Coronary Microvascular Reactivity to Sympathetic Stimulation in Patients with Idiopathic Dilated Cardiomyopathy

Alexander E. Drzezga, Rudolf Blasini, Sybille I. Ziegler, Frank M. Bengel, Wolfgang Picker, and Markus Schwaiger

Departments of Nuclear Medicine and Cardiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

The objective of this study was to assess noninvasively the microvascular reactivity to sympathetic stimulation in patients with idiopathic dilated cardiomyopathy (IDC) and in healthy volunteers, who underwent cardiac catheterization for exclusion of coronary artery disease. **Methods:** Myocardial flow was quantified with ^{13}N-ammonia PET and tracer kinetic modeling at rest and in response to cold pressor testing (CPT). Ten healthy volunteers (8 men, 2 women; mean age ± SD, 50.7 ± 15 y) and 10 matched patients (8 men, 2 women; mean age, 52.5 ± 14 y) with IDC (mean left ventricular ejection fraction, 0.30 ± 0.12) were included in the study. **Results:** Myocardial perfusion at rest was not significantly different between the groups. However, myocardial vascular resistance (MVR) was significantly lower in IDC patients at rest than in healthy volunteers. In response to CPT a significant decrease in MVR was found in healthy volunteers (1.9 ± 0.4 to 1.5 ± 0.4 mm Hg × 100 g/mL; 22% decrease) but not in IDC patients (1.5 ± 0.4 to 1.4 ± 0.3 mm Hg × 100 g/mL; 9% decrease). Consequently, the increase of the myocardial blood flow in response to CPT was significantly lower ($P < 0.008$) in IDC patients (56 ± 17 to 66 ± 18 mL/100 g/min; 20% increase) compared with healthy volunteers (52 ± 12 to 80 ± 30 mL/100 g/min; 52% increase), whereas both showed comparable hemodynamic reactions. **Conclusion:** The data indicate that CPT in combination with ^{13}N PET imaging is a valuable noninvasive tool for assessment of coronary microvascular reaction to sympathetic stimulation in IDC patients. Lower coronary vascular resistance was found in IDC patients at rest compared with healthy volunteers, suggesting possible exhaustion of sympathetically induced dilation of the coronary microvasculature in IDC patients at rest. This mechanism may explain the impaired flow response to cold in IDC patients in the present study.

Key Words: PET; idiopathic dilated cardiomyopathy; cold pressor test

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Previous studies assessing invasive parameters, such as intracoronary doppler flow measurements or angiographically defined changes in luminal diameter of coronary arteries, have shown reduced coronary blood flow reserve in patients with idiopathic dilated cardiomyopathy (IDC) (*1–3*). Reduction of coronary flow velocity after intracoronary infusion of papaverin and acetylcholine suggests the involvement of endothelial-independent and -dependent mechanisms (*4,5*). However, these invasive studies primarily addressed the relative flow dynamics in large epicardial vessels. PET, in combination with different flow tracers, allows absolute quantification of myocardial blood flow (MBF) at the capillary level. Thus, noninvasive assessment of microvascular reactivity can be performed. PET, as a noninvasive imaging approach, provides not only global assessment of myocardial perfusion but also regional definition of flow changes, which is relevant because previous studies in patients with cardiomyopathy have indicated regional alterations of myocardial perfusion, metabolism, and function (*6*).

Preliminary PET studies using pacing-induced tachycardia or dipyridamole as a stimulus have reproduced altered MBF response in patients with IDC (*7,8*). Flow response to sympathetic stimulation has not yet been examined with PET in IDC patients. Noninvasive sympathetic stimulation can be performed with cold pressor testing, an established procedure that induces sympathetic stimulation by cooling an extremity in ice water. The test has been shown to mirror the intracoronary administration of acetylcholine and is appropriate for the investigation of the integrity of endothelial function (*9*).

The hypothesis of our study was that a reduced myocardial microvascular flow response to sympathetic stimulation can be demonstrated in IDC patients noninvasively using PET and cold pressor testing.

