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Adrenergically Mediated Coronary Vasoconstriction in Patients with Syndrome X

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Summary. **Several studies have shown that coronary vasodilator reserve is impaired in some patients with chest pain and angiographically normal coronary arteries. In a subgroup of these patients, who additionally show ST depression on the electrocardiogram during exercise and are generally labelled as having Syndrome X, the impairment of coronary flow reserve is associated with metabolic and functional signs consistent with an increased sympathetic drive. The aim of the present investigation was to ascertain whether the impairment of coronary vasodilator reserve in patients with Syndrome X is due to adrenergically mediated vasoconstriction of coronary microcirculation. Myocardial blood flow (MBF), at baseline and following intravenous infusion of dipyridamole (0.56 mg/kg over 4 minutes), was measured by means of ^{13}N-ammonia and dynamic positron emission tomography in 10 females (mean age 52 ± 8 years) with a chest pain history, ST-segment depression during exercise, and angiographically normal coronaries. The first MBF study was performed while the patients were off therapy; a repeat MBF study was performed following 1 week of treatment with the alpha-1 blocker doxazosin (2 mg/day). Off therapy MBF was 1.13 ± 0.25 ml/min/g at baseline and increased to 2.35 ± 0.66 ml/min/g following dipyridamole. Coronary vasodilator reserve (dipyridamole/baseline MBF) was 2.18 ± 0.56. During treatment with doxazosin, baseline MBF was not different from the control value (1.25 ± 0.50 ml/min/g), while added dipyridamole significantly increased MBF to 3.52 ± 1.20 ml/min/g ($p < 0.01$ vs. off therapy). Coronary vasodilator reserve was significantly increased (2.91 ± 0.92, $p < 0.01$ vs. control value) by doxazosin. This study indicates that alpha-1 adrenoceptors might play a role in the reduction of coronary reserve in patients with Syndrome X. Further clinical studies are needed to ascertain the efficacy of alpha-1 blockers for the treatment of such patients.**

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Key Words. **Syndrome X, coronary angiography, coronary reserve, sympathetic nervous system, alpha-1 adrenoceptors, positron emission tomography**

Several studies have shown that coronary vasodilator reserve is impaired in some patients with chest pain and angiographically normal coronary arteries [1,2]. Cannon and Epstein have proposed that dysfunction of small intramural prearteriolar coronary arteries might be the cause of the reduced coronary vasodilator reserve in these patients [3]. In a subgroup of these patients, who additionally showed ST depression during exercise and are generally labelled as having Syndrome X, a reduced coronary vasodilator reserve was demonstrated during atrial pacing [4]. Furthermore, in this study metabolic and functional signs consistent with an increased sympathetic drive were observed.

In the absence of significant atherosclerotic disease of large epicardial arteries, almost all coronary resistance is located in the microcirculation. According to Chilian et al. [5], 40–50% of total coronary resistance resides in arterioles greater than 100 μm in diameter. Furthermore, there is evidence to suggest that in these arterioles there is sympathetic control of vessel tone, which is mediated by both alpha$_1$ and alpha$_2$ adrenoceptors [6]. It can, therefore, be hypothesised that the impairment of coronary vasodilator reserve in Syndrome X patients may be, at least in part, an adrenergically mediated phenomenon, probably through activation of alpha adrenoceptors on coronary microcirculation.

To test this hypothesis, a preliminary study was performed to assess the effect of treatment with the selective alpha-1 antagonist drug, doxazosin, on coronary vasodilator reserve in a group of patients with Syndrome X.

Methods

Study population

The study population consisted of 10 females (Table 1), who were recruited on the basis of the following criteria: a history of chest pain; horizontal or downsloping ST-segment depression (>0.1 mV of the base-

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Table 1. Study population

Patient (≠)	Age (years)	Baseline ECG	SBP (mmHg)	DBP (mmHg)	ST shift (mV)
1	53	Normal	140	95	0.15
2	58	Abnormal	160	105	0.15
3	53	Normal	120	85	0.20
4	50	Normal	130	70	0.15
5	45	Normal	140	80	0.15
6	51	Normal	130	80	0.15
7	56	Normal	140	80	0.10
8	45	Normal	140	92	0.20
9	43	Abnormal	125	85	0.15
10	70	Normal	165	100	0.20
Mean ± SD	52 ± 8		139 ± 14	87 ± 11	0.16 ± 0.03

