Right Ventricular Bifocal Stimulation in Treatment of Dilated Cardiomyopathy with Heart Failure

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Summary

QRS widening caused by conventional ventricular pacing decreases ventricular contractility, ventricular filling and mitral valve performance. Our aim was to study an alternative mode of multisite pacing in the right ventricle for decreasing QRS duration. 5 patients(pts, 4 male/1 female) with dilated cardiomyopathy (4 Chagas' disease, 1 idiopathic), chronic AF and high degree AV-block were included. They presented cardiac failure classified as NYHA III or IV. All were submitted to endocardial PM implants (Biotronik Dromos DR) with 2 right ventricular leads, one placed in the His bundle area (septal), the other in the right ventricular apex (conventional). AV delay could be programmed at 15 ms. 2 weeks post implant, each pt was evaluated echocardiographically during 3 stimulation modes in the same session. Modes were "AAI" (septal), VVI (conventional) and "DDT" with an AV interval at 15 ms (bifocal).

Key words

QRS, cardiomypathy

Results

The averages of the evaluated parameters were:

Mode	EF (%)	CO (l/min)	LAA (cm^2)	MR (cm^2)	QRS (ms)
Conventional	23.6	2.8	28.5	15.1	212
Septal	23.8	3.0	21.0	11.6	192
Bifocal	30.4	3.4	20.1	8.5	151

Echocardiographical comparison in the same pt during 3 stimulation modes revealed:

1. The conventional mode clearly caused the worst hemodynamic performance;
2. The bifocal mode showed the best results with a mean increase in EF of 6.8% and in CO of 0.6 l/min, a mean reduction in LAA of 7.5 cm^2 and in the area of mitral regurgitation of 7.6 cm^2.

Furthermore the QRS duration was reduced by 61 ms ($p < 0.03$). Bifocal right ventricular stimulation proved to be of more benefit compared to monofocal stimulation for pts with cardiomyopathy and severe heart failure, functional mitral regurgitation and pacemaker indication.

Background

The QRS enlargement produced by the artificial heart stimulation (Figure 1) provokes systolic and diastolic dysfunction, and mitral regurgitation. When the myocardial conduction is very slow, the delayed activated cells are distended in response to the increase pressure of those that were initially activated (Figure 2), reducing the systolic performance [1]. This causes an increase of the pre-ejection and the relaxation times with reduction of the ventricular filling time and an increase of the mitral regurgitation [2]. These abnormalities tend to be reduced when the heart is paced with a more narrow QRS. Recent works have been

showing good results pacing the right and left ventricles at the same time. The left ventricle stimulation has been performed by epicardial (thoracotomy) or endocardial approach (coronary sinus and heart veins). Such alternatives, besides adding technical difficulties, may increase morbidity and mortality. On the other hand, our observations have shown, that it is feasible to significantly reduce QRS duration by endocardial right ventricular bifocal stimulation.

Objective

The main purposes of this evaluation were:
1. To suggest an alternative method of endocardial right ventricular stimulation in severe cardiomyopathy by narrowing QRS via placement of two leads in the right ventricle, thus seeking for "ventricular resynchronization" without the need of left ventricular stimulation.
2. To propose a study method that allows to test this kind of pacing vs. conventional right heart stimulation in the same patient, thus eliminating intervening variables which could occur among different individuals.

Casuistry

5 patients (1 female and 4 male) were included with ages from 37 to 76 years (average: 52.2 ± 17.7 years). All patients suffered of severe dilated cardiomyopathy (4 Chagas' disease, 1 idiopathic). All presented atrial fibrillation with high degree AV block, furthermore cardiac failure classified NYHA III or IV and radiological heart shapes 3 to 4+.

Methods

All patients were submitted to endocardial right ventricular bifocal pacing with dual chamber pacemakers. They were programmed to bifocal simultaneous stimulation at 60 to 65 ppm. During 3 consecutive stimulation modes - conventional, septal and bifocal - hemodynamic performance was evaluated with bidimensional Doppler echocardiography.