MATERIALS AND METHODS

Patient Characteristics

The study included 10 patients with primary dilated cardiomyopathy (8 men, 2 women; mean age ± SD, 52.5 ± 14 y) in different stages. All patients had an enlarged left ventricle with global hypokinesia and reduced left ventricular (LV) ejection fraction assessed by LV angiography or radionuclide ventriculography (average, 0.30 ± 0.12). All patients underwent cardiac catheterization and showed no angiographic evidence of coronary artery disease (CAD). All patients were clinically stable. Major complaints were dyspnea and exhaustion after light-to-medium exercise.

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For correspondence or reprints contact: Alexander E. Drzezga, MD, Technische Universität München, Nuklearmedizinische Klinik u. Poliklinik, Klinikum rechts der Isar, Ismaningerstr. 22, München, 81675, Germany.

Patients were excluded when their medical histories included any of the following conditions: myocardial infarction, hypertension requiring medical treatment, cardiac surgery, coronary angioplasty, primary valvular abnormalities, insulin-dependent diabetes mellitus, alcohol abuse, current therapy with β-blockers, and smoking. Angiotensin-converting enzyme inhibitors were taken by 9, calcium antagonists by 1, and nitrates by 3 patients. Medication was administered in doses adapted individually for all patients, following usual clinical therapy schemes.

The second group included 10 healthy volunteers (8 men, 2 women; mean age, 50.7 ± 15 y). Volunteers were recruited from a cohort of patients who underwent diagnostic cardiac catheterization for exclusion of CAD. The cardiac catheterization showed no evidence of CAD or other cardiac diseases and demonstrated normal LV function. Exclusion criteria were identical to those for the patient group.

The groups were matched for age and sex. All participants entered the study after written consent. The protocol was approved by the human ethics committee at the Klinikum rechts der Isar, Technische Universität München. Patient characteristics are summarized in Table 1.

PET

Each group underwent PET imaging and cold pressor testing following the same protocols. All medications were stopped more than 12 h before the examinations. To prevent hypoglycemia and dehydration, the participants were free to eat and to drink small amounts (except caffeine-containing substances, such as tea or coffee).

PET imaging was performed using a whole-body PET scanner (model CTI 951-R/31; CTI, Knoxville, TN). ^{13}N-ammonia was synthesized using the method described by Gelbhard et al. (*10*). After placing the patient in the scanner and obtaining a scout scan for localization of the heart, a 15-min transmission scan was acquired for correction of photon attenuation.

Subsequently, 740 MBq ^{13}N-ammonia diluted in 20 mL saline solution were infused as a slow bolus in a peripheral arm vein over 30 s, and a dynamic imaging sequence was started (12 × 10, 6 × 30, and 3 × 300 s). To allow for sufficient decay of ^{13}N activity (physical half-life, 9.9 min) to <3% of the original activity, a break of at least 50 min was taken between the rest and the stress studies.

The second set of images was acquired in conditions of sympathetic stimulation using the cold pressor test. Because the position of each patient in the scanner made the forearm inaccessible, the left foot was cooled. For a period of 4 min each, the patient's left foot and ankle were immersed in a tub containing a mixture of ice and water (temperature, 0°C–1°C). Thirty seconds after placement of the patient's foot in the tub, the infusion of 925 MBq ^{13}N-ammonia was started. Dynamic PET data acquisition was performed in the same manner as in the baseline study. Electrocardiography was performed and monitored continuously, and heart rate and blood pressure were measured at intervals of 1 min throughout the study.

TABLE 1
Patient Characteristics

	Healthy volunteers	IDC patients	*P*
Number	10	10	NS
Male/female	8/2	8/2	NS
Age (y)	52.5 ± 14	50.7 ± 15	NS
Cholesterol (mg/dL)	234 ± 12	212 ± 24	NS
No. with diabetes	0	1 (not insulin dependent)	
Angiography	Normal	Normal	
Ejection fraction (%)	Normal	30 ± 12	

NS = not statistically significant.

