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Depressed Coronary Flow Reserve Is Associated With Decreased Myocardial Capillary Density in Patients With Heart Failure Due to Idiopathic Dilated Cardiomyopathy

Eleftheria P. Tsagalou, MD,* Maria Anastasiou-Nana, MD, FESC,† Emmanuel Agapitos, MD,‡ Apostolia Gika, MD,* Stavros G. Drakos, MD,* John V. Terrovitis, MD,* Argirios Ntalianis, MD,* John N. Nanas, MD, PHD, FESC*

Athens, Greece

Objectives We sought to examine the relationship between coronary flow reserve (CFR) and myocardial capillary density (MCD) in patients with idiopathic dilated cardiomyopathy, heart failure, and normal coronary arteries.

Background Coronary flow reserve is depressed in patients with idiopathic dilated cardiomyopathy, particularly in those with end-stage congestive heart failure.

Methods We studied 18 patients, 48 ± 10 years of age, who had a mean New York Heart Association functional class of 2.9 ± 1.3, mean left ventricular ejection fraction of 22 ± 8%, and mean pulmonary capillary wedge pressure of 23 ± 10 mm Hg. CFR measurements were made with a 0.014-inch pressure-temperature sensor-tipped guide wire placed in the distal left anterior descending coronary artery. Thermodilution curves were constructed in triplicate at baseline and during maximum hyperemia induced by intravenous adenosine. CFR was calculated from the ratio of mean transit times. Right heart endomyocardial biopsies were performed during the same procedure. Autopsied specimens from nonfailing hearts were used as controls. The tissue was histochemically stained with CD-34 for morphometric measurements of MCD.

Results We observed a close linear relationship between CFR and MCD ($r = 0.756$, $p = 0.0001$). The MCD in 7 patients with a CFR ≥2.5 (73.2 ± 16) was similar to that measured in normal control patients, (85 ± 11, p = NS). In contrast, the MCD in 11 patients with a CFR <2.5 was 33.2 ± 14, which was significantly lower than in patients with heart failure and normal CFR (73.2 ± 16, $p = 0.001$) or in controls (85 ± 11, $p < 0.0001$).

Conclusions A marked decrease in MCD was found in patients presenting with congestive heart failure as the result of idiopathic dilated cardiomyopathy and a depressed CFR. (J Am Coll Cardiol 2008;52:1391–8) © 2008 by the American College of Cardiology Foundation

Abnormalities in myocardial blood flow have been observed in patients with idiopathic dilated cardiomyopathy (IDC), despite angiographically normal epicardial coronary arteries. In particular, a decreased resting myocardial blood flow (1,2), along with an attenuated maximal flow response to metabolic (3) or pharmacological stimuli (4–11), has been reported. The former dysfunction, although present in the very early stages of disease, before the development of overt congestive heart failure (CHF) (2), appears particularly pronounced in patients whose disease has progressed (12,13).

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Several mechanisms involving functional and anatomical derangements of the coronary circulation have been proposed as possible explanations for the decreased coronary flow reserve (CFR) in these patients, including an increase in extravascular compressive forces due to elevated left ventricular end-diastolic pressure (7), impaired endothelium-dependent/nitric oxide-mediated relaxation of the coronary microvasculature (14), and anatomical disruption of the

From the *Third Cardiology Department, †Department of Clinical Therapeutics, and ‡Department of Pathology, University of Athens School of Medicine, Athens, Greece.

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Abbreviations and Acronyms

CFR = coronary flow reserve
CHF = congestive heart failure
FFR = fractional flow reserve
IDC = idiopathic dilated cardiomyopathy
IMR = intramyocardial resistance
LVEDP = left ventricular end-diastolic pressure
MCD = myocardial capillary density
PCWP = pulmonary capillary wedge pressure
VEGF = vascular endothelial growth factor

microcirculation due to widespread areas of interstitial and perivascular fibrosis (15).

Structural changes in the coronary microcirculation, known as coronary remodeling, including abnormal arterioles with narrowed lumen, as well as decreased myocardial capillary density (MCD) (6–19), have been proposed as mechanisms of reduced CFR in patients with hypertrophic cardiomyopathy. Furthermore, Jayaweera et al. (19), using a 3-compartment coronary arterial, capillary, and venous experimental model connected in series, concluded that the resistance offered by the capillaries is the major determinant of coronary blood flow during hyperemia, playing a key role in the regulation of CFR. The aim of the present study was to examine the relationship between CFR and MCD in patients with CHF secondary to IDC.

Methods

Study population. We studied 18 patients with chronic CHF secondary to IDC diagnosed on the basis of a left ventricular ejection fraction ≤40%, LV end-diastolic diameter ≥55 mm or left ventricular end-systolic diameter ≥45 mm, and the absence of coronary stenoses on angiography. All patients were optimally treated with drugs, including digoxin, enalapril, beta-adrenergic blockers, spironolactone, and diuretics. Patients with congenital, valvular, or hypertensive heart disease; hypertrophic cardiomyopathy; myocarditis, previous myocardial infarction; or atrial fibrillation were excluded from the study.

