Impaired Coronary Flow Reserve in Patients With Non-Ischemic Heart Failure

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Introduction and objectives. Coronary flow reserve (CFR) is impaired not only in ischemic heart disease, but also in cardiac diseases that may or may not course with heart failure. The aim of the present study was to determine if the severity of heart failure can influence CFR impairment.

Methods. Forty patients with non-ischemic heart disease and heart failure were studied 41 times. Four groups were established: *1.* 10 patients in functional class III-IV; *2.* 10 patients in functional class II not taking beta-blockers; *3.* 11 patients in class II treated with carvedilol, and *4.* 10 patients in class I. These patients had a history of heart failure and systolic dysfunction. Myocardial blood flow (MBF) was measured with positron emission tomography (PET) and N-13 ammonia at rest (r) and during adenosine triphosphate (ATP) infusion.

Results. MBF and CFR were significantly higher in group 4 (1.95 ± 0.58 and 2.40 ± 0.95 ml/min/g) than in group 1 (1.02 ± 0.52 and 1.46 ± 0.48 ml/min/g). CFR tended to be higher in groups 2 (1.73 ± 0.72), and 3 (1.89 ± 0.75) vs group 1. No significant correlation was found between CFR and the following variables: age, systolic blood pressure, ventricular mass index, ventricular volume indexes, and ejection fraction.

Conclusions. Coronary microvascular function is impaired in non-ischemic heart failure, and the impairment is related to functional class, regardless of the underlying responsible heart disease.

Key words: *Positron emission tomography. PET. Coronary flow reserve. Heart failure. ATP.*

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Disminución de la reserva de flujo coronario en pacientes con insuficiencia cardíaca no isquémica

Introducción y objetivos. La reserva de flujo coronario (RFC) se reduce no sólo en la cardiopatía isquémica, sino también en otras cardiopatías, con o sin insuficiencia cardíaca. El objetivo del estudio fue comprobar si la gravedad de la insuficiencia cardíaca influye en el deterioro de la RFC.

Métodos. Se estudió a 40 pacientes diagnosticados de cardiopatía no isquémica e insuficiencia cardíaca, en 41 ocasiones distintas. Fueron repartidos en 4 grupos: *1.* 10 pacientes en grado funcional III-IV; *2.* 10 pacientes en grado funcional II sin tratamiento con bloqueadores beta; *3.* 11 pacientes en grado funcional II tratados con carvedilol, y *4.* 10 pacientes en grado funcional I, que previamente habían tenido insuficiencia cardíaca por disfunción sistólica. El flujo miocárdico (FM) se midió mediante tomografía por emisión de positrones (PET) y N-13 amonio: en condiciones basales y durante la infusión de trifosfato de adenosina (ATP).

Resultados. El FM máximo y la RFC fueron significativamente más altos en el grupo 4 (1,95 ± 0,58 y 2,40 ± 0,95 ml/min/g) que en el grupo 1 (1,02 ± 0,52 y 1,46 ± 0,48 ml/min/g). La RFC tuvo tendencia a ser mayor en los grupos 2 (1,73 ± 0,72) y 3 (1,89 ± 0,75) que en el grupo 1. No hubo correlación significativa entre la RFC y las siguientes variables: edad, presión arterial sistólica, índice de masa ventricular, índices de volumen y fracción de eyección de ventrículo izquierdo.

Conclusiones. La función microvascular coronaria está alterada en la insuficiencia cardíaca no isquémica, y dicha alteración se relaciona con la situación funcional, cualquiera que sea la cardiopatía subyacente.

Palabras clave: *Tomografía por emisión de positrones. PET. Reserva de flujo coronario. Insuficiencia cardíaca. ATP.*

IINTRODUCTION

The dilatory capacity of the coronary microvasculature or coronary flow reserve (CFR) is altered in patients with significant coronary lesions.[1] This can also change in the presence of coronary risk factors,[2,3] with arterial hypertension,[4] in hypertrophic[5] or dilated[6,7]

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ABBREVIATIONS

CFR: coronary flow reserve.
MBF: myocardial blood flow.
ATP: adenosine triphosphate.
PET: positron emission tomography.

myocardiopathy, and in hypertrophy secondary to valve lesions.[8]