Image Processing

Three-Dimensional Reorientation. Using the transmission scan, both rest and stress data sets were corrected for attenuation. Transaxial images were reconstructed using filtered backprojection. Vertical and horizontal cardiac long-axis angles were defined and used for reorientation of all 21 frames into 12 transaxial images in the short-axis view of the heart (thickness, 0.8 cm).

Image Analysis. For analysis of PET data, we used the method of Muzik et al. (*11*) for automated region definition. The algorithm automatically defines myocardial regions of interest (ROIs) based on radial activity profiles, including a blood-volume fraction of ~60%. This definition allows for correction of in-plane partial-volume effects and blood-to-tissue cross-contamination in the model equation (*12–14*). In particular, the ROI strategy applied in this routine has been shown to be sufficient for correction of resolution distortions (*13*), which may occur in IDC patients because of reduced wall thickness. Visual control during the routine enables detection of miscalculations.

An arterial input function was calculated using a small circular ROI in the center of the left ventricle. The dynamic image set was sampled using 6 midventricular planes, and 72 (6 planes × 12 regions) time–activity curves were stored for further analysis. Inter- and intraobserver comparisons of the program showed no significant differences.

MBF Calculation

For calculation of MBF, the tracer kinetic model for ^{13}N-ammonia developed by Hutchins et al. (*13,14*) was used. It has been previously shown that this 3-compartment model allows exact calculation of myocardial perfusion (*12,14*).

In addition, averaged profiles were generated corresponding to 5 areas (anterior, septal, inferior, lateral, and apex), and fitting was performed for the averaged time–activity curves.

Calculation of Myocardial Vascular Resistance and Rate Pressure Product

Using the mean heart rate (HR), diastolic pressure (DBP), and systolic pressure (SBP) of each patient, the rate pressure product (RPP) was calculated as HR × SBP/100. Myocardial vascular resistance (MVR) was calculated by dividing the mean blood pressure ([2 × DBP + SBP]/3) by MBF. As there were no clinical symptoms or signs indicating an increased venous pressure in any patients, we assumed that the possible influence of different right atrial pressures on the MVR would have been small.

To exclude eventual influence of a different LV end-diastolic pressure on the MVR in the 2 groups, we performed a test calculation. Increased LV end-diastolic wall tension would result in a reduced perfusion pressure; thus, we subtracted 15 mm Hg of the perfusion pressure in the IDC group and 5 mm Hg in the healthy group, without finding significant changes in the calculated global vascular resistance.

Statistical Analysis

For all continuous variables, mean and SD were calculated. Hemodynamic values and the coronary blood flow were compared within each group in rest and stress conditions and between the groups using a Student t test. $P \leq 0.05$ was considered statistically significant. Correlation of the data was checked by calculation of the Pearson coefficient of correlation.

RESULTS

Hemodynamic Response

Table 2 shows the changes in the hemodynamic parameters, including HR, DBP, maximum SBP, and RPP, that were observed in both groups in response to cold pressor testing. In the healthy group, significant increases in SBP and RPP were found, as well as a significant increase in DBP. In the IDC group there was also a significant increase in SBP, RPP, and the heart rate. Comparison between the groups showed no significant differences between increases in hemodynamic values. The SBP at rest and stress and the DBP at rest were found to be significantly higher in the healthy group than in the IDC group.

Myocardial Perfusion

Table 3 shows the myocardial flow results obtained by PET imaging. Mean myocardial perfusion at rest was not significantly different between the groups. In both groups a significant increase in MBF (defined as coronary flow response [CFRP] or mean LV MBF during stress divided by baseline flow) was found in response to cold pressor. Comparison of the absolute whole myocardial flow values during stress between the groups did not reveal statistical significance. However, the increase in myocardial flow was significantly higher in the healthy group than in the IDC group (Fig. 1). Additional correction of perfusion values for RPP has been performed by division of resting flow by RPP and following multiplication of the result by a linear factor of 8000, as suggested in previous studies (*15*). No significant changes were observed compared with analysis without correction for RPP.