All patients underwent detailed clinical and laboratory evaluations, including radionuclide ventriculography, transthoracic echocardiogram, right heart catheterization, and biochemical tests. Coronary flow reserve in the area of the left anterior descending coronary artery was measured with the thermodilution technique. Our Institutional Review Board approved the study, and informed consent was obtained from all patients before their enrollment.

Catheterization protocol. After routine right heart catheterization from the right jugular vein, selective coronary angiography, with the use of 6-F standard catheters and standard views, was performed. Patients whose coronary arteries had ≥40% stenoses were excluded from the study.

After completion of the diagnostic angiography, 5,000 U of intravenous heparin was administered, and a 6-F left coronary guiding catheter was introduced into the left coronary artery. After the infusion of 200 μg of intracoronary nitroglycerin, a 0.014-inch coronary pressure wire (Radi Medical Systems, Uppsala, Sweden) was calibrated for pressure measurements and advanced to the tip of the guiding catheter, and the equality of pressure signals was verified. The temperature signal was also calibrated at that location, with the temperature at the coronary ostium as the reference temperature for further measurements. The wire was then advanced at least beyond the proximal two-thirds of the left anterior descending coronary artery.

Fractional flow reserve measurements. Simultaneous measurements were performed of the mean aortic pressure (by the guiding catheter) and mean distal coronary pressure (by the pressure wire) at baseline and during steady-state of maximum coronary hyperemia, induced by 140 μg/kg/min of adenosine administered through the jugular vein. Fractional flow reserve (FFR) was calculated as mean distal coronary pressure/mean aortic pressure at maximum hyperemia, considered to be reached approximately 3 min after the onset of adenosine infusion.

Obtaining CFR measurements by thermodilution. Coronary arterial thermodilution curves were obtained by brief manual injections of 3 ml of saline at room temperature. At baseline, triplicate measurements of the resting mean transit time were made and averaged. Adenosine was then infused in a dose of 140 μg/kg/min through the jugular vein. Careful fluid administration was infused to avoid hypotension during adenosine administration. Three injections of 3 ml of saline at room temperature were performed, starting approximately 3 min after the onset of adenosine infusion. The triplicate measurements of the hyperemic mean transit time thus obtained were averaged. Care was taken to keep the wire in a fixed position during the series of measurements. We defined CFR thermo as the average resting mean transit time divided by the average hyperemic mean transit time (Fig. 1). We calculated intramyocardial resistance (IMR) by using a previously published formula (20):

$$\text{IMR} = \text{distal coronary pressure} / \text{inverse of the mean transit time at peak hyperemia}$$

Histological examinations. The myocardial tissue samples were obtained from right ventricular septal endomyocardial biopsies, weighing between 0.5 and 1 mg, in 14 patients, or from 0.3- to 1-g samples obtained by left ventricular apical myectomies, performed during left ventricular assist device implantation in 4 patients. Autopsied samples from 5 nonfailing hearts were used as control specimens.

The specimens were immediately fixed in 10% buffered formalin, dehydrated, embedded in paraffin wax, prepared in 4-μm sections, and then stained with Masson's trichrome. The fibrosis content of the myocardium was measured with an automatic image analyzing system, with the use of planimetric analysis (NIH Image 1.61/ppc,

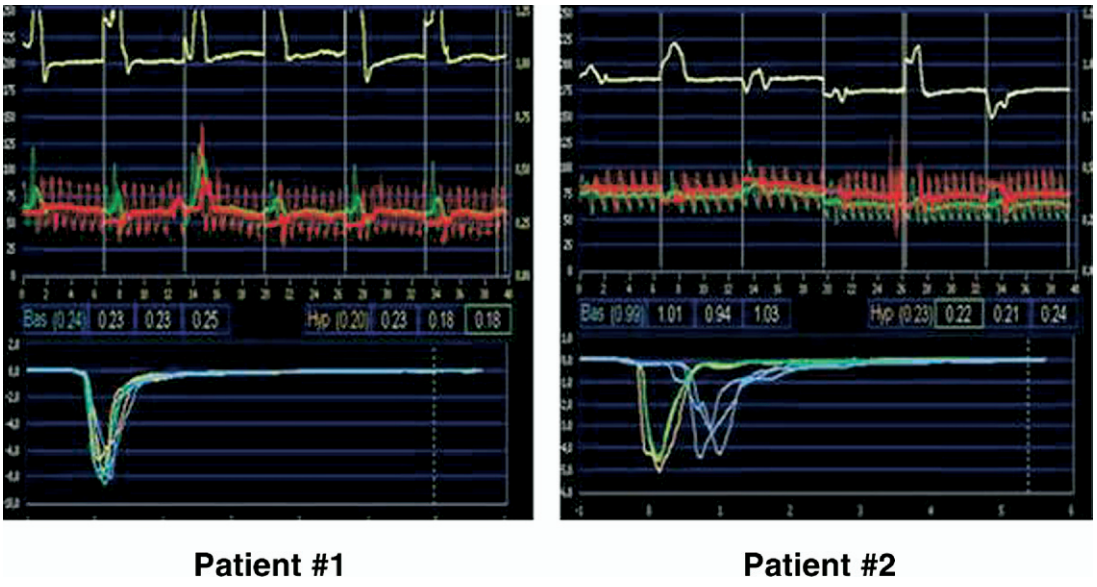

Figure 1 **Measurements of CFR**

In Patient #1, the thermodilution curves constructed at baseline and during hyperemia nearly overlap. The averaged mean transit time is 0.23 s at baseline and 0.20 s during hyperemia, which is consistent with a severe decrease in CFR. In Patient #2, the duration of the hyperemic thermodilution curve (averaged mean transit time = 0.23 s) is significantly shorter than at baseline (averaged mean transit time = 1.01 s), which is consistent with a normal CFR. CFR = coronary flow reserve.