CFR has been found to be altered in experimental heart failure.[9] Heart failure is associated with neurohumoral activation and changes in peripheral circulation.[10] It is possible that the increase in cytokines and the reduction in flow influence the development of endothelial dysfunction in these patients.[10,11] Endothelial dysfunction may contribute to an increase in peripheral vasomotor tone during exercise[12] and to abnormal control of brachial blood flow.[13] One experimental study[9] showed that coronary endothelial dysfunction with reduction of CFR appears before heart failure. It is possible that the vasoconstriction caused by the increase in enothelin-1 has a relationship with these changes, as carvedilol improved heart failure at the same time as it reduced concentrations of this substance.[14]

CFR can be measured by different methods; nevertheless, positron emission tomography (PET) is the only non-invasive technique that provides absolute measurement of overall and regional myocardial blood flow in mL/min/g.[15]

The aim of this study is to verify with PET whether patients in heart failure of non-ischemic origin have a functional alteration in coronary microvasculature, and if this change depends on the severity of the heart failure at the time of the study.

PATIENTS AND METHODS

We studied 40 patients with cardiopathy of non-ischemic origin who were in heart failure, New York Heart Association (NYHA) functional class III-IV, at the time of the study or prior to the study. A total of 41 PET studies were performed to measure the CFR. The study was approved by the ethics committee of our institution and all patients signed an informed consent form. We established the following groups according to the functional level of the patient at the time the study was performed: *1.* Ten patients in NYHA class III-IV; *2.* Ten patients in NYHA class II who were not receiving beta-blockers; *3.* Eleven patients in NYHA functional class II, treated with carvedilol, and *4.* Ten patients who had previously had heart failure with an ejection fraction <0.45 and at the time of the study, in addition to being in NYHA functional class I, had on ejection fraction of ≥0.45. Only 1 patient was studied twice: the first time in group 2 and the second time in group 3 (after 1 year of treatment with carvedilol). We obtained a clinical history, physical examination, 12-lead electrocardiogram, echocardiogram, usual blood work, and coronary angiography in all patients. Only patients with significant coronary lesions were included.

Table 1 shows the principal baseline characteristics of each group. Table 2 shows the diagnosis, ejection fraction, and mass and volume index of the left ventricle.

The patients in groups 2, 3, and 4 had previously been in NYHA functional class III-IV and improved with drugs or surgery (in the case of valve lesions). The 4 groups received digitalis, diuretics, and angiotensin converting enzyme inhibitors alone or in combination. In addition to these drugs, all patients in group 3 received carvedilol (the only beta blocker used), at a dose of between 6.25 mg/day and 50 mg/day. Treatment was established according to the criteria of the attending physician for each patient, who in general adjusted to the recommendations based on the evi-

TABLE 1. **Baseline characteristics of the different patient groups**

	Group 1	Group 2	Group 3	Group 4	*P*
Number of patients	10	10	11	10	
Age, years	68±7	58±11	60±10	66±10	.127
Men, n (%)	7 (70)	7 (70)	8 (72.7)	8 (80)	.573
BMI	29.1±5.7	27.9±3.7	29.2±2.8	24.5±3.7	.064
Smoking, n (%)	1 (10)	2 (20)	4 (36.3)	1 (10)	.287
Arterial hypertension, n (%)	3 (30)	6 (60)	7 (63.6)	8 (80)	.343
Diabetes mellitus, n (%)	2 (20)	0	2 (18.2)	2 (20)	.596
TC/HDL	5.3±1.7	4.7±1.1	4.3±1.2	4.7±1.5	.499

TC/HDL indicates total cholesterol/HDL cholesterol; BMI, body mass index (weight in kg/quadruple height measurement in m).

dence.[16] Only 1 patient in group 2 was able to be treated with carvedilol, and was then placed in group 3. The remaining patients in group 2 had some type of contraindication for treatment with betablockers.

All patients abstained from ingesting caffeine for at least 24 hours prior to the PET study. The patients who smoked stopped smoking for at least 1 week prior to the study. The morning of the study the patients took their usual medications and the PET study was performed in the afternoon.