Implantation techniques
Two endocardial leads were implanted in the right ventricle via dissection of the cephalic vein or puncture of the right subclavian vein. The first lead (named "conventional") was placed in the right ventricular apex according to the classical endocardial implantation

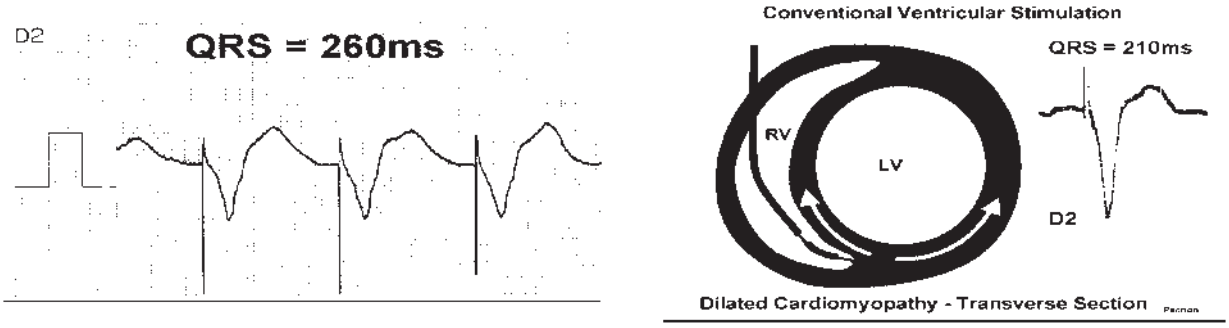

Figure 1. Representative scheme of conventional cardiac pacing with the stimulated QRS in dilated cardiomyopathy. By the fact of pacing monofocal, the complete activation of the myocardium is quite lingering, harming the contractile synergism, causing impairment of systolic and diastolic function and increasing mitral regurgitation.

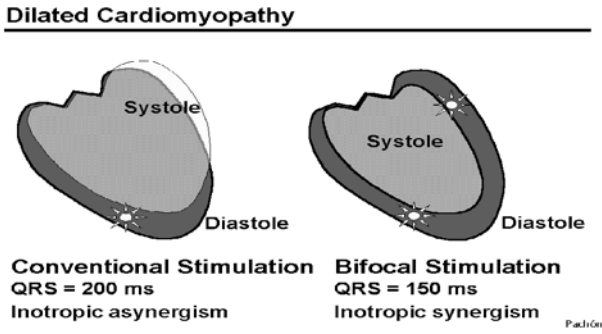

Figure 2. Scheme of the contraction failure caused by the lack of inotropic synchronism due to the very slow myocardial conduction. When the delayed region is activated the myofibril interposition is reduced by the contraction of the initial activated areas. The loss of optimal myofibril interposition and the activation after initial intraventricular pressure increase are strong factors to disfavour contractility.

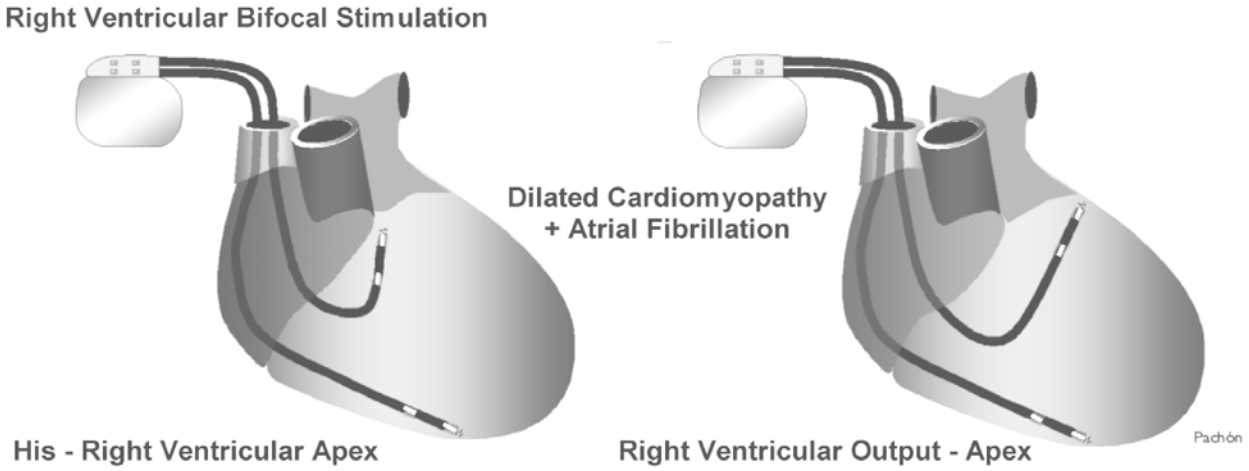

Figure 3. Scheme of the lead positions. Significant QRS narrowing was achieved by stimulating simultaneously in the right ventricular apex and the His bundle area or the right ventricular apex and the right ventricular outflow tract.