Bethesda, Maryland) with a Zeiss Axiovert 135 TV microscope (Carl Zeiss Jena GmbH, Germany). The entire sectional area of each histological sample was measured, and the fibrosis grade was calculated and expressed as a percent of total area.

Image analysis method. We measured MCD semiautomatically by using an image analysis system consisting of a Zeiss Axiolab microscope (Carl Zeiss Jena), interfaced with a Sony Video-camera and a Pentium III P/C (Dell, Austin, Texas) with Sigma Scan Pro 5.0 image analysis software (Systat Software GmbH, Erkrath, Germany). Digital images were stored as JPEG files (1.550 × 1.070 pixels, 16.7 million colors). We quantified MCD by using the Color Estimator version 2.0, a specific application developed in our laboratory in Microsoft Visual Basic 5.0 environment (Microsoft Corporation, Redmond, Washington) for the evaluation of histochemical and immunohistochemical color images (21,22).

Immunochemically stained slides for CD-34 were photographed at ×200, printed on high-quality photographic paper and stored as 24-bit bitmap files of 256 colors. The immunostained endothelial cells were colored in red on the digital images (Fig. 2). Microvessels were tagged by the pathologist on the monitor image and manually counted (Fig. 2). A 0.1215-mm^2 overall area was studied at ×200 magnification. The counts were expressed as number of microvessels per 0.1215 mm^2 of examined tissue.

Statistical analysis. Categorical variables are presented as counts and percentages, and continuous variables as mean ± SD. Continuous variables were compared with the Student paired *t* test. Variables were evaluated with the use of a linear single and stepwise multiple variables regression model. We included MCD, percentage of fibrosis, duration of disease, hematocrits, and pulmonary capillary wedge pressure (PCWP) in the multiple variable regression model and considered $p < 0.05$ statistically significant.

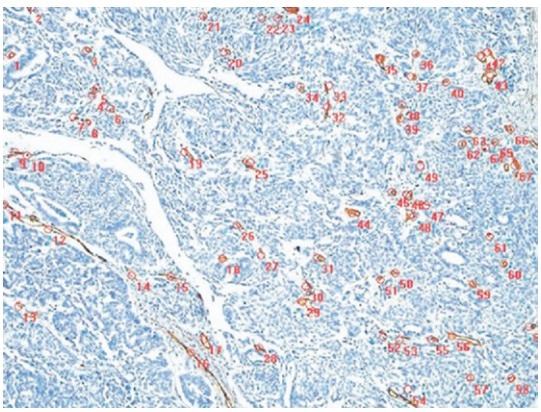

Figure 2 **Measurement of Capillary Density in Myocardial Biopsy Specimens**

Representative photomicrographs of microscopic fields from histological sections of left ventricular myocardium immunochemically stained for CD-34. The slides were photographed at ×200, printed on high-quality photographic paper, and stored as 24-bit bitmap files. The immunostained endothelial cells were colored red on the digital images. Microvessels were tagged by the pathologist on the monitor image, and manually counted.

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Table 1 Baseline Characteristics of the 18 Patients Presenting With Chronic Congestive Heart Failure Due to Idiopathic Dilated Cardiomyopathy

Age, yrs	48 ± 10
Men/women, n	17/1
Alcohol-induced cardiomyopathy, n (%) of patients	1 (6)
Duration of heart failure, yrs	5.7 ± 3.5
Left ventricular	
Ejection fraction, %	22 ± 8
End-diastolic diameter, mm	72 ± 11
End-systolic diameter, mm	59 ± 14
Systemic blood pressure, mm Hg	
Systolic	93 ± 12
Diastolic	60 ± 10
Heart rate, beats/min	71 ± 8.5
Mean right atrial pressure, mm Hg	8 ± 5
Right ventricular systolic pressure, mm Hg	50 ± 13
Mean pulmonary arterial pressure, mm Hg	34 ± 13
Pulmonary capillary wedge pressure, mm Hg	23 ± 10
Cardiac index, l/m^2/min	1.7 ± 0.4
Vascular resistance, Wood unit	
Pulmonary	3.4 ± 1.7
Systemic	20.6 ± 3.7
Maximum O_2 consumption, ml/kg/m^2	17 ± 8.7
NYHA functional class, n (%) of patients	
I/II	7 (39)
III/IV	11 (61)
Cardioactive drug regimen, n (%) of patients	
Digoxin	6 (33)
Angiotensin-converting enzyme inhibitor	14 (78)
Spironolactone	11 (61)
Amiodarone	14 (78)
Beta-adrenergic blocker	9 (50)
Intermittent dobutamine infusions	7 (39)

Unless specified otherwise, the values are means ± SD.
NYHA = New York Heart Association.