The regional analysis showed a significant increase in mean MBF in all areas (anterior, septal, lateral, inferior, and apical) of the healthy group and in all areas except the septal area of the IDC group. Comparison of the regions between the groups revealed significantly higher CFRPs in the septal, inferior, and apical areas of the healthy group. No statistically significant differences were found in the comparison of the regional flow values between the 2 groups in conditions of rest or stress.

Individual analyses showed increased MBF in all healthy volunteers, with a range of 19%–115% (SD = ±28). In IDC patients, increased MBF was observed in 8 individuals, with a range of 5%–35%, 1 subject remained unchanged, and in 1 a decrease of 7% was observed (SD = ±22).

TABLE 2
Hemodynamic Responses

Characteristic	Healthy volunteers	IDC patients	*P*
HR			
Rest (bpm)	59 ± 10	82 ± 18	0.022
Stress (bpm)	70 ± 21	91 ± 19	NS
Change	17%	11%	0.275
P	NS	0.052	
DBP			
Rest (mm Hg)	79 ± 10	71 ± 6	NS
Stress (mm Hg)	87 ± 11	75 ± 10	0.02
Change	11%	5%	NS
P	0.01	NS	
SBP			
Rest (mm Hg)	125 ± 15	103 ± 11	0.005
Stress (mm Hg)	143 ± 15	113 ± 13	0.002
Change	14%	9%	NS
P	0.0001	0.0002	
RPP			
Rest	74 ± 13	84 ± 18	NS
Stress	101 ± 38	101 ± 19	NS
Change	35%	20%	NS
P	0.04	0.002	

NS = not statistically significant.

MVR

The global MVR (Table 4) was significantly lower in the IDC group in conditions of rest than in the healthy group. It decreased significantly in response to cold pressor in the healthy group, whereas there was no significant decrease (P = not statistically significant) to be found in the IDC group (Figure 2). During the cold pressor test, no significant difference in MVR was found between the 2 groups.

Regional analysis of MVR in conditions of rest showed a significantly higher value in the septal region of the control group. In the remaining regions, no significant difference was calculated. Comparison of MVR showed a significant decrease during the cold pressor test in all areas, except for the septal area in the healthy group. In the IDC group, no significant decrease in MVR was found in any area. During cold pressor test, the MVR did not differ significantly in any region in the 2 groups.

In both groups, no significant correlation of the perfusion values with hemodynamic parameters, such as systolic and diastolic pressure, heart rate, ejection fraction, or increase of RPP in reaction to cold pressor, was found.

Heterogeneity Analysis

Visual analysis showed no perfusion abnormalities in either group. To assess the heterogeneity of perfusion, the means of the SDs of blood flow measurements in the different regions of every patient were calculated and compared. There was no significant difference in heterogeneity between the 2 groups (normal group rest, 9.15; stress, 12.72; IDC group rest, 10.32; stress, 13.71). Within the IDC group, however, the heterogeneity was significantly higher during cold pressor testing than in resting conditions (Fig. 3).

TABLE 3
Global Myocardial Perfusion

Global MBF	Healthy volunteers	IDC patients	*P*
Rest (mL/100 mg × min)	52 ± 12	56 ± 17	NS
Stress (mL/100 mg × min)	80 ± 30	66 ± 18	NS
CFRP (%)	52 ± 28	20 ± 22	0.01
P	0.002	0.01	

CFRP = coronary flow response; NS = not statistically significant.

TABLE 4
Global Myocardial Vascular Resistance

MVR mm HG/100 g/mL × min	Healthy volunteers	IDC group	*P*
Rest	1.9 ± 0.4	1.5 ± 0.4	0.054
Test*	1.86 ± 0.41	1.26 ± 0.3	0.007
Stress	1.5 ± 0.35	1.4 ± 0.3	NS
Test	1.45 ± 0.3	1.14 ± 0.2	0.05
Change (%)	22 ± 8	10 ± 15	0.03
Test	22 ± 8	8 ± 16	0.03
P	0.0001	NS	
Test	0.0001	NS	

*Test calculation results after subtraction of 15 mm Hg of the perfusion pressure in the IDC group and 5 mm Hg in healthy volunteers.
NS = not statistically significant.

