Comparison of Coronary Hemodynamics During Infusions of Dobutamine and Adenosine in Patients With Angina Pectoris

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Pharmacologic stress tests are used to evaluate the significance of coronary arterial stenosis, and adenosine and dobutamine are often used for this purpose. The aim of this study was to examine coronary hemodynamics in 16 patients with stable exertional angina who had organic stenosis (>90%) in the left anterior descending coronary arteries and in 13 control subjects at baseline and during separate intravenous infusions of dobutamine (20 mg/kg per min) and adenosine (140 mg/kg per min). Measurements of great cardiac vein blood flow and lactate and oxygen contents in the blood from the aortic root and great cardiac vein were analyzed in patients with ischemic signs of myocardial ischemia (ST-segment depression in the precordial ECG leads and/or myocardial lactate production) during the infusions (in 11 patients during adenosine infusion and in 12 patients during dobutamine infusion) and in control subjects. Myocardial oxygen consumption during adenosine infusion did not change compared with the baseline in both groups, whereas it increased during dobutamine infusion in both groups ($p < 0.01$ compared with the baseline in each case). However, great cardiac vein blood flow was significantly increased compared with the baseline during both infusions in both groups ($p < 0.01$ compared with baseline in each case), and the oxygen contents of great cardiac vein blood, which contains effluent from the ischemic region, showed no decrease but increased significantly during both infusions in the patients in comparison with control subjects. Although the global oxygen supply was excessive, myocardial ischemia occurred during dobutamine and adenosine infusions in the patients. As myocardial oxygen consumption remained unchanged during adenosine infusion, regional myocardial flow reduction, possibly as a result of flow maldistribution, may contribute, at least partly, to adenosine-induced myocardial ischemia. An increase in myocardial oxygen consumption may be the principal cause of myocardial ischemia during dobutamine infusion, but an inappropriate flow increase in normal myocardium may occur during dobutamine-induced ischemia.

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Stable exertional angina is believed to be caused by an increase in myocardial oxygen demand in the presence of coronary stenosis, which limits flow supply.^{1,2} However, recent clinical studies suggest that regional myocardial blood flow reduction caused by coronary “steal” may play an important role in the mechanism of exercise-induced myocardial ischemia in patients with stable exertional angina.^{3–7} Pharmacologic stress tests are used to evaluate the significance of coronary arterial stenosis in patients with stable

exertional angina who are unable to perform an exercise test,⁷ and adenosine and dobutamine are often used for this purpose.^{6,8–10} Adenosine is an endogenous vasodilator released from myocardium during exercise,^{11,12} myocardial ischemia,^{13,14} or catecholamine infusion.^{15,16} Intravenous administration of adenosine and dipyridamole, which increases endogenous adenosine levels, has been shown to cause myocardial ischemia in patients with stable exertional angina, probably through the mechanism of primary

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reduction in regional blood supply through coronary steal^{5,8,17,18}. On the other hand, dobutamine is a potent stimulator of β_1 -, β_2 -, and α_1 -adrenoreceptors^{19,20}. Intravenous infusion of dobutamine has been shown to induce an increase in myocardial oxygen demand, which is believed to cause myocardial ischemia in patients with stable exertional angina^{9,10,20-23}. However, coronary hemodynamics during intravenous infusion of dobutamine remains undetermined in humans in vivo, especially in patients with stable exertional angina.

Thus, we examined coronary hemodynamics during intravenous infusions of dobutamine and adenosine in patients with stable exertional angina and compared the parameters in the patients with those in control subjects.

Methods

Patients

Sixteen patients with stable exertional angina but without angina at rest (9 men and 7 women; age 47–73 years, mean 65 years) were involved in this study. All of the patients had a positive exercise test for angina and myocardial ischemia (horizontal and down-sloping ST-segment depression >1 mm) and had coronary artery disease [internal diameter reduction >90% of the left anterior descending coronary artery (LAD)]. Coronary angiography showed 1-vessel disease in 5 patients, 2-vessel disease in 7 patients, and 3-vessel disease in 4 patients. Collateral circulation to the LAD was detectable by angiography in 8 patients. All of the study patients with stable exertional angina underwent exercise thallium-201 myocardial scintigraphy²⁴ and were found to have transient perfusion defects in the myocardial areas perfused by the LAD. Thirteen control subjects (4 men and 9 women; age 58–75 years, mean 64 years) also participated in this study. These control subjects underwent diagnostic cardiac catheterization for the evaluation of atypical chest pain (10 patients) or abnormal T waves on the electrocardiograms (3 patients). All of the control subjects had a negative exercise test. Coronary arteriograms in the control subjects showed no organic stenosis (>25%) in any major coronary arteries and no coronary artery spasm during provocation by intracoronary injection of acetylcholine²⁵. Neither patients with stable exertional angina nor control subjects had previous myocardial infarction, valvular heart disease, congenital malformation of the heart, cardiomyopathy, evidence of left ventricular hypertrophy, or conduction defect that could interfere with interpretation of ST-segment