Results

Study population. The average age of the 18 patients suffering from CHF was 48 ± 10 years. Their baseline demographic, clinical, hemodynamic, and biochemical characteristics are presented in Table 1. Excessive alcohol consumption was considered the etiology of cardiomyopathy in 1 patient, whereas CHF was secondary to IDC in 17 patients. Seven of the 18 patients were in New York Heart Association functional class I or II, 1 patient was in class III, and 10 patients in class IV. All patients were under maximum doses of medical therapy, including furosemide, angiotensin-converting enzyme inhibitors, digoxin, beta-adrenergic blockers, and spironolactone. Patients intolerant of beta-adrenergic blockers were placed on an alternate treatment with amiodarone. In 7 patients experiencing refractory end-stage CHF, 8-h dobutamine infusions were administered on a weekly basis. In those patients, the hemodynamic study was performed the day after dobutamine was infused.

Assessment of CFR. We measured FFR and CFR in all patients. The infusion of adenosine did not have any effect on either systolic (93 ± 12 mm Hg baseline vs. 92 ± 11 mm Hg, p = 0.367) diastolic (60 ± 10 mm Hg baseline vs. 64 ± 7.5 mm Hg, p = 0.06) or mean arterial blood pressure (73 ± 9 mm Hg baseline vs. 74 ± 8 mm Hg, p = 0.3). The heart rate remained also unchanged (71 ± 8.5 beats/min baseline vs. 73 ± 11 beats/min, p = 0.122).

No adverse effects were observed during adenosine infusion. Pulmonary congestion developed after the end of the procedure in 3 patients (17%) who were stabilized with brief infusions of inotropes and intravenous furosemide. The mean FFR was 0.92 ± 0.6, and mean CFR was 2.3 ± 1.4 (range 1 to 5.2). We found that CFR was <2.5 in 11 patients (61%).

Histological data and MCD. The percentage of fibrosis was 1.78 ± 1.6. We found that MCD was significantly lower in patients with CHF (48.7 ± 25; range, 18 to 85) than in control patients (85 ± 11; range, 74 to 101; p = 0.005) (Fig. 3). The average MCD in the 4 patients who had left-sided sampling done at the time of LVAD implantation was 33.7 ± 10 vs. 53 ± 26, (p = 0.177) in the 14 patients who had undergone right heart biopsies. There was no correlation between the percentage of fibrosis and MCD (p = 0.4). In the tissue specimens of hearts of patients with IDC, there was a narrowing of the lumen of the myocardial capillaries, which also appeared more tortuous. The mean value of capillary diameter was 5 μm, whereas the lumen of myocardial capillaries in normal hearts (controls) was 7 μm.

Reproducibility of measurements. Repeated measurements of MCD showed a satisfactory intrarater and interrater variability (range 0.85 to 0.97). The same applied for

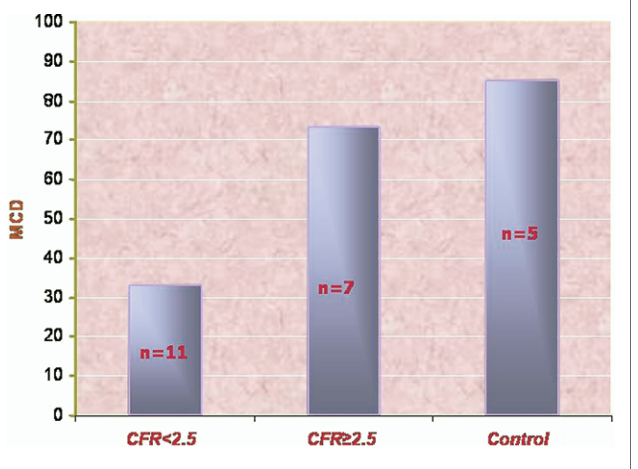

Figure 3 MCD in Patients With Normal and Low CFR

Shown is the myocardial capillary density (MCD) in patients with heart failure secondary to idiopathic dilated cardiomyopathy (IDC) and normal (≥2.5, **column 2**) or low (<2.5, **column 1**) coronary flow reserve (CFR). In **column 3**, MCD in control patients without heart disease is presented. In IDC patients with normal CFR, MCD was slightly lower, although not significantly different than in normal control patients. In contrast, IDC patients with low CFR had a significantly lower MCD than IDC patients with normal CFR or control patients.

Table 2 CFR, Hemodynamic Parameters, and MCD in Individual Patients

Patient #	CFR	SBP/DBP (mm Hg)	HR (beats/min)	CDP Baseline (mm Hg)	CDP Hyperemia (mm Hg)	PCWP (mm Hg)	MCD
1	1.02	85/75	78	58	63	24	18
2	1.20	100/70	66	66	66	37	20
3	1.30	90/68	78	70	70	24	23
4	1.17	85/60	72	60	60	22	43
5	1.30	70/55	71	37	44	39	46
6	1.2	90/70	78	68	71	20	56
7	1.16	85/60	66	63	63	25	32
8	1.6	95/60	65	65	66	33	21
9	1.02	95/60	70	52	51	37	19
10	3.5	88/65	100	65	60	32	37
11	1.8	95/65	57	74	74	11	36
12	1.8	90/60	72	66	66	22	51
13	4.8	100/70	80	76	65	12	72
14	5.2	100/60	55	72	72	24	76
15	2.8	110/75	72	88	83	23	79
16	4.4	90/60	64	68	60	11	81
17	3	110/65	72	78	80	15	83
18	3.4	80/50	82	59	49	4	85

CDP = coronary driving pressure (mean aortic-mean RA pressure); CFR = coronary flow reserve; HR = heart rate; MCD = myocardial capillary density; PCWP = pulmonary capillary wedge pressure; SBP/DBP = systolic blood pressure/diastolic blood pressure.

the reproducibility of the measurements (coefficient of variation 0.7 to 3.8).