DISCUSSION

Patients with IDC exhibit a significantly attenuated coronary flow response to cold pressor testing compared with a healthy group, despite the presence of comparable hemodynamic reactions. MBF was comparable in both groups in rest conditions, but the baseline MVR was significantly lower in IDC patients. MVR decreased significantly in the healthy group, whereas there was no change observed in the IDC group. These results are equally valid for the global and the regional analyses.

To our knowledge, this study uses ^{13}N-ammonia PET as a noninvasive means to examine the reaction to cold pressor testing by quantitative measurement of myocardial microcirculation in patients with IDC. Our study shows that PET and cold pressor testing represent a valuable procedure to assess noninvasively coronary microvascular reaction to sympathetic stimulation.

Extravascular and Hemodynamic Factors

In both groups, no correlation was found between the hemodynamic parameters, including blood pressure, heart frequency, and RPP following CPT, and the flow values. Although significant differences were found in the flow response of both groups, the changes of the hemodynamic parameters did not differ significantly. This indicates that the differences of the perfusion in both groups were not caused primarily by differences in cardiac work.

In several previous studies, a reduced coronary and peripheral flow response to different vasodilating stimuli, such as adenosine, acetylcholine, papaverine, dipyridamole, or pacing tachycardia, has been shown in patients with IDC, which is in accordance with our results (*1–5*). The absolute flow values, however, have been a subject of controversy. In many studies, a flow velocity catheter, which allows only comparison of flow ratios, was used for assessment of the flow response; thus, no assessments of absolute flow values at rest and during stimulation were made (*1–4*). In some studies using techniques that allow estimation of the absolute blood flow (argon technique, thermodilution catheter), a significantly lower coronary blood flow was detected in conditions of maximum vasodilative stimulation in IDC patients, whereas comparison of coronary blood flow in rest conditions revealed no significant differences between patients and healthy volunteers (*16*). In contrast, in another study using an animal model of heart failure, significantly lower perfusion at rest has been shown (*8*). Furthermore, in a study by Parodi et al. (*17*), a markedly depressed MBF was observed using the microsphere method in IDC patients with end-stage heart failure undergoing heart transplantation. Neglia et al. (*7*) found reduced rest perfusion measured with ^{13}N-ammonia PET in IDC patients without overt heart failure.

LV failure and the resulting increase in LV end-diastolic pressure was discussed as a possible reason for decreased coronary flow response and lower absolute flow values in IDC patients (*2,8*). In other studies, a hypothesis of a

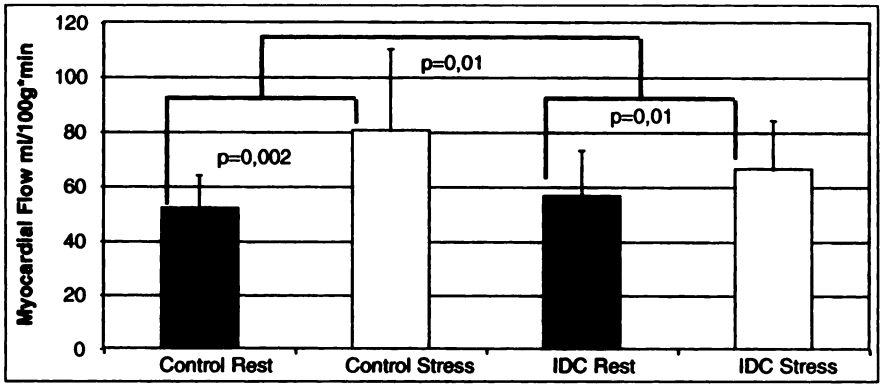

FIGURE 1. Global myocardial flow values at rest and in response to cold pressor test.