SBP = systolic blood pressure; DBP = diastolic blood pressure; ST shift = ST-segment depression during exercise.

line value 0.08 seconds after the J point) on the electrocardiogram (ECG) during exercise; a negative ergonovine test (incremental doses starting from 0.025 mg up to 0.20 mg intravenously) for both symptomatic and ECG criteria; and angiographically normal coronary arteries without minimal irregularities. The resting ECG was normal in eight patients, and in the remaining two patients showed nonspecific disturbances of ventricular repolarization (flat and low-voltage negative T waves). However, none of the patients had conduction abnormalities in the ECG, either at rest or during exercise (Table 1). All patients had a normal resting echocardiogram. Borderline hypertension (defined as a blood pressure >140/90 and <165/95 mmHg) was present in three patients, while one patient had a blood pressure ≥165/95 mmHg (Table 1). None of the patients had diabetes mellitus, hyperlipidemia, mitral valve prolapse, primary myocardial disease, or any other cardiac or extracardiac disease. All patients had normal blood potassium levels.

Measurement of regional myocardial blood flow

Regional myocardial blood flow was measured by means of ^{13}N-ammonia and dynamic positron emission tomography (PET) [7,8]. The patient was positioned on the bed of the two-ring ECAT III positron tomograph (CTI, Knoxville, TN) in order to have the center of gravity of the left ventricle as close as possible to the center of both the axial and transaxial fields of view. This machine provides three simultaneous sections, two from the primary planes and one from the interplane. Before performing the emission study, a circular ring source filled with about 2 mCi ^{68}Ge was used for the blank and transmission data acquisition. A rectilinear transmission scan was used as a low-resolution X-ray film, in order to identify the heart profile. Thereafter, the transmission scan was performed in order to measure the attenuation correction coefficients to be used for each line of response of the sinogram. For each flow measurement, ^{13}N-ammonia (0.2 mCi/kg body weight), prepared as reported elsewhere [9], was slowly injected intravenously over a period of 15–20 seconds. Dynamic PET acquisition was started simultaneously with the beginning of the injection of the tracer, and a total of 28 frames (16 × 3 seconds, 11 × 12 seconds, and 1 × 300 seconds) were acquired over 8 minutes.

Initially, myocardial blood flow during baseline conditions and following an intravenous infusion of dipyridamole (0.56 mg/kg over 4 minutes) was measured while patients were off treatment. Blood flow during hyperemic conditions was assessed by injecting ^{13}N-ammonia 4 minutes after the end of dipyridamole infusion. Three ECG leads (V2, V4, and V6) were continuously monitored during the study period and a complete 12-lead ECG was recorded every minute during dipyridamole infusion and for up to 10 minutes following the end of infusion. Blood pressure was measured every minute by a cuff sphygmomanometer during dipyridamole infusion and for 10 minutes thereafter. A period of pharmacological washout of at least 72 hours was allowed before this study (no patient was on treatment with beta-blockers before entering the study).

A repeat PET study (baseline + dipyridamole) was performed in all patients whilst on treatment with the selective alpha-1 blocker doxazosin (2 mg once a day, p.o.). All patients received the drug for a minimum of 7 days. All PET studies (off and on treatment) were performed between 2 and 4 p.m. The protocol of the study was approved by the Institutional Review Board of the C.N.R. Institute of Clinical Physiology. Each subject was informed of the investigative nature of the study, and written consent was obtained before entry.

Data analysis

The sinograms were normalized according to the tomograph disuniformity map, corrected for attenuation, and then reconstructed with a transaxial spatial

resolution of about 9 mm (full width at half-maximum). The sum of the rates of randoms and multiples related to each sinogram was used for dead-time loss corrections [10]. Three regions of interest, encompassing the septum, and the anterior and free wall of the left ventricle, were drawn automatically in each tomogram [7,8]. Mean left ventricular wall activity was calculated by averaging the counts of the different regions of interest. The coefficient of variation of counts in the three contiguous planes at rest and following dipyridamole was calculated and found to be comparable. As a consequence, quantitative analysis of flow was performed in only one of the three planes at midventricular level.

The rate-pressure product was calculated as heart rate multiplied by systolic blood pressure. Coronary reserve was calculated by dividing the myocardial blood flow achieved following dipyridamole infusion by the baseline blood flow.