Positron emission tomography

The transmission and emission images were obtaied with a Siemens Ecat Exact HR+ tomograph. This equipment consisted of a system of 32 crystal ring detectors that allowed acquisition, with 32 direct planes and 31 crossed planes, of 63 simultaneous transaxial images that covered a 15.5 cm field, with a 2-dimensional resolution of 4.5 mm in the transaxial plane and 4.5 mm in the axial plane in the center of the viewing field.

Myocardial blood flow (MBF) was measured at baseline and during hyperemia induced by adenosine triphosphate (ATP) using N-13 ammonia and dynamic PET acquisition. First, an transmission image was obtained for 15 minutes to correct photon attenuation. After the first intravenous injection of N-13 ammonia (9.25 MBq/kg, up to a maximum of 740 MBq), serial images were obtained at rest, with a variable length dynamic sequence (12 images×10 seconds, 4 image×15 seconds, 4 images×30 seconds, 3 images×300 seconds). The protocol used for PET data acquisition has been described by other authors.[17] After acquisition of the baseline study, we waited 50 minutes to allow N-13 ammonia radioactive fall-out (T1/2=9.9 minutes). ATP was infused for 6 minutes at a dose of 0.160 mg/kg/min. During the infusion cardiac frequency, arterial pressure, and a 12-lead electrocardiogram were monitored continuously. At the 4th minute of the ATP infusion, the second injection of N-13 ammonia was administered. The acquisition of the stress images began from the moment of the injection and followed the same protocol as for the images obtained with the patient at rest.

Image processing. The images were reconstructed using a Hann filter with an 0.4 slice frequency, providing an effective resolution for a 7 mm plane. The transaxial mages were reoriented on the short axis and on the long vertical and horizontal axes. The angles of the long horizontal and vertical axes were defined by using the last 3 images from the dynamic sequence, and then were used for the reorientation of the 23-image sequence. For quantitative analysis we used 6 continuous sections of the short axis corresponding to the middle of the left ventricle.

MBF measurement. Regional MBF was calculated in accordance with a 3-compartment model,16 which represented vascular and extravascular N-13 ammonia, and the N-13 ammonia metabolically trapped in the form of glutamine, which allowed estimation of the constant K1 that represented MBF in mL/g/min.

The *informatics program* used to calculate the regional MBF was developed by Muzic et al.[18] To determine the radioactivity input function, an area of interest in the most basal planes of the left ventricular cavity on the short axis was delimited. Twelve areas of interest were defined per plane on the 6 planes in the last image of the dynamic sequence. A sample of the collection of dynamic images was taken and 72 activity-time curves were obtained. Regional MBF was analyzed in 4 areas of the left ventricle: anterior, septal, inferoposterior, and lateral.

Statistical analysis

Descriptive statistics were expressed as mean±standard deviation. Quantitative measurements were compared via ANOVA, followed by the Tukey test. The differences in percentages between groups were compared with Fisher exact test (PEPI statistical packet, J.H. Abramson and P.M. Gahlinger, 1993-2000). In order to establish a possible relationship between variables, we used the Pearson product moment correlation test. We calculated the coefficient of variation of the regional MBF at rest in order to evaluate the spatial heterogeneity of myocardial perfusion,[19] determining in each subject the quotient of the standard deviation and the mean regional MBF in 4 areas of the myocardium.

RESULTS

Baseline characteristics

We did not find any significant differences between the 4 patient groups with regard to age, sex, body mass index, smoking habits, diabetes mellitus, arterial hypertension, or the total cholesterol/high density lipoprotein cholesterol quotient (Table 1). Given that CFR tends to be reduced after the age of 70 years,[20] we found that 12 patients were older than 69 years of age: 3 in group 1, 2 in group 2, 2 in group 3, and 5 in group 4 (differences were without statistical significance). We also found no significant differences in the proportion of the various types of cardiopathy among the 4 groups (Table 2). All valvulopathy was rheumatic, mitroaortic or degenerative in nature, with different degrees of stenosis and insufficiency. Three of these patients also had serious tricuspid insufficiency. Only 1 patient had restrictive myocardiopathy of unknown cause. Eight of the patients in group 4 were diagnosed with dilated myocardiopathy (hypertensive in origin in 6 patients). Ten patients in this group, who previously