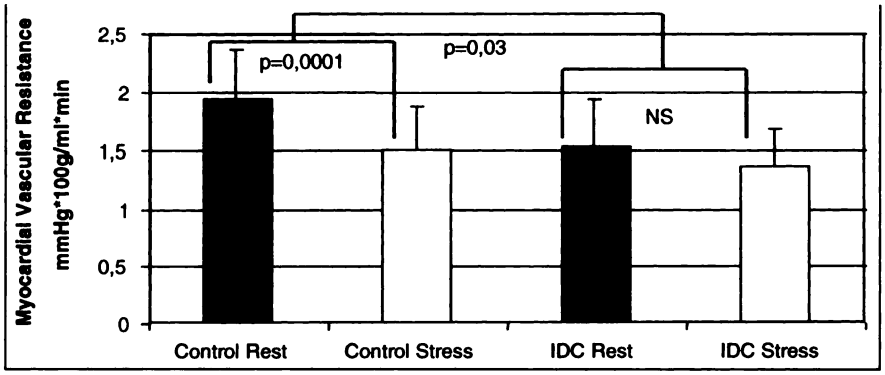

FIGURE 2. Global myocardial vascular resistance at rest and in response to cold pressor test.

multifactorial genesis of the decreased flow response and the lower absolute flow values was preferred (*3,7,16,17*).

In contrast to most other investigators, De Marco et al. (*18*) could show increased resting coronary sinus blood flow in combination with increased oxygen consumption in IDC patients using a thermodilution catheter. In our study, the myocardial resting flow was not significantly different in IDC patients compared with that in healthy volunteers. MVR, however, was found to be significantly lower in IDC patients than in healthy volunteers in conditions of rest and did not change significantly in reaction to cold pressor testing. Furthermore, no correlation was found between ejection fraction and the flow response to cold pressor or the absolute flow values in the IDC group. These results clearly contradict the hypothesis that increased LV end-diastolic pressure may be responsible for the impaired flow response in IDC patients. Instead, the data indicate that high-grade vasodilation may be present in IDC patients already in rest conditions. Dilated myocardium has been shown to have an increased oxidative metabolism, resulting in an increased perfusion demand (*19*). Thus, reduced MVR may be necessary in IDC patients in rest conditions to guarantee sufficient oxygen supply of the dilated myocardium. As sympathetic vasodilation is already exhausted, further dilation in reaction to cold pressor is limited.

However, because our study was performed noninvasively, we did not measure LV end-diastolic pressure and cannot completely exclude its possible influence on the results. In contrast to our results, Neglia et al. (*7*) reported a decreased resting flow in IDC patients without overt heart failure. No correlation of the MBF in response to dypiridamole infusion with the LV end-diastolic pressure was observed in rest conditions their study; however, the reduced MBF in IDC patients did correlate significantly with the LV end-diastolic pressure. It seems possible that resting perfusion levels may be different in IDC patients, depending on LV function, but further dilation in response to vasodilating stimuli is impaired, possibly because of extensive dilation already present in resting conditions. Furthermore, endothelial dysfunction, postendothelial defects, or changed reactivity of the smooth muscles after chronically increased sympathetic overstimulation must be taken in consideration.

Sympathetic Stimulation

In our study, the cold pressor test was used for assessment of vascular reactivity. Nabel et al. (*20*) showed that the reaction of normal coronary arteries to cold pressor testing is vasodilation.

Sympathetic stimulation by the cold pressor test results in increased plasma catecholamine levels and increased sympathetic nervous tone. Di Carli et al. (*21*) recently showed a close relation between increased myocardial flow (measured with ^{13}N-ammonia PET) in response to the cold pressor test and the integrity of the sympathetic nervous system (assessed with ^{11}C-hydroxyephedrine).

Plasma catecholamines and sympathetic nervous stimulation are known to cause dilation of the coronary arteries (*22*). In our study, we found a lower vascular resistance in IDC patients in conditions of rest and an inability to decrease the resistance in reaction to cold stress. Myocardial flow in rest conditions was not lower in IDC patients than in the healthy volunteer group, results that are in contrast to previous studies (*7,16*). According to our hypothesis, elevated catecholamine levels or increased sympathetic ner-