Statistical analysis

All values are expressed as means ± SD. Correlations between two variables were calculated by simple linear regression. Repeated measurements ANOVA was used to compare count rates in the three tomographic planes and regional flow rates in the different left ventricular walls. Student's two-tailed paired t test was used to compare data before and after treatment. A p value < 0.05 was considered significant.

Results

Hemodynamic parameters

One subject complained of mild and transitory headache during doxazosin treatment, but the drug was well tolerated by the other patients. Treatment produced a significant decrease in baseline systolic blood pressure and the rate-pressure product. Both systolic and diastolic pressure following dipyridamole infusion were significantly lower during treatment (Table 2).

Coronary vasodilator reserve

Study 1 (off treatment). At baseline, average left ventricular blood flow was 1.13 ± 0.25 ml/min/g (Figure 1). Its regional distribution is shown in Figure 2. Six patients experienced chest pain and significant ST-segment depression following dipyridamole infusion, while two patients had ST-segment depression without associated chest pain. Average left ventricular blood flow following dipyridamole administration increased significantly to 2.35 ± 0.66 ml/min/g ($p < 0.01$ vs. baseline value; Figure 1). Following dipyridamole infusion, flow in the interventricular septum was significantly higher than flow in both the free and anterior wall of the left ventricle (Figure 2). Coronary vasodilator reserve (dipyridamole/baseline blood flow) was 2.18 ± 0.56 (Figure 3).

Table 2. *Hemodynamic parameters before and after alpha 1 blockade*

	Off treatment	$Alpha_1$ blockade	p
Baseline			
HR (beats/min)	75 ± 12	74 ± 12	N.S.
SBP (mmHg)	139 ± 14	127 ± 15	<0.01
DBP (mmHg)	87 ± 11	82 ± 12	N.S.
RPP (mmHg* beats/min)	10326 ± 1941	9337 ± 1940	<0.05
Dipyridamole			
HR (beats/min)	103 ± 14	105 ± 13	N.S.
SBP (mmHg)	140 ± 16	128 ± 17	<0.01
DBP (mmHg)	87 ± 10	77 ± 9	<0.01
RPP (mmHg* beats/min)	14455 ± 3042	13522 ± 2903	N.S.
ST depression (mV)	0.11 ± 0.04	0.08 ± 0.06	N.S.

HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; RPP = heart rate times systolic pressure; N.S. = not significant. All values are means ± SD.

Study 2 (following alpha-1 block). At baseline, average left ventricular blood flow was 1.25 ± 0.50 ml/min/g (p = NS vs. off treatment; Figure 1). Regional myocardial blood flow distribution remained comparable to that during study 1 (Figure 2). Seven patients experienced chest pain following dipyridamole infusion (four of whom had chest pain also while off treatment and three who did not experience chest pain while off treatment). A slight, although statistically not significant, reduction in the degree of ST depression following dipyridamole administration was observed during treatment (Table 2). Average left ventricular blood flow following dipyridamole infusion was higher (3.52 ± 1.20 ml/min/g) than the corresponding value off treatment ($p < 0.01$; Figure 2). Although higher, septal flow was not statistically different from flow in both the free and anterior walls of the left ventricle. Coronary reserve during treatment (2.91 ± 0.92) was significantly higher ($p < 0.01$) than that off treatment (Figure 3).

Discussion

In agreement with previous reports, the results of the present study show that in patients with Syndrome X, coronary vasodilator reserve following dipyridamole infusion is reduced below the value generally reported in normal subjects (i.e., ≥2.5) with PET [8,11,12] and intracoronary Doppler probes [13]. In the same patients, however, coronary vasodilator reserve increased significantly during treatment with the selective alpha-1 adrenoceptor blocker doxazosin, reaching values similar to those reported for normal subjects.