technique (Figure 3). The second lead (named "septal") was implanted in the sub-pulmonary area. Initially, the septal lead was introduced into the lung artery and was connected to the stimulator, which was programmed to 80 ppm and to an output of 2 V/0.5 ms. Then, the lead was slowly withdrawn until obtaining ventricular stimulation from the sub-pulmonary area. In this position, it was carefully manipulated, using the radiological left anterior oblique view for control to obtain the closest distance to the left ventricle. Satisfied, it was fixated using the active screw mechanism.

Pacemakers and leads

The pacemakers used were the Biotronik "Dromos DR" and the leads were 4 Biotronik Tir 60 BP, 3 Medtronic Capsure-Fix and 3 Guidant-CPI 4244.

Programming and echocardiographic evaluation

The patients were evaluated after 15 minutes of rest in the left lateral position. The first step was to programme the pacemakers to the VVI mode using a pacing rate between 60-65 ppm. Allowing 5 minutes for hemodynamic stabilization the echocardiographic parameters were measured with the Hewlett Packard Sonus 2500. As second step and shortly afterwards, the pacemakers were programmed to the "AAI" mode (septal stimulation). Echocardiographic measurements were taken again after 5 minutes of absolute rest. As third step, the pacemakers were programmed to the "DDT" mode (bifocal right ventricular stimulation), again performing echocardiography evaluation after 5 minutes of absolute rest (Figure 4). As step four, the pacemakers were programmed to the VVI mode with a further echocardiographic evaluation. The final programming was maintained according to the best echocardiographic result.

Parameters analyzed

The following variables were analyzed:

1. QRS duration in 3 simultaneous ECG leads (I, II, III)
2. Ejection fraction
3. Cardiac output
4. Mitral regurgitation area
5. Left atrium area

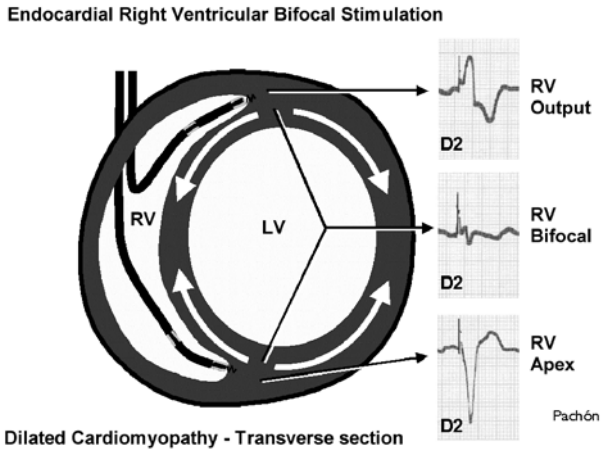

Figure 4. Scheme of 3 stimulation modes used in this study with the resultants commanded QRS.

Statistical analysis was performed using the analysis of variance and paired t-test for samples of equivalent variances. All hypotheses were 2-tailed and a p value of < 0.05 was considered as significant.

Results

Patient	AGE	SEX	EF/S	EF/C	EF/BF	CO/S	CO/C	CO/BF
1	37	M	9	13	18	2.26	2.35	2.42
2	76	M	27	32	35	3.7	3.58	3.99
3	44	M	17	18	27	2.39	1.99	2.97
4	66	F	34	27	35	3.65	3.19	3.93
5	38	M	32	28	37	3.2	2.9	3.9
Average	52.2		23.8	23.6	30.4	3.0	2.8	3.4
SD	17.7		10.6	7.8	7.9	0.7	0.6	0.7
P			0.4676		0.0024	0.0382		0.0114

Table 1. Echocardiographic Parameters. EF: ejection fraction; CO: cardiac output; S: septal stimulation; C: conventional stimulation (right ventricular apex); BF: bifocal stimulation between high septal region and right ventricular apex; SD: standard deviation; p: p-value (paired t-test comparing septal and bifocal right ventricular stimulation with the conventional stimulation).

