Original articles

Myocardial perfusion and metabolic changes induced by conventional right and biventricular pacing in dilated cardiomyopathy evaluated by positron emission tomography

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Background. **Biventricular pacing induces well-known effects on myocardial wall function, apparently providing better results in comparison with conventional right pacing in patients presenting with dilated cardiomyopathy (DCM). However, at the moment the secondary changes in myocardial metabolism induced by pacing devices are unclear. The aim of our study was to evaluate the possible changes in myocardial metabolism and perfusion induced by cardiac pacing in these patients.**

Methods. **Twenty-eight patients presenting with DCM were submitted to positron emission tomography. Eighteen patients were examined during cardiac pacing, 6 had dual chamber pacemakers implanted for conventional reasons (group A), 12 biventricular pacemakers (group B) for resynchronization purposes; the other 10 patients were considered as controls. Myocardial metabolism was evaluated using ^{18}F-fluorodeoxyglucose (FDG), by the glucose load-insulin technique and perfusion using ^{13}N-ammonia (NH3), injected at rest. A visual and a semiquantitative analysis were performed, calculating on the basis of the regions of interest the septum to lateral uptake (S/L) ratio.**

Results. **In all the 6 patients of group A, a selective defect in FDG uptake was observed in the septum (mean S/L ratio 0.67 ± 0.15, $p < 0.01$ with respect to controls), while both the patients in group B and the controls presented a homogeneous distribution of FDG uptake in the myocardial wall (mean S/L ratio 1.01 ± 0.10 and 0.95 ± 0.13 respectively, p = NS). On the contrary, at the NH3 positron emission tomography studies no significant difference in myocardial perfusion was found in the three groups of patients, both at the visual and at the semiquantitative analysis (mean S/L ratio group A 1.01 ± 0.21, group B 0.99 ± 0.17, controls 0.94 ± 0.11, p = NS).**

Conclusions. **Our experience could suggest that, in patients with DCM, conventional right pacing could induce interference in the metabolism of the septum not correlated with perfusion changes. On the other hand, biventricular pacing improves myocardial wall function without interfering with myocardial metabolism and perfusion.**

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Introduction

Dilated cardiomyopathy (DCM) is characterized by structural abnormalities of the ventricular myocardium affecting both the ventricular activation and mechanical contraction. Electrical activation may be delayed as a consequence of the pathological involvement of the conduction system or due to nonhomogeneous spread of excitation wavefronts across scarred tissue[1].

New forms of ventricular pacing are increasingly being studied as an option in the management of these patients. Biventricular pacing induces well-known effects on myocardial wall function, apparently providing better results in comparison with conventional right pacing in patients presenting with DCM[2]. At the moment, the causes and the underlying pathophysiological mechanisms are not well understood. In particular, even though in preliminary reports a diminished energy cost[3] and a reduced blood flow[4] during cardiac pacing in DCM patients have been reported, the secondary changes in myocardial metabolism and perfusion induced by pacing devices are unclear.

In this paper our experience concerning the effects of conventional right pacing and biventricular pacing on myocardial perfusion and metabolism in a group of patients

presenting with DCM is reported, and compared with a reference population presenting with DCM but no cardiac pacing. The glucose uptake and the myocardial perfusion were evaluated by positron emission tomography (PET), respectively using ^{18}F-fluorodeoxyglucose (FDG) and ^{13}N-ammonia (NH3) as tracers.

Methods

Patients. Eighteen patients presenting with DCM and submitted to cardiac pacing, 6 to dual chamber pacing (conventional right pacing, group A) for conventional reasons, and 12 to biventricular pacing (group B) for resynchronization purposes were enrolled. All the patients presented left ventricular dilation with an end-diastolic volume index ≥ 80, were in NYHA functional class III and had an ejection fraction, as evaluated at echocardiography, of < 45%. At coronary angiography, no patient presented significant coronary stenoses. In order to avoid possible interference with FDG uptake, patients with diabetes were excluded from the study.

The patients in group A had no intraventricular conduction disorders and the indications to pacemaker implantation were II or III degree atrioventricular block or sick sinus syndrome with atrioventricular conduction disorders. The patients in group B had a left bundle branch block (LBBB) and QRS duration > 150 ms; they also were in NYHA class III. Ten subjects presenting with left ventricular dilation, no significant coronary stenoses and no LBBB were considered as controls (group C).

All the paced patients were males, except for 1 female in group A, 1 in group B and 3 in group C. The mean age was 65 ± 14 years for patients in group A, 69 ± 4 years for group B and 59 ± 6 years for group C. Informed consent was obtained from all the patients.