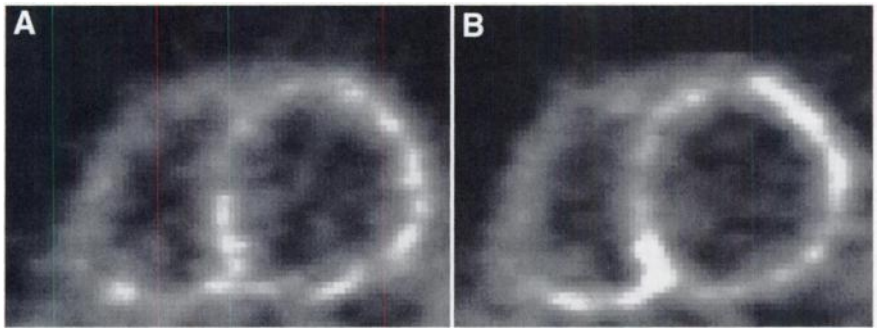

FIGURE 3. Transaxial slice of dilated heart at rest (A) and during cold pressor stimulation (B).

vous stimulation may be present at rest, resulting in a constant vasodilation that guarantees adequate perfusion at rest and satisfies the increased need of oxygen. In stress conditions, further vasodilation may be limited because of exhaustion of catecholamine reserves or downregulation or saturation of receptors. It is well known that there is an activation of the adrenergic system in IDC patients. Previous studies in patients with severe heart failure have also shown increased plasma noradrenaline levels at rest, but significantly lower exercise-induced levels, when compared with patients with milder forms of disease or with healthy subjects (*23*).

Endothelial Dysfunction

Chronic sympathetic overstimulation may result in damage of the myocardial microvascular endothelium. In multiple invasive studies assessing the endothelial function, impaired function of the peripheral and coronary vasculature has been shown in heart failure, IDC, and in animal models (*1–3,5,7,17,24–27*). The authors came to the conclusion that the impaired coronary vasodilatory response in IDC patients to diverse stimuli may be caused by endothelial dysfunction, increased vascular tone, diffuse vascular disorder, or microvascular hyperreactivity. Most of these studies used invasive techniques, such as intracoronary infusion of endothelium-dependent substances (acetylcholine, methacholine) and endothelium-independent agents (nitroglycerine, papaverine, adenosine, etc.) and measurement of blood flow with transcutaneous sonography or intracoronary Doppler catheter. In addition, in their recent study using PET and dipyridamole infusion, Neglia et al. (*7*) speculated that functional disorders of the small vessels, such as increased tone or endothelial dysfunction, may be responsible for the reduced coronary flow reserve in IDC patients.

The vasomotor response of epicardial arteries, as well as of the coronary microvasculature to the cold pressor test used in our study, has been shown previously to be intimately related to the integrity of endothelial function (*9*). Nabel et al. (*20*) showed that vasodilation of normal coronary arteries in reaction to cold pressor testing is in part mediated by endothelial α_2-adrenergic receptors. The α_2-adrenergic-receptor–mediated endothelial dilation (*22,27,28*) has been suggested to cause smooth-muscle relaxation by the release of endothelial-derived relaxation factor (EDRF, or nitric oxide). In arteries with endothelial dysfunction, the balance between the vasoconstrictive effects of sympathetic stimulation on smooth-muscle adrenergic receptors and the endothelial-derived relaxation is disturbed (*29*). In atherosclerosis, hypertension (*20,25*), and heart failure, diminished EDRF activity have been detected (*30*). Campisi et al. (*31*) found abnormal MBF response to cold pressor in long-term smokers and suggested endothelial dysfunction in this group. Holdright et al. (*4*) proposed reduced production, release, or diffusion of EDRF to be responsible for reduced flow response to acetylcholine in IDC patients.

In considering these mechanisms in the vasodilative response to cold pressor testing, endothelial changes appear to be a possible cause for decreased flow response and sustained MVR after sympathetic stimulation in IDC patients. Under our hypothesis, increased oxygen needs could be satisfied by increased levels of catecholamines at rest, causing endothelial changes (downregulation of endothelial α_2-adrenergic or other receptor density, or decreased EDRF activity) that inhibit further dilation at stress.