Relationship of MCD, hemodynamic parameters, duration of disease, and CFR. Individual values of MCD, arterial blood pressure, heart rate, PCWP, coronary artery driving pressure, and CFR are presented in Table 2. An important and highly significant correlation was observed between MCD and CFR ($r = 0.756$; $p = 0.0001$) (Fig. 4). In 7 patients with a CFR ≥2.5, MCD was slightly lower, although not significantly different than in normal controls (73.2 ± 16 vs. 85 ± 11, $p = 0.445$). In contrast, in 11 patients with a CFR <2.5, MCD was significantly lower (33.2 ± 14) than in patients suffering from CHF and a normal CFR ($p = 0.001$) or in controls ($p < 0.001$). A significant correlation was also observed between MCD and PCWP ($r = 0.584$, $p = 0.002$) whereas no correlation existed between MCD and arterial blood pressure, heart rate, or duration of disease. By multiple variables analysis, MCD was the only significant correlate of a reduced CFR ($r = 0.693$, $p = 0.011$).

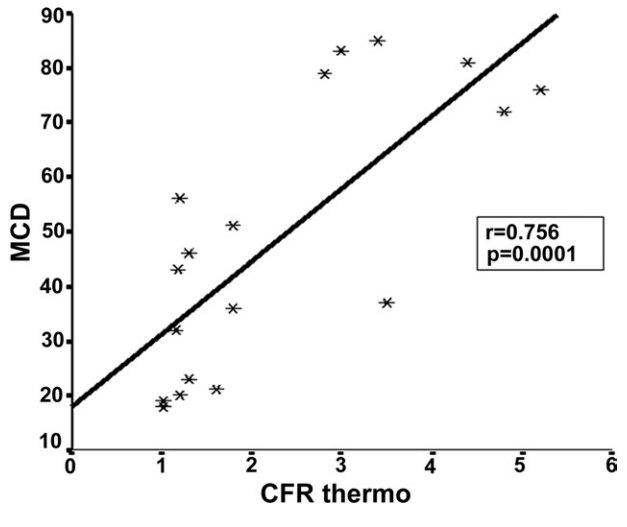

Figure 4 Correlation Between MCD and CFR

Pearson correlation analysis showed a strong linear relationship between myocardial capillary density (MCD) and coronary flow reserve (CFR).

Relationship between MCD and IMR. There was a strong correlation between MCD and IMR ($r = -0.705$; $p = 0.003$). In patients with a CFR equal to or greater than 2.5, IMR was significantly lower (20 ± 11 U) than in patients with a normal CFR (89 ± 44 U; $p = 0.001$).

Factors affecting microvascular resistance. There was no significant difference in hematocrit (40 ± 4.5% vs. 42 ± 3.2%, $p = 0.380$), total cholesterol (167 ± 42 mg/dl vs. 193 ± 44 mg/dl, $p = 0.260$) and triglycerides (93 ± 29 mg/dl vs. 97 ± 49 mg/dl, $p = 0.872$) between patients with low versus those with normal CFR. On the contrary, the PCWP was significantly greater in patients with low CFR values (26 ± 9 vs. 17 ± 9, $p = 0.046$).

Discussion

The main finding of the present study was an important and highly significant correlation between CFR and MCD in patients with CHF due to IDC. In patients with a CFR ≥2.5, the number of capillaries per unit area was similar to that found in controls, whereas patients with reduced CFR had a significantly lower density of myocardial capillaries.

Because coronary blood flow is significantly influenced by hemodynamic conditions, great efforts were made to omit any bias in the CFR measurements introduced by such factors. Fluid administration prevented any decrease in the arterial blood pressure during adenosine infusion. Neither baseline, nor hyperemic systolic, diastolic or mean arterial blood pressure correlated with CFR. Baseline heart rate ranged between 55 and 100 beats/min and remained unchanged during adenosine infusion. There was no correlation between CFR and baseline or hyperemic heart rate.

However, PCWP was strongly correlated with CFR in the univariate analysis. The increase in extravascular compressive forces by the high left ventricular end-diastolic pressure (LVEDP) (4) compresses myocardial capillaries and probably accounts for the decreased lumen area identified in the heart failure population compared with the control population. Shannon et al. (23) reported that an acute decrease in LVEDP caused a partial increase in subendocardial CFR in response to adenosine in a dog model of pacing-induced HF. However, in other experimental and clinical studies of CHF, this explanation was not a sufficient one, because CFR was reduced in absence of an increased LVEDP (23,24). Furthermore, the correlation between PCWP and CFR was not found to be significant in the multivariate analysis. Blood viscosity represents another major determinant of capillary resistance. Both the volume and the rheology of erythrocytes have been shown to influence hyperemic blood flow (25–27).

