confirmed, the ergonovine challenge test was done with sequential dosages (0.05 mg — 0.10 mg–0.25 mg) given intravenously. About 15 min after a negative ergonovine challenge test, a Baim coronary sinus flow catheter was inserted into and wedged in the great cardiac vein. The position of the tip of the catheter was proven by 3–5 cc contrast injection. The design of the Baim coronary sinus catheter allows us to measure coronary sinus flow (CSF) and great cardiac venous flow (GCVF) simultaneously.¹⁰ Before each measurement, the position of the sensor for CSF was checked and confirmed to be > 2 cm within the orifice of the coronary sinus. Thus, in each case, both CSF and GCVF were simultaneously measured by thermodilution method at baseline and 4–12 min after dipyridamole, 0.56 mg/kg, intravenous injection for 4 min. Systemic hemodynamic parameters including heart rate and systolic, diastolic and mean arterial blood pressure were also monitored via a fluid-filled system throughout the entire coronary hemodynamic study.

Another 10 age- and sex- matched subjects with atypical chest pain, negative TET, and normal coronary angiograms and echocardiograms underwent the coronary hemodynamic study as control.

Calculated coronary hemodynamic parameters: CFR was obtained via the ratio of maximum (after dipyridamole infusion) to baseline CSF or GCVF. Coronary vascular resistance (CVR) was also calculated as mean arterial pressure divided by CSF or GCVF, at baseline and after dipyridamole infusion. The CVR ratio (CVRR) was determined as the ratio of CVR after dipyridamole infusion to that at baseline.

Statistics: Patients were divided to 2 groups, TET+ and TET–, according to the results of the TET. The differences among the TET+, TET–, and control groups were first evaluated by one-way ANOVA. Intergroup differences were then determined by unpaired student *t* test. A *p* value < 0.05 was considered to be

statistically significant.

RESULTS

Basic characteristics of the patients: A total of 20 consecutive MVP patients who fulfilled the inclusion criteria were studied. There were 10 patients (7 males and 3 females) in the TET- group and 10 (6 males and 4 females) in the TET+ group. Another 10 subjects (7 males and 3 females) with atypical chest pain and no TET, echocardiogram or coronary angiograms abnormalities were enrolled in the control group. Basic demographic data were similar among the 3 groups (Table I).

Coronary hemodynamics: Table II presents the coronary hemodynamic pa-

Table I. Basic Characteristics of Mitral Valve Prolapse Patients with Negative (TET-) and Positive (TET+) Results of Treadmill Exercise Test and Control Subjects

	TET-	TET+	Control
Case number	10	10	10
Male/female	7/3	6/4	7/3
Age (years)	46 ± 18	52 ± 12	49 ± 16
LVEF (%)	53 ± 7	53 ± 5	55 ± 4
RVEF (%)	43 ± 7	42 ± 8	47 ± 8

LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction.

Table II. Coronary and Systemic Hemodynamic Changes at Baseline and after Dipyridamole Infusion in Mitral Valve Prolapse Patients with Negative (TET-) and Positive (TET+) Treadmill Exercise Test and Control Subjects

	TET- (n = 10)	TET+ (n = 10)	Control (n = 10)
At baseline			
GCVF (ml/min)	50 ± 15	53 ± 19	45 ± 7
CVR-GCV (mmHg × min/ml)	2.21 ± 1.00	2.26 ± 0.86	2.25 ± 0.41
CSF (ml/min)	77 ± 24	96 ± 26 ^Δ	75 ± 12 ^Δ
CVR-CS (mmHg × min/ml)	1.37 ± 0.43	1.17 ± 0.39	1.34 ± 0.21
After dipyridamole infusion			
GCVF (ml/min)	141 ± 37	157 ± 78	134 ± 19
CVR-GCV (mmHg × min/ml)	0.62 ± 0.30	0.75 ± 0.32	0.66 ± 0.12
CSF (ml/min)	167 ± 25*	219 ± 85	238 ± 80*
CVR-CS (mmHg × min/ml)	0.49 ± 0.14	0.48 ± 0.19	0.42 ± 0.13
CFR-GCV	3.00 ± 1.00	3.09 ± 1.24	3.00 ± 0.33
CFR-CS	2.26 ± 0.40*	2.31 ± 0.70 ^Δ	3.18 ± 0.95* ^Δ