TABLE 2. **Diagnosis and echocardiographic variables in each patient group**

	Group 1	Group 2	Group 3	Group 4	*P*
Dilated myocardiopathy, n (%)	6 (60)	3 (30)	8 (72.7)	8 (80)	.671
Mitroaortic valvulopathy, n (%)	4 (40)	6 (60)	3 (27.3)	2 (20)	.654
Restrictive myocardiopathy, n (%)	0	1 (10)	0	0	—
Ejection fraction, %	35±19	43±15	34±14	52±5	.045
LV mass index, g/m^2	149±48	159±76	136±49	128±28	.524
LV TDV index, mL/m^2	122±68	113±49	125±45	92±35	.508
LV TSV index, mL/m^2	83±65	67±42	81±42	43±19	.186

*Group 4 versus groups 1 and 3. LV indicates left ventricle; TDV, telediastolic volume; TSV, telesystolic volume.

TABLE 3. **Hemodynamic variables and coronary flow in baseline conditions and with ATP infusion**

	Group 1	Group 2	Group 3	Group 4	*P*
SAP, mm Hg	135±22	139±22	137±15	154±37	.391
Baseline CF × SAP	10 287±2073	9360±2439	10 120±2690	9388±2937	.753
CF×SAP with ATP	10 448±2073 11	160±2020	12 531±2987	11 213±3957	0.461
MBF_b, mL/g/min	0.69±0.25	0.75±0.24	0.70±0.14	0.90±0.35	.225
Normalized MFBb	0.67±0.16	0.81±0.19	0.73±0.22	1.03±0.53	.07
MBF_{ATP}	1.02±0.52	1.40±0.71	1.37±0.71	1.95±0.58	.03*
CFR (MBF_{ATP}/MBF_b)	1.46±0.48	1.73±0.72	1.89±0.75	2.40±0.95	.03
Baseline coronary resistance	143±43	127±35	139±28	129±57	.773
ATP coronary resistance	95±35	89±47	88±49	54±24	.114

*Group 4 versus group 1. ATP indicates adenosine triphosphate; CF, cardiac frequency in beats/min; MBF, myocardial blood flow; MBFb, baseline MBF; SAP, systolic arterial pressure; CFR, coronary flow reserve.

had a reduced ejection fraction and were in NYHA functional class III-IV, improved with treatment. At the time of the study they were in NYHA functional class I with a normal ejection fraction.

The ejection fraction was significantly higher in the patients in group 4 than those in groups 1 and 3. We did not observe a significant difference between groups 2 and 4. This was due to the fact that some patients in group 2, with valve lesions, had normal ejection fractions. There was no significant difference between patient groups with regard to left ventricle mass and volume indices (Table 2).

Hemodynamic findings

Table 3 shows that there was no significant difference in baseline arterial systolic pressure among the 4 patient groups. The double product (cardiac frequency ×arterial systolic pressure), indicative of the consumption of myocardial oxygen, increased slightly but significantly (*P*=.001) with ATP. There were no significant differences in this parameter among the 4 groups either at rest or during the infusion of ATP.

Myocardial flow

There was no significant spatial heterogeneity (*P*=.798) in baseline regional myocardial blood flow (BMFb) between the 4 myocardial regions studied: anterior, septal, inferoposterior, and lateral. For this reason, we only analyzed the overall BMFb.

MBF, coronary resistance and CFR

Table 3 shows that there was no significant difference in MBF among the 4 groups. As BMFb increases when the double produce is raised,[21] we calculated the normalized BMFb (quotient of BMFb×10 000/double product). We did not find significant differences between the 4 groups, although we did note higher values in group 4 and lower values in group 1. MBFATP was significantly higher in group 4 than in group 1.

Given than ATP disrupted the relationship between MBF and cardiac load, hyperemic flow was not corrected for the double product. The CFR (uncorrected BMFATP/BMFb) was significantly higher in group 4 than in group 1. No significant differences were observed among the 4 groups with regard to baseline coronary resistance (mean arterial pressure/BMFb) or minimal coronary resistance (with ATP), but there was more of a tendency toward less coronary resistance with ATP in group 4 than in the other groups. Figure 1 shows the uncorrected BMFb the BMFATP, and the CFR in the 4 patient groups. Compared with reported CFR values[21] (3.01±0.73) in healthy volunteers of 64 years of age±9 years of age, the CFR was clearly reduced in the 4 patient groups, especially in group 1. Although the CFR was slightly higher in groups 2 and