The hematocrit values in our study ranged between 33% and 44%. We found no correlation between blood hematocrit and CFR. Furthermore, there was no significant difference between the hematocrit values of patients with low and those with normal levels of CFR. Unfortunately, parameters that could affect erythrocyte rheology such as red cell charge deformability, and mobility were not measured in this study. However, factors that are known to affect the erythrocyte rheology were uniform in our patient population. All patients received intracoronary nitroglycerin before being measured for CFR, whereas total cholesterol and triglyceride levels were not different between patient groups.

Approximately one-third of the total blood volume contained in the coronary circulation, including arteries, arterioles, capillaries, venules, and veins, is present within the myocardium (28). Nearly 90% of this myocardial blood volume is in the capillaries (29). Jayaweera et al. (19), by using a 3-compartment model of coronary arteries, capillaries and venules connected in series, showed that, as a result of a prominent decrease in arterial and venular resistance during hyperemia, capillary resistance is the main determinant of hyperemic coronary flow. Because capillaries are placed in parallel, their volume is the major determinant of their resistance (30). This volume can vary through changes in capillary dimensions, or through variable capillary recruitment. In a heart with normal capillary density, under resting conditions, red blood cells traverse only a fraction of open capillaries (31,32), which are recruited by increases in oxygen demand. However, in the presence of severely decreased myocardial capillary density, one might hypothesize that the entire volume of capillaries is recruited to accommodate the coronary blood volume. The high capillary resistance offered by the reduced capillary volume might not be able to accommodate the increased coronary flow during hyperemia, causing a reduction in hyperemic flow and, therefore, a reduction in CFR.

Remodeling of the coronary microcirculation has been suggested as a mechanism of reduced coronary flow reserve in patients with hypertrophic cardiomyopathy (17,18). Abnormal arterioles (17), fewer capillaries, and dysfunction of the remaining capillaries due to luminal narrowing (18), have been correlated with the abnormal response to hyperemia observed in these patients. To our knowledge, this study was the first to examine the relationship between CFR and MCD in patients with IDC.

Myocardial structural abnormalities involving the microvascular bed have been reported in patients with IDC (1,33), and a possible relationship with abnormal myocardial perfusion has been suggested. From the results of a positron-emitting tomographic study, Neglia et al. (2) suggested that resting and maximal myocardial blood flow might be decreased in some patients with increased myocardial fibrosis. However, the observation of abnormal myocardial perfusion in patients whose histology is normal, as well as the absence of correlation between degree of myocardial blood flow reduction and extent of myocardial fibrosis in explanted hearts from patients with end-stage disease (1), seems to indicate that fibrosis is not a critical determinant of myocardial blood flow. Accordingly, in this study, we found no correlation between extent of fibrosis and CFR or MCD.

The decrease in MCD is probably mediated by mechanisms other than macroscopic disruption of the myocardial architecture or replacement of myocardium and vessel by fibrotic tissue. We discovered that MCD in patients with IDC has been examined in very few studies that included small numbers of patients. Abraham et al. (34) found a 66% decrease in the MCD of heart transplantation candidates with idiopathic dilated cardiomyopathy compared with nonfailing hearts. This decrease was accompanied by the selective down-regulation of messenger ribonucleic acid transcript levels of vascular endothelial growth factor $(VEGF)_{165}$ and $VEGF_{189}$ and the protein levels of VEGF and type 1 VEGF receptor.

In 8 human hearts, Figulla et al. (35) found an average functional density of 1,245 ± 345 capillaries/mm. In another study, the average number of capillaries was 1,592 ± 289/mm^2 in 5 patients with IDC versus 1,956 ± 231/mm^2 in control patients (36). The patients included in these studies suffered from end-stage disease, with biopsy specimens harvested either before (35) or at the time of cardiac transplantation (36). In contrast, our patient population included patients who were clinically and hemodynamically stable, as well as patients presenting with end-stage disease.

This heterogeneity in disease severity might explain the wide range of MCD, from normal to severely depressed. Myocardial structural abnormalities that decrease MCD are likely to progress as the disease evolves, as shown in a streptozotocin-induced diabetic rat model, where the MCD was decreased in proportion to the duration of diabetes, with the difference versus control becoming significant at 6 months after induction of the disease (37). In our study, a reduced MCD was present among patients in poor clinical and hemodynamic conditions, in patients with New York Heart Association functional classes III or IV despite maximal therapy, and in patients with a significantly lower left ventricular ejection fraction and greater mean capillary wedge pressure than among healthier patients. However, we found no correlation between duration of disease and MCD.

An alternative explanation could be that selected patients might have decreased MCD, which could be related with disease progression in an etiopathogenetic manner. Previous studies have suggested that, in patients with IDC, an abnormal coronary microcirculatory flow causes impairment of myocardial perfusion and regional metabolic changes similar to myocardial ischemia (38,39). Chronic myocardial hypoperfusion, repetitive ischemia, or both, as the result of an impaired microvascular flow, may cause progressive left ventricular dilation and promote disease progression. Furthermore, a close relationship between regional CFR and corresponding contractile reserve has been reported (40). Serial MCD measurements in patients with IDC and those who demonstrate significant left ventricular reverse remodeling would provide some answer to that question.