CFR = coronary flow reserve; CFR-CS = coronary flow reserve calculated with coronary sinus flow; CFR-GCV = coronary flow reserve calculated with great cardiac venous flow; CSF = coronary sinus flow; CVR = coronary vascular resistance; CVR-CS = coronary vascular resistance calculated with coronary sinus flow; CVR-GCV = coronary vascular resistance calculated with great cardiac venous flow; GCVF = great cardiac venous flow. (* = $p < 0.05$ as TET- vs control subjects; ^Δ = $p < 0.05$ as TET+ vs control subjects).

rameters of the 3 groups. There were no differences in GCVF, either at baseline or after dipyridamole infusion, and its related CFR among the 3 groups. However, baseline CSF was higher in the TET+ group (TET- vs TET+ vs control: 77 ± 24 vs 96 ± 26 vs 75 ± 12 ml/min, $p < 0.05$) and maximum CSF was lower in the TET- group (TET- vs TET+ vs control: 167 ± 25 vs 219 ± 85 vs 238 ± 80 ml/min, $p < 0.05$), both resulted in reduced CFR, calculated based on CSF, in the TET- and TET+ groups as compared with control subjects (TET- vs TET+ vs control: 2.26 ± 0.4 vs 2.31 ± 0.7 vs 3.18 ± 0.95 ml/min, $p < 0.01$). There were no differences in any of the hemodynamic parameters between the TET- and TET+ groups.

DISCUSSION

The major findings of the present study are that 1) CFR calculated on CSF was significantly reduced while that based on GCVF was preserved in all MVP based patients as compared with control subjects. 2) There were no differences in any of the coronary hemodynamic parameters, including CFR, either calculated based on GCVF or on CSF, between MVP patients with TET+ and those with TET-. Accordingly, coronary microvascular function was regionally impaired in all MVP patients. In these patients, coronary microvascular dysfunction, though present, can not account for the ischemic-like ECG during exercise.

Regional impairment of coronary microvascular function in symptomatic MVP patients: The coronary sinus usually drains myocardial blood flow that comes from most parts of the left ventricle while the great cardiac vein drains the territory of the left anterior descending coronary artery. Thus, CFR calculated based on CSF is approximately related to coronary microvascular function of global left ventricle and that based on GCVF may imply only regionally over the anterior wall of the left ventricle.¹¹⁾ In the present study, CFR calculated based on GCVF was preserved while that based on CSF was impaired in MVP patients, suggesting that coronary microvascular function was preserved over anterior wall of the left ventricle and probably regionally impaired in other areas of the left ventricle. It is unknown whether the regional impairment of coronary microvascular function can be attributed to a geographic factor related to the mitral leaflet that was prolapsed.¹⁾

The results of the present study are in partial agreement with those reported by Tentolouris *et al.* recently.¹²⁾ Both in their and our study, CFR was preserved in the territory of the left anterior descending artery in MVP patients with positive exercise test. They also showed that coronary flow velocity reserve was normal in the other two coronary arteries: the left circumflex and right coronary arteries. They concluded that CFR was normal in patients with MVP, a positive

exercise test and normal coronary arteries. However, in the present study, CFR calculated based on CSF was significantly reduced while that based on GCVF was preserved in all MVP patients, suggesting that coronary microvascular function might be regionally impaired outside the territory of the left anterior descending artery. As compared with ours (4 females and 6 males; mean age of 52 years), there were more female patients (8 females and 4 males) with much younger age (mean age of 38 years) in the study of Tentolouris *et al.* While estrogen may be involved in vascular protection in female patients before menopause,^{13,14)} coronary microvascular dysfunction could be significant in the males and post-menopause females who made up the majority of our patients. It has also been shown that myocardial flow reserve is reduced with age in normal subjects.¹⁵⁾ Nevertheless, the results of the present study confirm previous findings that myocardial perfusion could be regionally decreased in MVP patients.¹⁶⁾