changes. Antianginal medications were discontinued more than 5 days before the studies. All patients and control subjects gave informed consent for participation in this study. This study protocol was in agreement with the guidelines of the ethics committee at our institution.

Coronary Hemodynamics at Cardiac Catheterization

Cardiac catheterization was carried out in the morning after overnight fasting. All patients and control subjects had cardiac catheterization with thermodilution measurement of great cardiac vein blood flow as previously reported²⁶. In brief, great cardiac vein blood flow (ml/min) was determined by the injection of non-heparinized normal saline solution through the thermodilution catheter (CCS-7U-90B, ball end, Webster Labs, CA, USA), placed between the anterior interventricular vein and the origin of the posterior veins of the left ventricle in the coronary vein system, with a constant infusion pump at a rate of 36 ml/min and calculated with use of a Thermo Flow RF (Good Man). Twelve electrocardiographic (ECG) leads and arterial pressure were continuously monitored during the study. Blood samples were obtained from the aortic root and great cardiac vein blood for the measurements of lactate concentration and oxygen content. The plasma lactate concentration was determined by an enzymatic method using determiner LA (Kyowa Medix, Tokyo, Japan). The lactate extraction ratio was calculated as follows:²⁷

(difference in lactate levels in blood between aortic root and great cardiac vein)/lactate level in blood of aortic root $\times 100$

Oxygen content (vol%) was calculated as follows:

hemoglobin content (g%) $\times 1.34 \times$ oxygen saturation (%) $/ 100 + PO_2$ (mmHg) $\times 0.003$

Myocardial oxygen consumption (ml O_2 /min per 100 g) was calculated from the Fick equation:

(difference in oxygen content in blood between aortic root and great cardiac vein) $\times$ great cardiac vein flow/100

After baseline blood sampling and measurements of heart rate, blood pressure, and great cardiac vein flow, adenosine (Sigma Chemical, St. Louis, MO, USA) dissolved in warmed saline was infused through the femoral vein at a rate of 50 mg/kg per min, then at 75 mg/kg per min, 100 mg/kg per min for 2 min at each dose, and finally at 140 mg/kg per min for 4 min. Adenosine solution was passed through a sterile filter and autoclaved. For the last minute, the blood sampling and the coronary hemodynamic measurements were repeated. After a 30-min rest period, hemodynamic measurements were obtained to corroborate the return

Table 1 Frequency of Lactate Production and Ischemic ST-Segment Change in Patients With Stable Effort Angina (n=16)

	Lactate production	Chest pain with ST change	Lactate production or chest pain with ST change	Lactate production and chest pain with ST change	Negative in both signs
Adenosine	9 (56%)	8 (50%)	11 (69%)	6 (38%)	5 (31%)
Dobutamine	7 (44%)	8 (50%)	12 (75%)	4 (25%)	4 (25%)

Values indicate the number of patients who showed lactate production and/or chest pain with ischemic ST-segment change during adenosine or dobutamine infusion. Values in parentheses are percent frequency in total patients (n=16).

Table 2 The Effects of Adenosine and Dobutamine on Hemodynamic Parameters, Oxygen Content, and Lactate Extraction Ratio

	Control subjects (n=13)				SEA patients			
	Base 1	ADO	Base 2	DOB	Base 1	ADO	Base 2	DOB
HR (beats/min)	71±12	85±15#	70±13	105±21#	70±12	82±11#	71±14	103±32#
SBP (mmHg)	164±24	143±27#	168±34	188±42#	160±28	133±25#	148±24	178±23#
RPP (mmHg×beats/min)×10 ⁻²	116±18	120±29	118±18	192±28#	118±30	110±28	113±26	175±49#
Percent increase of GCVF	—	200±62	—	153±48	—	102±48*	—	76±35*
Percent increase in O ₂ content in GCV	—	127±45	—	52±32	—	124±34	—	56±36
MVO (ml O ₂ /min per 100 g)	11±6	12±7	11±7	20±9#	10±3	8±4	9±6	16±3#
Percent increase of MVO	—	20±23	—	96±58	—	-16±15*	—	40±27*
Lactate extraction ratio (%)	38±11	19±10	—	17±13	38±142	-8±8#*	—	-10±9#*