A reduced CFR, including in the early stages of disease, has been found to be an independent predictor of prognosis (41). One might hypothesize that, although left ventricular remodeling has already taken place, its adverse effects on left ventricular function has not become apparent. It might be appropriate to consider these patients at significant risk of disease progression and to undertake vigorous therapeutic efforts against cardiac remodeling, in the hope of halting or reversing the progression of disease. In the streptozotocin-induced diabetic rat model, VEGF replacement successfully reversed multiple microvascular bed abnormalities, increased capillary density, and improved myocardial function significantly (37).

Study limitations. In the majority of patients, the endomyocardial biopsy was performed in the right mid-ventricular septum, whereas CFR was measured in the left anterior descending territory. Although most of the blood to the mid-ventricular septum is supplied by the left anterior descending, branches from the right coronary artery might also contribute. A single biopsy was performed in each patient, confining the measurement of MCD to a relatively small amount of tissue. However, because IDC is characterized by global myocardial dysfunction, we hypothesized that MCD is homogeneously distributed throughout the myocardium.

Conclusions

A reduced MCD was measured in patients with IDC, which correlated well with CFR. These observations suggest that a reduced MCD might contribute to the perfusion abnormalities found in these patients, causing recurrent or persistent myocardial ischemia and promoting progression of the disease.

Reprint requests and correspondence: Dr. John N. Nanas, Makedonias 24, 104 33 Athens, Greece. E-mail: jnanas@ath.forthnet.gr.

REFERENCES

1. Parodi O, De Maria R, Oltrona L, et al. Myocardial blood flow distribution in patients with ischemic heart disease or dilated cardiomyopathy undergoing heart transplantation. Circulation 1993;88:509–22.
2. Neglia D, Parodi O, Gallopin M, et al. Myocardial blood flow response to pacing tachycardia and to dipyridamole infusion in patients with dilated cardiomyopathy without overt heart failure. A quantitative assessment by positron emission tomography. Circulation 1995;92:796–804.
3. Pasternac A, Noble J, Streulens Y, Elie R, Henschke C, Bourassa MG. Pathophysiology of chest pain in patients with cardiomyopathies and normal coronary arteries. Circulation 1982;65:778–89.
4. Opherk D, Schwarz F, Mall G, Manthey J, Baller D, Kubler W. Coronary dilatory capacity in idiopathic dilated cardiomyopathy: analysis of 16 patients. Am J Cardiol 1983;51:1657–62.
5. Nitenberg A, Foult JM, Blanchet F, Zouioueche S. Multifactorial determinants of reduced coronary flow reserve after dipyridamole in dilated cardiomyopathy. Am J Cardiol 1985;55:748–54.
6. Cannon RO 3rd, Cunnion RE, Parrillo JE, et al. Dynamic limitation of coronary vasodilator reserve in patients with dilated cardiomyopathy and chest pain. J Am Coll Cardiol 1987;10:1190–200.
7. Treasure CB, Vita JA, Cox DA, et al. Endothelium-dependent dilation of the coronary microvasculature is impaired in dilated cardiomyopathy. Circulation 1990;81:772–9.
8. Inoue T, Sakai Y, Morooka S, et al. Coronary flow reserve in patients with dilated cardiomyopathy. Am Heart J 1993;125:93–8.
9. Inoue T, Sakai Y, Morooka S, et al. Vasodilatory capacity of coronary resistance vessels in dilated cardiomyopathy. Am Heart J 1994;127:376–81.
10. van den Heuvel AF, van Veldhuisen DJ, van der Wall EE, et al. Regional myocardial blood flow reserve impairment and metabolic changes suggesting myocardial ischemia in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 2000;35:19–28.
11. Canetti M, Akhter MW, Lerman A, et al. Evaluation of myocardial blood flow reserve in patients with chronic congestive heart failure due to idiopathic dilated cardiomyopathy. Am J Cardiol 2003;92:1246–9.
12. Santagata P, Rigo F, Gherardi S, et al. Clinical and functional determinants of coronary flow reserve in non-ischemic dilated cardiomyopathy: an echocardiographic study. Int J Cardiol 2005;105:46–52.
13. Ellis AK, Klocke FJ. Effects of preload on the transmural distribution of perfusion and pressure-flow relationships in the canine coronary vascular bed. Circ Res 1980;46:68–77.
14. Dec GW, Fuster V. Idiopathic dilated cardiomyopathy. N Engl J Med 1994;331:1564–75.
15. O' Gara PT, Bonow RO, Maron BJ, et al. Myocardial perfusion abnormalities in patients with hypertrophic cardiomyopathy: assessment with thallium-201 emission computed tomography. Circulation 1987;76:1214–23.
16. Spaan JAE. Coronary blood flow: mechanics, distribution, and control. In: Spaan JAE, editor. Developments in Cardiovascular Medicine. Boston, MA: Kluwer Academic Publishers, 1991:124.
17. Takemura G, Takatsu Y, Fujiwara H. Luminal narrowing of coronary capillaries in human hypertrophic hearts: an ultrastructural morphometrical study using endomyocardial biopsy specimens. Heart 1998;79:78–85.