Although the sympathetic activation induced by

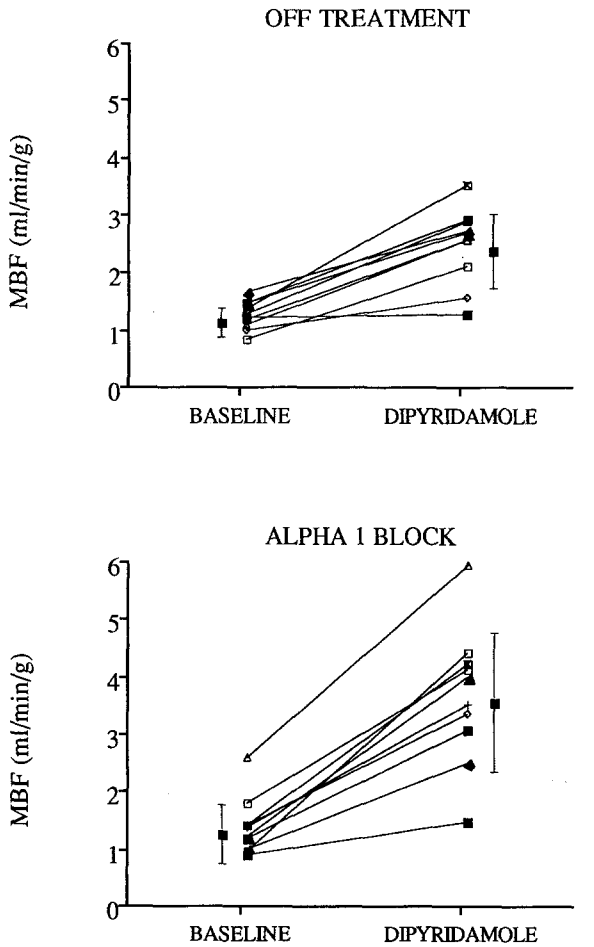

Fig. 1. Individual values of myocardial blood flow at baseline and following IV dipyridamole infusion (0.56 mg/kg over 4 minutes) in patients with Syndrome X off treatment (upper panel) and during treatment with doxazosin (2 mg o.d.; lower panel).

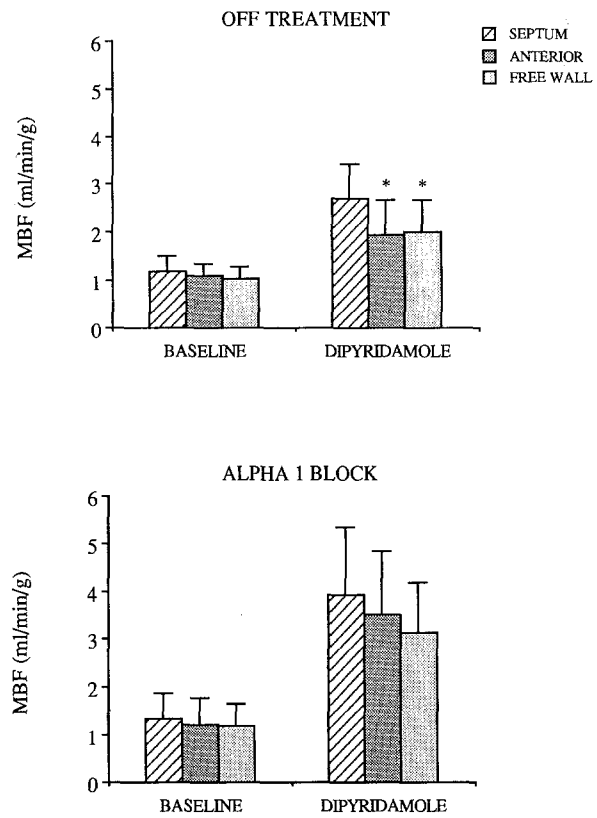

Fig. 2. Mean (±SD) values of regional myocardial blood flow in the septal, anterior, and free wall of the left ventricle at baseline and following IV dipyridamole infusion (0.56 mg/kg over 4 minutes) in patients with Syndrome X off treatment (upper panel) and during treatment with doxazosin (2 mg o.d.; lower panel).

physical exercise or excitement produces a net increase in coronary blood flow secondary to metabolically induced vasodilatation, the direct effect of noradrenaline on coronary vascular smooth muscle is vasoconstriction through activation of alpha adrenoceptors [6]. Constriction of arterioles with a resting diameter greater than 100 μm has been demonstrated in cats following administration of noradrenaline in the presence of beta blockade [14]. Adrenergic vasoconstriction has been demonstrated to oppose metabolic coronary vasodilatation during exercise in normal dogs, and the nonselective alpha-adrenergic blocker phentolamine is able to produce an increase in coronary flow during exercise [15]. This phenomenon of adrenergic vasoconstriction is more pronounced in hypertensive animals with left ventricular hypertrophy in which alpha-adrenergic blockade produced a greater effect [16]. This is in line with the inverse linear relationship between the reduction of systolic