Extra- and Postendothelial Factors and Transduction Barrier

Nabel et al. (*20*) discussed participation of α_1-, α_2-, and β-receptors on the smooth muscle in vasodilative response to cold pressor. Thus, in addition to endothelial reasons, a dysfunction in 1 of the several following steps of the vasodilatory cascade may be responsible for the impaired flow response in IDC patients. Katz et al. (*24*) concluded in their study that endothelial dysfunction and abnormal vascular smooth muscle responsiveness may contribute to abnormal peripheral vasomotor tone in IDC patients. Bohm et al. (*32*) assumed enhanced inhibition of the signal transmission pathway by which the receptors stimulate the contractile apparatus in IDC. For example, increased levels of the inhibitory G_i-protein have been found in heart failure patients (*33*) and β_2-receptor uncoupling has been suggested (*34*). Holdright et al. (*4*) and Hirooka et al. (*35*) reported that impaired flow response to acetylcholine in patients with heart failure or IDC might be caused by enhanced smooth muscle cell muscarinic receptor responsiveness or altered postreceptor coupling mechanisms or signal transducing properties.

Constant adrenergic stimulation (*36*) or anti–β-receptor antibodies that have been reported in patients with dilated cardiomyopathy (*37*) may result in receptor downregulation. A significant reduction in β_1-receptor density, a reduced reactivity of β_2-receptors, and, consequently, a decrease in response to exogenously administered β agonists have been shown in IDC (*38*). In view of this information and the effect of the cold pressor test, postendothelial mechanisms may be factors in our results in IDC patients.

Other Possible Factors

An unequal relation of coronary microvasculature to ventricular hypertrophy and possible structural changes of the small intramyocardial vessels have been suggested in previous studies as possible causes for the impaired flow reserve in IDC and cannot be ruled out as reasons for the results of this study (*2,5*). However, additional studies have shown no correlation of histopathologic structural abnormalities with the degree of MBF impairment in IDC patients (*7,17*).

Gustavsson et al. (*39*) found a significantly higher blood viscosity in IDC patients compared with healthy volunteers and concluded that this may impair myocardial perfusion and contribute to the reduced coronary flow reserve in IDC patients. It should be noted also that in our study hemorrheologic differences may have influenced the results.

Limitations of the Study

The cold pressor test was shown to be an appropriate tool to examine coronary vascular reaction to sympathetic stimulation. However, the effects of cold pressor are mediated multifactorally, i.e., they cannot be exactly specified. Evaluation of endothelial function by cold pressor testing may be limited by patients' varying sensitivities to cold (*40*). Still, all 20 patients in our study showed significant and comparable hemodynamic reactions to cold pressor testing mediated by sympathetic stimulation.

One limitation of our study could be the small number of patients, and a second, the angiotensin-converting enzyme inhibitor therapy for all IDC patients. Although no medication was administered to patients on the day of the examination, this substance may have long-term effects on receptor density, vasoreactivity, and endocrinology.

We did not measure plasma catecholamine levels in patients and healthy volunteers. Plasma catecholamine levels in IDC have been well discussed in previous studies, and it seemed speculative to draw conclusions about myocardial catecholamine levels from plasma catecholamine levels in peripheral blood samples. LV mass or blood viscosity was not assessed in our study and we did not perform biopsies. Thus, future studies should examine the CFRP in IDC patients in relation to these factors and before induction of angiotensin-converting enzyme inhibitor therapy.

CONCLUSION

The data indicate that cold pressor testing in combination with ^{13}N-ammonia PET imaging is a valuable noninvasive tool for global and regional assessment of coronary microvascular reaction to sympathetic stimulation in IDC patients. Lower coronary vascular resistance was found in IDC patients at rest, compared with healthy volunteers, suggesting possible exhaustion of sympathetically induced dilation of the coronary microvasculature in IDC patients at rest. This mechanism may explain the impaired flow response to cold in IDC patients shown in the present study, in correspondence with previous invasive studies. This hypothesis should be further evaluated in studies assessing absolute flow reserve in IDC patients. PET perfusion imaging in combination with cold pressor testing offers various clinical and scientific applications for investigation of IDC.

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