Positron emission tomography. The PET studies were performed using a PET scanner Ecat Exact, which allows simultaneous acquisition of 47 contiguous transaxial images, with a total axial field of view of 16.2 cm. The calculated resolution of our scanner was 4.8 ± 0.6 mm in the axial direction and 6.1 ± 0.2 mm in the transaxial planes.

Initially, using retractable 68G rod sources, a transmission scan of 15 min was obtained for attenuation correction. For emission studies, the tracers were NH3 (dose 10 MBq/kg), administered at rest, and FDG (dose 4 MBq/kg), administered after an oral glucose load coupled with intravenous insulin, as suggested by Lewis et al.[5]. The emission scan started 4 min after the administration of NH3 and 45 min after the administration of ^{18}F-FDG. The acquisition lasted 15 min with both tracers. Short-axis and vertical and horizontal long-axis slices, each 0.8 cm thick, were reconstructed using a Hanning filter (cut-off 1.18 cycle/cm), and corrected for attenuation.

Both studies were performed on the same day, first the NH3 study, and 2 hours later the FDG study. To avoid artifacts due to misalignment, the repositioning of the patient in the scanner was checked using a cross-shaped low power laser beam and pen skin markers.

A semiquantitative analysis of the images was performed by the consensus of two skilled observers, blinded to when the scans were performed. Briefly, the left ventricular wall was divided into four walls (anterior, lateral, inferior and septum) and each wall was further divided into three segments (basal, midventricular and distal), equal in dimensions, for a total of twelve segments. After individual normalization of each set of images to the maximum count in the left ventricular wall, a three-point semiquantitative score was applied both for the FDG and NH3 images: 2 = normal uptake (> 75%), 1 = moderate defect (50-75%), 0 = severe defect (< 50%). A reverse mismatch was considered present in the segments presenting an FDG score inferior to the corresponding NH3 score.

The reverse mismatch phenomenon has been defined as a pattern of decreased FDG uptake relative to the myocardial blood flow that has been found in patients with LBBB, coronary disease and previous myocardial infarction, and also in patients with LBBB and angiographically normal coronary arteries[6,7].

Moreover, assuming the lateral wall as reference, the septal-to-lateral count rate density ratios (S/L ratio) for FDG and NH3 were calculated in the midventricular horizontal long-axis slice (interpolated at a thickness of 1.6 cm) with the region-of-interest technique, drawing for each patient two different regions extending from the base to the apex and normalizing the counts to the extension of each region.

Statistical analysis. The data are usually reported as mean ± SD. The one-way ANOVA analysis of variance was applied, when appropriate, to compare the mean values, considering significant a p value of ≤ 0.05.

Results

Patient characteristics. The main characteristics of the enrolled patients are reported in table I. At echocardiography, the mean ejection fraction, evaluated after pacemaker implantation in the first two groups, was 35 ± 6% in group A, 39 ± 5% in group B, and 32 ± 6% in group C (p = NS). No statistically significant difference in ejection fraction was found among the three groups.

Positron emission tomography. At visual analysis all the subjects with conventional right pacing (group A) presented a relatively lower septal FDG uptake compared to the NH3 uptake. The images relative to one of our patients are shown in figure 1. This reverse mismatch also involved the inferior wall in 2 patients and both the anterior and inferior walls in the other 2 pa-

Table I. Main characteristics of the patients and positron emission tomography results.

Patient	Age (years)	Sex	Pacing	EF (%)	RM site	RM extent*	S/L ratio	
							FDG	NH3
Group A								
1	48	M	DDD	44	Septum-inferior	4	0.90	1.10
2	76	M	DDD	30	Septum-anterior-inferior	8	0.46	0.84
3	71	M	DDD	40	Septum-inferior	6	0.75	1.02
4	80	F	DDD	30	Septum	3	0.79	1.00
5	48	M	DDD	38	Septum	2	0.45	0.88
6	68	M	DDD	29	Septum-anterior-inferior	6	0.65	1.14
Mean ± SD	65 ± 14			35 ± 6		4.8 ± 2.2	0.67 ± 0.18**	0.99 ± 0.1
Group B								
1	72	M	BVP	34	–	–	0.90	1.11
2	60	M	BVP	48	–	–	1.10	1.06
3	72	M	BVP	40	–	–	1.00	1.15
4	70	M	BVP	41	–	–	0.93	1.16
5	66	M	BVP	43	–	–	1.02	1.12
6	69	F	BVP	38	–	–	0.66	0.92
7	66	M	BVP	45	–	–	0.60	0.61
8	71	M	BVP	42	–	–	0.87	0.88
9	79	M	BVP	35	–	–	0.94	1.02
10	70	M	BVP	39	–	–	0.96	1.06
11	70	M	BVP	36	–	–	1.04	1.12
12	68	M	BVP	28	–	–	0.91	1.37
Mean ± SD	69 ± 4			39 ± 5	–	–	0.91 ± 0.1§	1 ± 0.1
Group C								
1	65	M		25	–	–	0.82	0.93
2	68	F		40	–	–	1.02	0.88
3	52	M		43	–	–	0.85	0.98
4	50	M		32	–	–	0.78	0.85
5	63	M		34	–	–	1.10	1.20
6	58	M		28	–	–	0.95	0.85
7	61	F		30	–	–	1.05	0.98
8	55	M		22	–	–	1.15	1.02
9	62	M		32	–	–	1.02	0.85
10	60	F		34	–	–	0.80	0.85
Mean ± SD	59 ± 6			32 ± 6	–	–	0.95 ± 0.13	0.94 ± 0.11