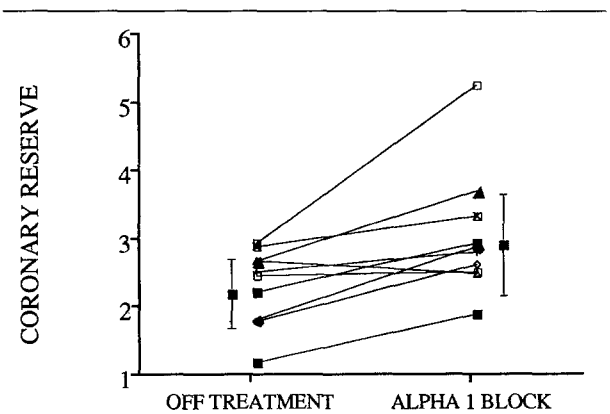

Fig. 3. Individual values of coronary flow reserve (dipyridamole/baseline myocardial blood flow) measured in patients with Syndrome X off treatment and during treatment with doxazosin (2 mg o.d.).

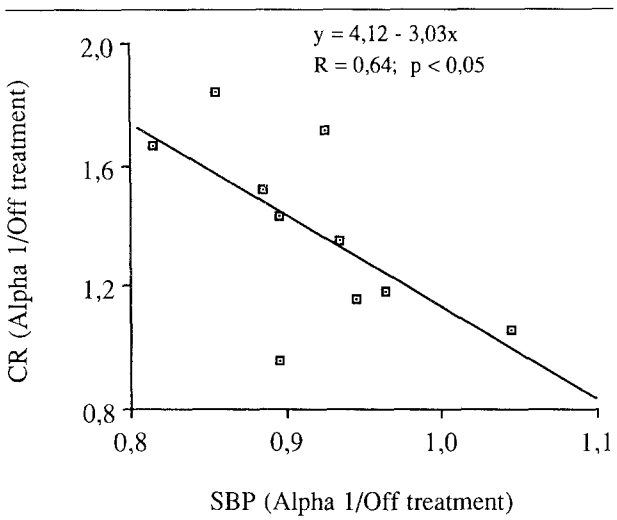

Fig. 4. *A graph showing the correlation between the ratio of systolic blood pressure during treatment to systolic blood pressure off treatment (abscissa), and the ratio of coronary vasodilator reserve during treatment to coronary vasodilator reserve off treatment (ordinate).*

blood pressure and the increase in coronary vasodilator reserve found in our patients during treatment with doxazosin (Figure 4). However, an improvement in coronary reserve during treatment was observed in all but one patient (patient #8, Table 1), independent of the values on arterial blood pressure (Figure 3).

Our data show that overall there is little adrenergically mediated coronary tone in these patients during baseline conditions, as evidenced by the comparable values of myocardial blood flow both on and off treatment. Similarly, no changes in resting coronary flow velocity were observed in normal subjects following alpha blockade with phentolamine [17]. The mechanisms responsible for the blunted coronary vasodilator response following intravenous dipyridamole infusion in patients with Syndrome X remain to be elucidated. However, the beneficial effect of alpha$_1$ blockade on coronary reserve suggests that adrenergically mediated vasoconstriction of coronary microcirculation, probably through baroreflex sympathetic activation triggered by dipyridamole infusion, may play a role in reducing coronary reserve in these patients.

There is no obvious explanation for the higher flow values observed in the interventricular septum as compared to the ventricular free wall, although they might be related to different regional oxygen demands. Recently, regional differences in myocardial 13-ammonia uptake in control subjects have been reported [18]. In no instance, however, were regional flow defects demonstrated in any of the patients at baseline or following stress. This is in agreement with previous observations by Geltman et al. [19].

Previously there has been considerable debate whether the chest pain experienced by patients with angiographically normal coronary arteries is of ischemic origin. Recent evidence in patients with Syndrome X has failed to demonstrate changes in myocardial metabolism characteristic of ischemia [4]. The observation made in the present study that in 7 out of 10 patients dipyridamole-induced chest pain persisted despite a significant improvement of coronary vasodilator reserve is consistent with the hypothesis that in Syndrome X chest pain is probably not of ischemic origin.

Although the conclusions that can be derived from this study are limited because of the absence of a control group and due to its open design, these preliminary data suggest that adrenergically mediated vasoconstriction may play a role in the reduction of coronary vasodilator reserve observed in some patients with Syndrome X. Further clinical studies are needed to ascertain the efficacy of alpha$_1$ blockade for the treatment of such patients, as well as to test the effect of alpha$_1$ blockade on coronary vasodilator reserve in normal subjects.

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