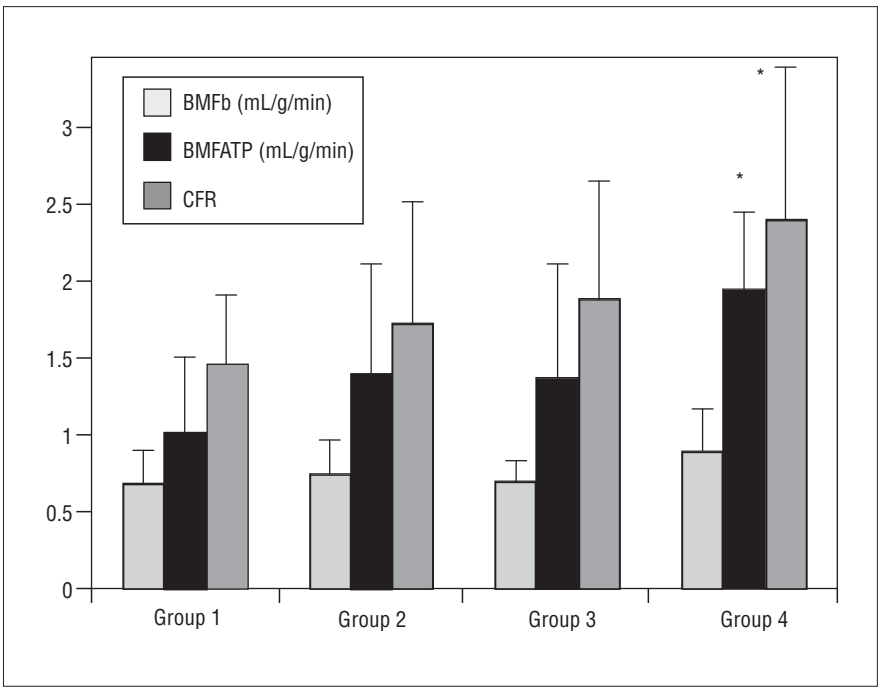

Fig. 1. Graph showing myocardial blood flow (MBF) in each group: at baseline (BMFb) and with adenosine triphosphate (MBFATP). Coronary flow reserve (CFR) represents the quotient of MBFATP/BMFb. Only group 4 had MBFATP and CFR values that were significantly higher than those of group 1.

3 than in group 1, only group 4 had values that were significantly higher than group 1. The patient who underwent 2 PET studies had a CFR of 1.63 when in group 2 and of 2.99 when included in group 3, after a year of treatment with carvedilol. The ejection fraction was 0.25 during the first study and 0.35 during the second study.

There was no significant correlation between CFR and: age (r=0.171; *P*=.143), systolic arterial pressure (r=-0.022; *P*=.445), ejection fraction (r=0.096; *P*=.275), left ventricle mass index (r=0.047; *P*=.388), left ventricular telediastolic volume index (r=0.025; *P*=.439), or left ventricular telesystolic volume index (r=0.056; *P*=.368).

None of the following co-variables significantly changed the CFR: age, body mass index, ejection fraction, total cholesterol/HDL cholesterol quotient, or left ventricular mass or volume indices. Sex, smoking habits, diabetes, and arterial hypertension likewise did not affect the differences between the patient groups (data not expressed).

DISCUSSION

CFR in heart failure

Our study shows for the first time with PET that patients with heart failure that is non-ischemic in origin, whatever the etiology, have depressed CFR, which is related to their functional class. The CFR was 1.46±0.48 in patients in NYHA functional class III-IV; 1.73±0.72 and 1.89±0.75 in patients in NYHA functional class II (with and without carvedilol, respectively), and 2.40±0.95 in patients in NYHA functional class I. These differences cannot be attributed to age, which was similar for patients in all 4 groups. Actually, it is not clear whether CFR diminished in the elderly (patients >69 years of age) due to deficient dilation of coronary microvasculature[20] or due to an increase in cardiac load (double product), which elevated the BMFb[20] CFR measured in healthy volunteers of a similar age to that of our patients was 3.01±0.73.21 In our study, the difference in CFR between the patients in groups 1 and 4 was significant. Theoretically, ventricular dysfunction can influence the diminishment of CFR. Nevertheless, in our patients, neither the ejection fraction nor the ventricular volume indices, taken as co-variables, significantly changed the results. It is probable that the functional class was more a determinant of CFR than the underlying cardiac disease.