BVP = biventricular pacing; DDD = dual chamber pacing; EF = ejection fraction evaluated at echocardiography (after implantation of DDD pacing or biventricular pacemakers in groups A and B); FDG = ^{18}F-fluorodeoxyglucose; NH3 = ^{13}N-ammonia; RM = reverse mismatch; S/L = septum to lateral uptake. * = extent of the reverse mismatch, calculated as the number of segments; ** = $p < 0.01$ with respect to S/L ratio FDG in patients of group C; § = $p < 0.05$ with respect to S/L ratio FDG in group A patients.

tients; in all cases matched perfusion and FDG uptake in the other regions of the left ventricular wall were observed, and in no patient was a reverse mismatch present in the lateral regions. The mean of the extension of reverse mismatch, considered as the number of segments involved, was 4.8 ± 2.2 (range 2-8) (Table I).

Semiquantitative analysis, assuming the lateral wall as reference, confirmed the reverse mismatch between glucose uptake and perfusion, with a mean S/L ratio of 0.67 ± 0.18 (range 0.45-0.90) and of 0.99 ± 0.1 (range 0.84-1.14) respectively. At one-way ANOVA analysis of variance the difference appeared highly significant ($p < 0.01$).

On the contrary, both in the patients submitted to biventricular pacing (group B) and in the control group (group C), a matched distribution of both tracers was present in the left ventricular wall. The images relative to a biventricular pacing patient are shown in figure 2. At semiquantitative analysis (Table I) the S/L ratio in the biventricular pacing group was 0.91 ± 0.1 for FDG (range 0.60-1.10, $p < 0.05$ with respect to conventional right pacing patients), and 1 ± 0.1 (range 0.61-1.37) for NH3. In the control group (Table I) the mean values were 0.95 ± 0.13 for FDG (range 0.78-1.15) and 0.94 ± 0.11 (range 0.85-1.20) for NH3, with a significant difference only with respect to FDG values in conventional right pacing patients ($p < 0.01$).

Discussion

Population aging and the new therapies that significantly reduce the risk of acute events, but increase the frequency of long-term complications, have rendered chronic heart failure and DCM an increasingly relevant health problem[2]. Despite new advances in medical ther-