18. Krams R, Kofflard M, Duncker D, et al. Decreased coronary flow reserve in hypertrophic cardiomyopathy is related to remodeling of the coronary microcirculation. Circulation 1998;97:230–3.
19. Jayaweera AR, Wei K, Coggins M, Bin JP, Goodman C, Kaul S. Role of capillaries in determining coronary blood flow reserve: new insights using myocardial contrast echocardiography. Am J Physiol 1999;277: H2363–72.
20. Fearon WF, Balsam LB, Farouque HM, et al. Novel index for invasively assessing the coronary microcirculation. Circulation 2003; 107:3129–32.
21. Agapitos E, Nanas J, Kavantzas N, et al. The application of image analysis in the measurement of the myocardial infarct area in an experimental model. Gen Diagn Pathol 1997;143:215–8.
22. Pavlopoulos P, Konstantinidou A, Agapitos E, et al. A morphometric study of neovascularization in colorectal carcinoma. Cancer 1998;83: 2067–75.
23. Shannon RP, Komamura K, Shen YT, Bishop SP, Vatner SF. Impaired regional subendocardial coronary flow reserve in conscious dogs with pacing-induced heart failure. Am J Physiol 1993;265: H801–9.
24. Knecht M, Burkhoff D, Yi GH, et al. Coronary endothelial dysfunction precedes heart failure and reduction of coronary reserve in awake dogs. J Mol Cell Cardiol 1997;29:217–27.
25. Pries AR, Secomb TW, Gaehtgens P, Gross JF. Blood flow in microvascular networks. Experiments and simulation. Circ Res 1990; 67:826–34.
26. Bin JP, Doctor A, Lindner J, et al. Effects of nitroglycerin on erythrocyte rheology and oxygen unloading: novel role of S-nitrosohemoglobin in relieving myocardial ischemia. Circulation 2006;113:2502–8.
27. Rim SJ, Leong-Poi H, Lindner J, Wei K, Fisher NG, Kaul S. Decrease in coronary blood flow reserve during hyperlipidemia is secondary to an increase in blood viscosity. Circulation 2001;104: 2704–9.
28. Kaul S, Jayaweera A. Coronary and myocardial blood volumes: noninvasive tools to assess the coronary microcirculation? Circulation 1997;96:719–24.
29. Kassab G, Lin D, Fung Y. Morphometry of pig coronary venous system. Am J Physiol 1994;267:H2100–13.
30. Bosman J, Tangelder G, Oude Egbrink M, Reneman R, Slaaf D. Capillary diameter changes during low perfusion pressure and reactive hyperemia in rabbit skeletal muscle. Am J Physiol 1995;269:H1048–55.
31. Friedman B, Grinberg O, Isaacs K, Walczak T, Swartz H. Myocardial oxygen tension and relative capillary density in isolated perfused rat hearts. J Mol Cell Cardiol 1995;27:2551–8.
32. Henquell L, Honig C. Intercapillary distances and capillary reserve in right and left ventricles: significance for control of tissue PO_2. Microvasc Res 1976;12:35–41.
33. Strain JE, Grose RM, Factor SM, Fisher JD. Results of endomyocardial biopsy in patients with spontaneous ventricular tachycardia but without apparent structural heart disease. Circulation 1983;68:1171–81.
34. Abraham D, Hofbauer R, Schäfer R, et al. Selective downregulation of VEGF-A(165), VEGF-R(1), and decreased capillary density in patients with dilative but not ischemic cardiomyopathy. Circ Res 2000;87:644–7.
35. Figulla HR, Vetterlein F, Wiegand V, Schuler S, Kreuzer H. Capillary density and oxygen supply in human dilated cardiomyopathy. Z Kardiol 1987;76 Suppl 3:152–4.
36. Mosseri M, Schaper J, Admon D, et al. Coronary capillaries in patients with congestive cardiomyopathy or angina pectoris with patent main coronary arteries. Ultrastructural morphometry of endomyocardial biopsy samples. Circulation 1991;84:203–10.
37. Yoon Y, Uchida S, Masuo O, et al. Progressive attenuation of myocardial vascular endothelial growth factor expression is a seminal event in diabetic cardiomyopathy: restoration of microvascular homeostasis and recovery of cardiac function in diabetic cardiomyopathy after replenishment of local vascular endothelial growth factor. Circulation 2005;111:2073–85.
38. Picano E, Landi P, Bolognese L, et al. Prognostic value of dipyridamole echocardiography early after uncomplicated myocardial infarction: a large-scale, multicenter trial. The EPIC Study Group. Am J Med 1993;95: 608–18.
39. Picano E, Sicari R, Landi P, et al. Prognostic value of myocardial viability in medically treated patients with global left ventricular dysfunction early after acute uncomplicated myocardial infarction: a dobutamine stress echocardiographic study. Circulation 1998;98: 1078–84.
40. Skalidis E, Parthenakis F, Patrianakos A, Hamilos M, Vardas P. Regional coronary flow and contractile reserve in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 2004;44:2027–32.
41. Neglia D, Michelassi C, Trivieri M, et al. Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. Circulation 2002;105:186–93.

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