Previous studies

PET and intracoronary echo-Doppler studies[22] of patients with dilated myocardiopathy and heart failure have shown a reduction in CFR. Intracoronary Doppler reveals endothelial dysfunction in patients with both microvascular and epicardial dilated myocardiopathy.[23] Peripheral resistance is elevated in heart failure12 and brachial hyperemic flow is reduced due to endothelial dysfunction.[13]

Our study was performed with ATP. This drug, similar to adenosine,[24] had been shown to be useful in myocardial perfusion studies,[25] and some studies[26] report that its vasodilator effect is dependent on the endothelium.

Cardiac hypertrophy

The majority of our patients had dilated myocardiopathy or mitroaortic valve disease. Dilated myocardiopathy is associated with reduced CFR in the absence of heart failure, probably due to vasodilation anomalies.[7] The progression of this disease is associated with greater depression of myocardial perfusion, both at rest18 and after the administration of dipiridamol.[7,18] This depression cannot be totally explained by the elevation of left ventricular diastolic pressure or by reduced coronary perfusion pressure.[27] Arterial hypertension is another cause of the reduction of CFR,[4] partly due to structural arterial changes. Nevertheless, CFR in hypertrophy secondary to valvulopathy has been studied less frequently. One study8 showed less change in the CFR in ventricular hypertrophy secondary to aortic stenosis than in arterial hypertension. Our patients had a decrease in CFR related to the functional class of their heart failure, and not to the type of underlying heart disease. These findings suggest that heart failure, on its own, may change coronary microvascular dilation, independent of its cause. This change was in addition to that produced by their baseline cardiopathy.

Neurohumoral factors

In heart failure there is an increase in different neurohumoral and inflammatory factors[28-31] that can induce not only peripheral vasoconstriction, but also coronary vasoconstriction. It is possible to diminish the vasoconstriction when the heart failure is controlled and these factors are reduced. We believe that this is the most likely explanation for our findings, although the study itself does not allow confirmation of this. It is also unknown how much time is needed for the CFR to normalize when heart failure improves clinically. The patients in group 4, in NYHA functional class I, are those who had the highest CFR. Although their ejection fraction had normalized by the time the study was performed, this variable had no significant relation to the CFR. This fact may indicate that the diminishment of CFR was not due to a decrease in the need for oxygen in the face of a reduced ejection fraction, but to a microcirculation problem.

Carvedilol

The patients in group 3, who were being treated with carvedilol, had a tendency toward a higher CFR than those in group 2, who were in the same functional class, although their ejection fraction was somewhat higher (but without statistical significance) in group 3. This may be attributable to the reduced BMFb in group 3 (Table 3). Nevertheless, the patients in group 1 had a lower CFR (but without statistical significance) than those in group 3, in spite of having a lower BMFb (not statistically significant). The patient who underwent 2 different studies (with and without carvedilol) had an increase in CFR with carvedilol that was disproportionate to the increase in the ejection fraction. Carvedilol is a beta and adrenergic alpha-1 antagonist that also has antioxidant[32] and antiendothelin-1 properties.[33] These properties may explain, at least in part, the slightly elevated CFR in group 3. A previous study[14] showed that the plasma changes in endothelin-1 reflect the clinical response to carvedilol in patients with heart failure. Several patients in group 4, who were those patients who had the highest CFR, also received carvedilol.

Study limitations

1. We did not have a fifth group of healthy volunteers of similar ages to compare with the 4 patient groups, but we believe that they can be compared with the healthy volunteers of a similar age in the study by Czernin et al[21] as these authors used methods similar to ours and obtained results similar to ours (unpublished data) in young volunteers.

2. It would have been ideal to have studied the same patients in 4 different situations during the course of their illness, but this was not possible. The majority of the patients in group 1 received a heart transplant or died. In contrast, the patients in group 2 had some contraindication for treatment with beta blockers.