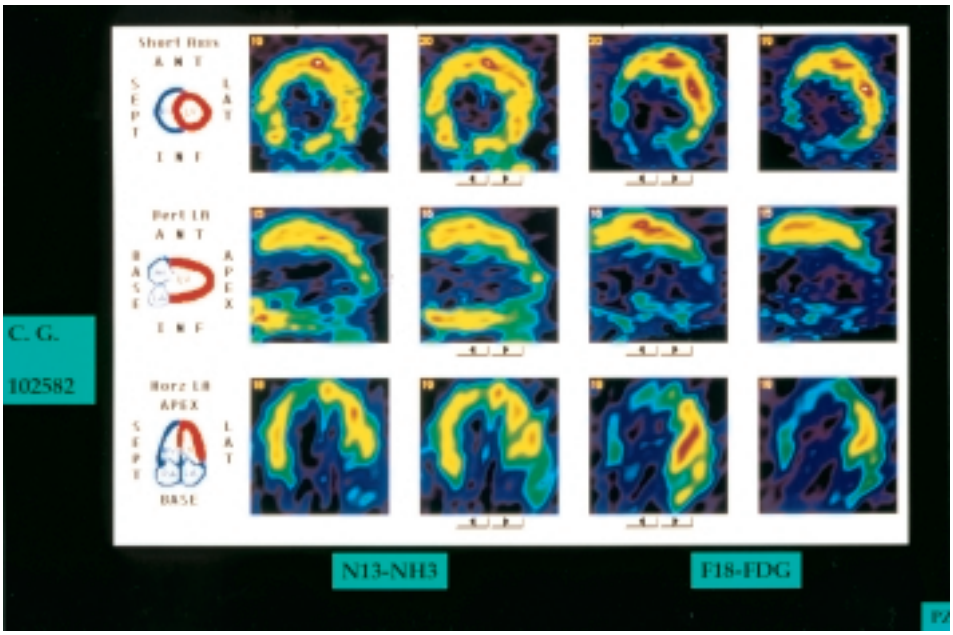

Figure 1. *Patient with dual chamber pacing pacemaker: a clear defect in ^{18}F-fluorodeoxyglucose (FDG) uptake in the septum and inferior wall, not associated with a defect in perfusion, is present.* On the left *^{13}N-ammonia (NH3),* on the right *^{18}F-FDG;* top panels: *midventricular short-axis slices,* middle panels: *midventricular vertical long-axis slices,* bottom panels: *midventricular horizontal long-axis slices.*

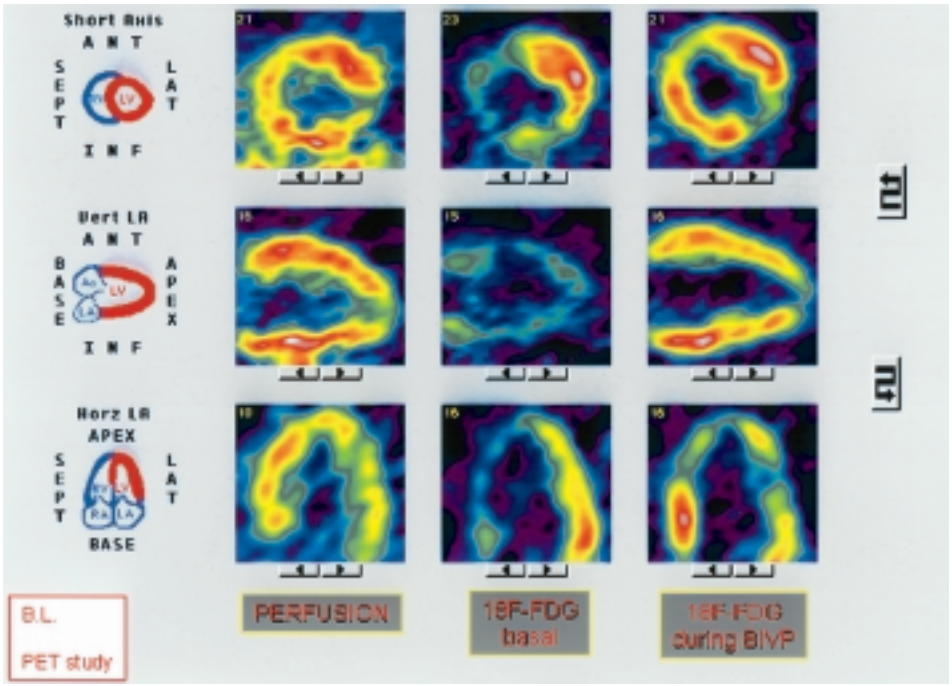

Figure 2. *Patient with a biventricular pacemaker: a clear defect in ^{18}F-fluorodeoxyglucose (FDG) uptake in the septum, not associated with a defect in perfusion, is present before implant; a homogeneous distribution of FDG uptake in the myocardial walls during biventricular pacing may be observed.* Left panels: *^{13}N-ammonia;* middle panels: *^{18}F-FDG before implant;* right panels: *^{18}F-FDG during biventricular pacing;* top panels: *midventricular short-axis slices,* middle panels: *midventricular vertical long-axis slices,* bottom panels: *midventricular horizontal long-axis slices.*

apy, the long-term prognosis of these patients remains poor.

Multisite ventricular pacing has recently been proposed as an additional treatment for patients with severe heart failure and intraventricular conduction delay[8]. One third of patients with chronic heart failure present a major intraventricular conduction delay, which may worsen left ventricular systolic dysfunction through asynchronous ventricular contraction. The results of several studies using biventricular pacing showed an improvement in the patients' clinical conditions as evaluated by means of the NYHA class and

Minnesota Living with Heart Failure score and by means of the oxygen consumption during the cardiopulmonary test and the distance covered during the 6-min walk test[2,4,8,9].