HE, heart rate; SBP, systolic blood pressure; RPP, rate-pressure product; GCVF, great cardiac vein blood flow; MVO, myocardial oxygen consumption; SEA, stable exertional angina; Base 1 and 2, baseline values before the infusions of adenosine and dobutamine, respectively; ADO, adenosine (n=11); DOB, dobutamine (n=12); #p<0.01 vs the corresponding baseline values, *p<0.01 vs the corresponding values in the control subjects. Values are mean±SD.

to baseline values. Then, dobutamine (Shionogi, Osaka) was infused through the femoral vein at a rate of 5 mg/kg per min, then at 10 mg/kg per min for 3 min, and finally at 20 mg/kg per min for 4 min. For the last minute, the blood sampling and hemodynamic measurements were performed again. These infusion rates of adenosine and dobutamine were previously reported to be well tolerated and are used routinely for the pharmacologic stress test^{5,7-10}. If chest pain or dyspnea associated with ST-segment depression, serious arrhythmia or systolic blood pressure >250 mmHg or <80 mmHg occurred before the maximal dosages, blood sampling and hemodynamics measurements were performed immediately, and thereafter the infusions were stopped.

Statistical Analysis

Student's unpaired t test was used to determine the significance of differences of hemodynamic variables between the patients and control subjects. When the parameters baselines and during adenosine and dobutamine infusions were compared in the same group, analysis of variance followed by paired t test was used. Fisher's exact test was used to compare the incidences

of chest pain with ST-segment depression and myocardial lactate production during infusions between patients and control subjects. A value of p<0.05 was considered significant. Data are presented as means±standard deviation (SD).

Results

Chest pain associated with ST-segment depression in the precordial ECG leads occurred in 8 (50%) patients with stable exertional angina during the adenosine and in 8 (50%) patients during the dobutamine, as shown in Table 1, whereas it did not occur in any of the control subjects during both infusions (p<0.01 in each case). Chest pain with ST-segment depression induced by adenosine disappeared within 5 min of stopping the adenosine infusion. Myocardial lactate production occurred in 9 of 16 (56%) patients during the adenosine and in 7 of 16 (44%) patients during the dobutamine infusion, but not in any of the control subjects during both infusions (p<0.05 in each case). Chest pain associated with ST-segment depression in the precordial ECG leads and/or myocardial lactate production, which are considered to be signs of

Fig 1. Oxygen content (vol%) in great cardiac vein (GCV) blood during adenosine and dobutamine infusion. CONTROL, control subjects (13 cases); SEA, patients with stable exertional angina (11 receiving adenosine infusion and 12 dobutamine infusion); ADO, adenosine infusion; DOB, dobutamine infusion; Base, baseline value before the infusion.

Fig 2. Great cardiac vein (GCV) flow (ml/min) during adenosine and dobutamine infusion. CONTROL, control subjects (13 cases); SEA, patients with stable exertional angina (11 receiving adenosine infusion and 12 dobutamine infusion); ADO, adenosine infusion; DOB, dobutamine infusion; Base, baseline value before the infusion.

myocardial ischemia, occurred in 11 patients during the adenosine infusion and in 12 patients during the dobutamine infusion. Signs of myocardial ischemia occurred in all 8 patients with collateral circulation to the LAD during the adenosine infusion and in 7 of the 8 patients during the dobutamine infusion. Measurements of systemic hemodynamics, great cardiac vein blood flow, and lactate and oxygen contents in the blood from the aortic root and great cardiac vein were analyzed in the patients with signs of myocardial ischemia (ST-segment depression in the precordial ECG leads and/or myocardial lactate production) during the infusions (11 patients during adenosine infusion and 12 patients during dobutamine infusion) and in the control subjects. As shown in Table 2, there was no

significant difference in the corresponding baseline measurements before the adenosine infusion between the 2 groups of patients and control subjects. The baseline hemodynamics after the adenosine infusion returned to the levels before the infusion, and there was no significant difference between the 2 baseline values before adenosine and dobutamine. The adenosine infusion in the present study was tolerated in all patients with stable exertional angina as well as in all control subjects. The dobutamine infusion was stopped before the maximal dosage in 2 patients with stable exertional angina because chest pain with ST depression occurred at the infusion rate of 10 mg/min per kg. All of the control subjects tolerated the maximum dose of dobutamine.