3. Mixing patients with valve disease with patients with myocardiopathy could be considered a limitation. Nevertheless, CFR is changed with both pathological processes. In figure 1 it can be seen that there is no appreciable difference in the standard deviation among the patient groups; therefore, from the statistical point of view, there is no heterogeneity amongst them. There was only a significant difference in the ejection fraction, which was higher in group 4, as it was a selection criterion for this group. If group 4 had been made up of healthy volunteers, their greater CFR would have to be attributed to the absence of cardiopathy. Nevertheless, the group was made up of patients with cardiopathy whose heart failure had improved; therefore, the difference between group 4 and the rest of the groups must be attributed to their distinct functional class, once the existence of a correlation between hemodynamic variables and CFR was discarded.

CLINICAL IMPLICATIONS

CFR measured with PET provides greater knowledge of the coronary microvascular physiopathology in non-ischemic heart failure. Patients who are in a better functional class are those who present with higher CFR levels. If low CFR is due to a primary microcir-

culatory problem, as it seems to be, microcirculation must be a therapeutic objective. Other studies are needed with evolutionary followup to establish a possible relationship between CFR, neurohumoral and inflammatory factors, and the prognosis of patients in heart failure.

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REFERENCES

1. Uren NG, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary artery stenosis. N Engl J Med 1994;330:1782-8.
2. Baller D, Notohamiprodjo G, Gleichmann U, Holzinger J, Weise R, Lehmann J. Improvement in coronary flow reserve determined by positron emission tomography after 6 months of cholesterol-lowering therapy in patients with early stages of coronary atherosclerosis. Circulation 1999;99:2871-5.
3. Pitkanen OP, Nuutila P, Raitakari OT, Porkka K, Iida H, Nuotio I, et al. Coronary flow reserve is reduced in young men with IDDM. Diabetes 1998;47:248-54.
4. Gimelli A, Schneider-Eicke J, Neglia D, Sambuceti G, Giorgetti A, Bigalli G, et al. Homogeneously reduced versus regionally impaired myocardial blood flow in hypertensive patients: two different patterns of myocardial perfusion associated with degree of hypertrophy. J Am Coll Cardiol 1998;31:366-73.
5. Choudhury L, Elliott P, Rimoldi O, Ryan M, Lammertsma AA, Boyd H, et al. Transmural myocardial blood flow distribution in hypertrophic cardiomyopathy and effect of treatment. Basic Res Cardiol 1999;94:49-59.
6. Drzezga AE, Blasini R, Ziegler SI, Bengel FM, Picker W, Schwaiger M, et al. Coronary microvascular reactivity to sympathetic stimulation in patients with idiopathic dilated cardiomyopathy. J Nucl Med 2000;41:837-44.
7. Neglia D, Parodi O, Gallopin M, Sambuceti G, Giorgetti A, Pratali L, et al. Myocardial blood flow response to pacing tachycardia and to dipyridamole infusion in patients with dilated cardiomyopathy without overt heart failure. Circulation 1995;92:796-804.
8. Choudhury L, Rosen SD, Patel DP, Nihoyannopoulos P, Camici PG. Coronary flow reserve in primary and secondary left ventricular hypertrophy: a study with positron emission tomography. Eur Heart J 1997;18:108-16.
9. Knecht M, Burkhoff D, Yi GH, Popilskis S, Homma S, Packer M, et al. Coronary endothelial dysfunction precedes heart failure and reduction of coronary reserve in awake dogs. J Mol Cell Cardiol 1997;29:217-27.
10. Drexler H, Hornig B. Importance of endothelial function in chronic heart failure. J Cardiovasc Pharmacol 1996;26(Suppl 2):S9-12.
11. Dexler H, Hornig B. Endothelial dysfunction in human disease. J Mol Cell Cardiol 1999;31:51-60.
12. Katz SD. The role of endothelium-derived vasoactive substances in the pathophysiology of exercise intolerance in patients with congestive heart failure. Prog Cardiovasc Dis 1995;38:23-50.