Moreover, a recent paper by Nelson et al.[3] documented that biventricular pacing improves cardiac function at a lower energy cost in patients with DCM and LBBB. Posma et al.[10], in a previous PET study, documented a decrease in resting left ventricular myocardial blood flow during dual chamber pacing in patients with symptomatic hypertrophic cardiomyopathy, with a more homogeneously distributed perfusion reserve.

On the contrary, univentricular, right-sided pacing in patients with sinus rhythm has been found to benefit only a limited subgroup of patients[11-13]. Using ^{123}I-beta-methyl iodophenyl pentadecanoic acid single photon emission computed tomography (SPECT), a reduced uptake of this metabolic tracer was referred at the septal, inferior and apical regions during conventional right pacing[14].

However, at the moment, a comparative analysis of myocardial blood flow and metabolic changes induced by different kinds of cardiac pacing is lacking and the possible causes of the relevant differences on the clinical conditions of the patients are not well understood.

To these ends and to better understand the underlying mechanism, we evaluated two different groups of patients submitted to cardiac pacing, one submitted to conventional right pacing, the other to biventricular pacing, evaluating both the myocardial perfusion and metabolism by means of PET, and assuming as reference a group of patients affected by DCM not submitted to cardiac pacing.

The indications to pacemaker implantation were: II or III degree atrioventricular block or sick sinus syndrome with atrioventricular conduction disorders for group A, and resynchronization purposes for patients of group B who presented with an intraventricular conduction delay > 150 ms.

In our experience conventional right pacing induces a reduction, not correlated to alterations in perfusion, in the uptake of the metabolic tracer in the septum and bordering areas of all patients. This phenomenon, the so-called "reverse mismatch", could imply a local reduction in cardiac metabolism and confirms the previous experience of Yoshida et al.[14], obtained using fatty acids and SPECT.

The possible explanation is not clear. Of interest is that a similar septal defect in the uptake of FDG was previously referred in patients presenting with total persistent LBBB[7]. In this situation the asynchronous ventricular contraction is similar to the motion alteration induced by conventional right pacing, and similar underlying mechanisms could be supposed.

A reduced perfusion caused by the asynchronous wall motion associated with this conduction defect and also occurring in conventional right pacing, was supposed to be the cause[15]: the septal contraction occurs during diastole, thus hampering the coronary filling and causing a flow reduction. However, in the conventional right pacing patients evaluated in the present study, the deficit in glucose utilization appears unrelated to the reduction in perfusion. Alternatively, it could be hypothesized that the delayed conduction and depolarization of myocardial cells may directly interfere with regional glucose uptake and metabolism, such as that of fatty acids[14]. This phenomenon can also explain the experimental observation in dogs that conventional right pacing proportionally increases myocardial oxygen consumption up to 50% in relation to the hemodynamic determinants[16].

On the contrary, all the patients submitted to biventricular pacing presented a distribution of myocardial flow and a metabolism similar to those of the control population consisting of patients with DCM and heart failure but without intraventricular conduction delays. This aspect is also confirmed in a recently published case report[17], in which a septal FDG uptake defect, present in an LBBB patient, disappeared when the patient was submitted to biventricular pacing. This could justify the significant differences in exercise tolerance and quality of life obtained by resorting to biventricular pacing instead of conventional right pacing, especially in patients also presenting with LBBB[2]. The probable mechanism could be based on a better utilization or uptake of the metabolic substrates in the myocardial cells, due to a normalization of the transmembrane transport and/or phosphorylation kinetics. It is possible that resynchronization of the septal contraction requires more energy than that necessary for a septum contracting asynchronously and at a low chamber pressure, whereas the opposing non stimulated walls remain distensible[3].

The clinical implication of our study could be that, in patients presenting with DCM who need pacemaker implantation for conventional reasons, it should be preferable to implant a biventricular device even in the absence of an intraventricular delay, in order to prevent abnormalities in septal contraction and, as we have seen in our patients, abnormalities in septal glucose metabolism.

Limitations of the study. The analysis of PET data was only semiquantitative. The application of real quantitative measures of myocardial blood flow and glucose utilization, as well as the use of other metabolic tracers, such as C11-acetate, could be desirable.

In conclusion, our experience suggests that in patients with DCM, conventional right pacing could induce an alteration in the metabolism of the septum, not correlated with changes in perfusion. On the contrary, this phenomenon is usually not present when biventricular pacing is employed. It may be that this difference constitutes one of the reasons of better clinical results obtained using biventricular pacing in DCM patients

and could suggest the implantation of this type of pacemaker even in patients with DCM and no intraventricular conduction disorder when there is an indication for conventional pacing.

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