As shown in Table 2, rate-pressure product was increased during dobutamine infusion compared with baseline ($p < 0.01$) but remained unchanged during adenosine infusion in both groups of patients and control subjects, and there was no significant difference in the values between the 2 groups at baseline and during infusion of either adenosine and dobutamine. Table 2 and Fig 1 show that the oxygen content of great cardiac vein blood increased from baseline during both infusions in both groups ($p < 0.01$ in each case), but there was no significant difference in the values between the 2 groups at baseline and during infusion of either adenosine and dobutamine. Great cardiac vein blood flow increased from baseline during both infusions in both groups ($p < 0.01$), but the percent increases in great cardiac vein blood flow during both infusions were significantly smaller in the patients than in the control subjects, as shown in Table 2 and Fig 2. Myocardial oxygen consumption during adenosine infusion did not change from baseline in both groups, whereas it increased during dobutamine infusion in both groups ($p < 0.01$ as compared with the baseline in each case) but its percent increase was lower during both infusions in the patients than in the control subjects ($p < 0.01$ between the patients and control subjects), as shown in Table 2.

Discussion

The present study demonstrated that intravenous adenosine infusion induced angina with ST-segment depression and/or myocardial lactate production, indicating myocardial ischemia, in 11 (69%) of the 16 patients with stable exertional angina but in none of the control subjects, although there was no increase in rate-pressure product or myocardial oxygen consumption, indicators of myocardial oxygen demand. Further, great cardiac vein blood flow was significantly increased during adenosine infusion in patients with stable exertional angina as well as in control subjects. Because adenosine and dipyridamole, which increase endogenous adenosine levels, have been suggested to induce coronary steal in patients with coronary artery disease^{5,8,17,18} there is a possibility that primary reduction in regional myocardial blood flow caused by coronary steal in the myocardial region supplied by the stenotic coronary artery may be an underlying mechanism(s) of adenosine-induced myocardial ischemia.

Intravenous dobutamine infusion also induced angina with ST-segment depression and/or myocardial lactate production in 12 (75%) of the 16 patients with stable exertional angina but not in any of the

control subjects. Although rate-pressure product in the patients was increased from baseline during the dobutamine infusion by the same magnitude as in the control subjects, the percent increase in great cardiac vein blood flow during the dobutamine infusion was smaller in the patients than in the control subjects, probably as a result of coronary stenosis, suggesting that blood supply may not be sufficient in the patients during the dobutamine infusion. This limiting blood supply is mainly responsible for the dobutamine-induced myocardial ischemia. However, the present study demonstrated that the oxygen content of great cardiac vein blood, which contains effluent from the ischemic region, was not decreased but increased in the patients during dobutamine infusion and by a similar magnitude to that observed control subjects, suggesting the presence of an excessive increase in global oxygen supply. This was probably because oxygen imbalance may be restricted in the regional myocardium or in the endocardium and the excessive blood flow in the normal myocardium or in the epicardium might compensate for the decrease in oxygen content in great cardiac vein blood, which is the effluent mixed from the normal and ischemic regions. This increase in myocardial flow occurring during dobutamine infusion may be due to endogenous release of adenosine from myocardium or direct β -adrenergic vasodilation on the basis of the previous reports.^{19,20,28} Thus, there is a possibility that, like adenosine infusion, the increase in blood supply to the non-ischemic myocardium during dobutamine infusion may be caused at least partly by coronary steal at the expense of a reduction in blood flow to the ischemic area, where the resistance vessels are already maximally dilated as a result of metabolic stimuli, leading to exacerbation of myocardial ischemia.

In conclusion, myocardial ischemia occurred during dobutamine and adenosine infusions in patients with stable effort angina, although the global oxygen supply was excessive. As myocardial oxygen consumption remained unchanged during adenosine infusion, regional myocardial flow reduction, possibly owing to flow maldistribution, may contribute, at least partly, to adenosine-induced myocardial ischemia. An increase in myocardial oxygen consumption may be the main cause of myocardial ischemia during dobutamine infusion, but an inappropriate flow increase in normal myocardium may occur during dobutamine-induced ischemia.

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