Coronary microvascular dysfunction is irrelevant to ischemic-like ECG during exercise in MVP patients: In the present study, there was no difference in CFR, either calculated based on GCVF or on CSF, between MVP patients with TET- and those with TET+. Accordingly, coronary microvascular dysfunction, though regionally presented, was not related to the presence of ischemic-like ECG during exercise. Together with these findings and those of Tentolouris *et al.*,¹²⁾ it seems that in patients with symptomatic MVP, regardless of age and gender, the cause of ischemic-like ECG during exercise can not be attributed to coronary microvascular dysfunction. Mechanisms other than coronary microvascular dysfunction, including coronary artery spasm, papillary muscle ischemia by excessive chordae stretching, and subendocardial ischemia during sudden tachycardia, should be considered.¹⁾ The latter few mechanisms are more likely since a large part of our MVP patients responded well to treatment with β -adrenergic blockers. Factors such as increased adrenergic tone,^{3,17)} abnormal myocardial metabolism¹⁶⁾ with excessive myocardial lactate production,⁸⁾ hyperventilation and extracardiac causes might also contribute to the dilemma of ischemic-like symptoms in these patients.

Differential coronary hemodynamics in symptomatic MVP patients: While chest pain is usually seen in patients with symptomatic MVP, myocardial ischemia suggested by TET or myocardial perfusion imaging was much less frequently detected.¹⁸⁾ The underlying mechanisms of chest pain have not been well defined in MVP patients.¹⁾ Though the results of the present study did not support reduced CFR as the cause of ischemic-like ECG during exercise, it is likely that regional coronary microvascular dysfunction or altered myocardial metabolism or both may be associated with chest pain in these patients.^{8,16)} In MVP patients with TET+, CSF was abnormally increased at baseline and remained normal after dipyridamole infusion. We speculate that it may be related

to altered cardiac metabolism or increased myocardial work, as mentioned by others before.¹⁵⁾ On the other hand, coronary microvascular function was paradoxically impaired with limited maximum CSF in MVP patients with TET-. In these patients, coronary microvascular insufficiency might be dynamic and subclinical even without ECG evidence of myocardial ischemia during exercise.^{7,19)}

Study limitations: In the present study, the method we used to evaluate coronary microvascular function was different from that by Tentolouris *et al.*¹²⁾ We could only measure myocardial blood flow from the territories of left coronary artery. However, while measuring simultaneously, the dissociated response of CSF and GCVF to dipyridamole injection in our MVP patients might be attributed to regional impairment of coronary microvascular function rather than to technical bias. However, it is still not known why myocardial flow reserve was similarly impaired in symptomatic MVP patients, unrelated to the presence of ischemic-like ECG during exercise. Further study is needed to evaluate whether other non-vascular mechanisms, especially abnormal myocardial metabolism, either at rest or during exercise, may result in the presence of ischemic-like ECG.^{8,16)} Recently, we²⁰⁾ and others²¹⁾ have reported that ischemic-like ECG during exercise could be improved by nicorandil, a potassium channel opener, or enalapril, an angiotensin converting enzyme inhibitor, in patients with microvascular angina. It would be interesting to determine whether they can improve exercise performance and/or chest pain in symptomatic MVP patients.

Conclusion: Coronary microvascular function could be impaired in patients with symptomatic MVP. Such impairment, when presented, was probably regional and located outside the territory of the left anterior descending coronary artery, and could be subclinical without ECG evidence of myocardial ischemia. In these patients, the mechanisms of ischemic-like ECG during exercise might be multi-factorial other than coronary microvascular dysfunction.

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