13. Takeshita A, Hirooka Y, Imaizumi T. Role of endothelium in control of forearm blood flow in patients with heart failure. J Card Fail 1996;2:S209-15.
14. Krum H, Gu A, Wilshire-Clement M, Sackner-Bernstein J, Goldsmith R, Medina N, et al. Changes in plasma endothelin-1 levels refects clinical response to b-blockade in chronic heart failure. Am Heart J 1996;131:337-41.
15. Camici PG. Positron emission tomography and myocardial imaging. Heart 2000;82:475-80.
16. Agustí Escasany A, Durán Dalmau M, Arnau de Bolós JM, Rodríguez Cumplido D, Diogène Fadini E, Casas Rodríguez J, et al. Tratamiento médico de la insuficiencia cardíaca basado en la evidencia. Rev Esp Cardiol 2001;54:715-34.
17. Muzik O, Beanlands R, Wolfe E, Schwaiger M. Automated region definition for cardiac nitrogen-13-ammonia PET imaging. J Nucl Med 1993;34:336-44.
18. Muzik O, Beanlands RSB, Hutchins GD, Mangner TJ, Nguyen N, Schwaiger M. Validation of nitrogen-13-ammonia tracer kinetic model for quantification of myocardial blood flow using PET. J Nucl Med 1993;34:83-91.
19. Shikama N, Himi T, Yoshida K, Nakao M, Fujiwara M, Tamura T, et al. Prognostic utility of myocardial blood flow assessed by N-13 ammonia positron emission tomography in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 1999;84:434-9.
20. Uren NG, Camici PG, Melin JA, Bol A, de Bruyne B, Radvan J, et al. Effect of aging on myocardial perfusion reserve. J Nucl Med 1995;36:2032-6.
21. Czernin J, Muller P, Chan S, Brunken RC, Porenta G, Krivokapich J, et al. Influence of age and hemodynamics on myocardial blood flow and flow reserve. Circulation 1993;88:62-9.
22. Merlet P, Mazoyer B, Hittinger L, Valette H, Saal JP, Bendriem B, et al. Assessment of coronary reserve in man: comparison between positron emission tomography with oxygen-15-labeled water and intracoronary Doppler technique. J Nucl Med 1993;34:1899-904.
23. Mathier MA, Rose GA, Fifer MA, Miyamoto MI, Dinsmore RE, Castano HH, et al. Coronary endothelial dysfunction in patients with acute-onset idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1998;32:216-24.
24. Jeremias A, Filardo SD, Whitbourn RJ, Kernoff RS, Yeung AC, Fitzgerald PJ, et al. Effects of intravenous and intracoronary adenosine 5'-triphosphate as compared with adenosine on coronary flow and pressure dynamics. Circulation 2000;101:318-23.
25. Bravo N, Giménez M, Mejía S, García-Velloso MJ, Coma-Canella I. Prognostic value of myocardial perfusion imaging with adenosine triphosphate. J Nuclear Cardiol 2002;9:395-401.
26. De Mey JG, Vanhoutte PM. Role of the intima in cholinergic and purinergic relaxation of isolated canine femoral arteries. J Physiol (Lond) 1981;316:347-55.
27. 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.
28. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Mabuchi N, Hayashi M, et al. Plasma brain natriuretic peptide level as a biochemical marker of morbidity and mortality in patients with asymptomatic or minimally symptomatic left ventricular dysfunction. Comparison with plasma angiotensin II and endothelin-1. Eur Heart J 1999;20:1799-807.
29. Adamopoulos S, Parissis J, Kroupis C, Kroupis C, Georgiadis M, Karavolias G, et al. Physical training reduces peripheral markers of inflammation in patients with chronic heart failure. Eur Heart J 2001;22:791-7.
30. Vidal B, Roig E, Pérez-Villa F, Orús J, Pérez J, Jiménez V, et al. Valor pronóstico de los niveles de citocinas y neurohormonas en la insuficiencia cardíaca severa. Rev Esp Cardiol 2002;55:481-6.
31. Herrera Garza EH, Herrera Garza JL, Rodríguez González H, Treviño A, Ibarra Flores M, Torre Amione G. Importancia del factor de necrosis tumoral alfa en la patogenia de la insuficiencia cardíaca. Rev Esp Cardiol 2002;55:61-6.
32. Feuerstein GZ, Bril A, Ruffolo RR Jr. Protective effects of carvedilol in the myocardium. Am J Cardiol 1997;80(Suppl):L41-5.
33. Ohlstein EH, Arleth AJ, Storer B, Romanic AM. Carvedilol inhibits endothelin-1 biosynthesis in cultured human coronary artery endothelial cells. J Mol Cell Cardiol 1998;30:167-73.