Patient	LAA/S	LAA/C	LAA/BF	MR/S	MR/C	MR/BF	QRS/S	QRS/C	QRS/BF
1	32.3	49.4	36.4	24.1	31	20.2	185	220	140
2	29.2	34	27.1	12.1	14	7.1	200	190	155
3	18.1	22.1	18.3	8.5	7.5	6.3	175	240	160
4	7.11	12.8	3.93	5.6	10.7	3.48	220	200	160
5	18.2	24.1	19.1	7.6	12.5	5.5	182	210	140
Average	21.0	28.5	21.0	11.6	15.1	8.5	192.4	212.0	151.0
SD	10.1	13.9	12.0	7.4	9.2	6.7	17.9	19.2	10.2
p	0.0182		0.0049	0.0315		0.0063	0.275		0.003

Table 2. Continuation of table 1. LAA: left atria area (cm^2); MR: functional mitral regurgitation area (cm^2); QRS: length of the QRS complex measured in 3 simultaneous ECG leads (I, II, III).

Discussion

The aim of the current artificial heart stimulation besides correcting the heart rate is to obtain the best synchronization between the cardiac chambers for optimizing cardiac output and electrophysiological stability. In 1990, Hochleitner et al. studied 16 patients with dilated drug resistant cardiomyopathy and heart failure, who were treated with dual chamber pacing in absence of bradyarrhythmia [3]. In all patients, the AV interval was programmed to 100 ms. Their clinical performance and the echocardiographic measurements improved greatly in the early postoperative period. Apparently, dual chamber pacing programmed with a short AV delay could be a new exciting alternative for the treatment of heart failure in dilated cardiomyopathy. However, these results were not reproducable by other authors [4,5], or for the same group 2 years later. In spite of the apparent failure, Hochleitner demonstrated an important "potential hemodynamic benefit " of pacemakers in heart failure.

Considering short AV intervals was not clearly useful in the treatment of heart failure. There was more interest in "ventricular resynchronization" [6]. Mechanically, wide QRS (common in severe cardiomyopathy and in right ventricular pacing) is clearly less effective than narrow QRS [7,8]. Contractility is the more decreased, the more enlarged the QRS is. The activation of all the myocardial cells almost at the same time causes a synergic action with a contraction of great mechanical efficiency. However, in the pres-

ence of slow conduction, the contraction of a myocardial region is lessened by other areas, which are not contracted (Figure 2). When the heart is very dilated, this phenomenon increases in importance, thus contributing to the contractile dysfunction on top of the cardiomyopathy itself. Beside the systolic dysfunction, the enlargement of QRS provokes an increase in functional mitral regurgitation and diastolic dysfunction [9], reducing the ventricular filling time.

There are several studies in process, testing the viability and clinical usefulness of the "ventricular resynchronization", stimulating the right and left ventricles at the same time [10,11,12]. The left ventricular stimulation, however, encloses some technical difficulties. Endocardial approach has to be done by the coronary sinus and through heart veins or epicardial access by thoracotomy. The endocardial left ventricular stimulation through trans-septal puncture is not advisable due to the risk of systemic tromboembolism. Heart stimulation via the cardiac veins frequently encompasses difficulties in accessing the venous system and imposes additional problems as: need of a special lead for cardiac veins, long term stability of the lead, tendency to higher stimulation thresholds and phlebitis of heart veins. On the other hand, the epicardial stimulation classically has higher acute and chronic thresholds besides imposing the need of a thoracotomy, which is highly undesirable in patients with congestive heart failure in severe and definitive cardiomyopathy and therefore is of high surgical risk.

Due to these considerations, we decided to develop a new method of definitive right endocardial ventricular stimulation to obtain a more narrow QRS in dilated cardiomyopathy and a protocol for answering the following questions:

1. Is it possible to partially "resynchronize" the left ventricular myocardium by stimulating the right ventricle only?
2. Does the resulting "resynchronization degree" have a beneficial effect in cases of severe heart failure from dilated cardiomyopathy with functional mitral regurgitation?
3. Is the implantation technique safe, easy to do, of low risk and applicable to critical patients?

For bifocal right-ventricular stimulation, an AV sequencial DDD pacemaker was implanted (Figure 3). These connections allow stimulation at two points at the same time, programming the AV interval to 0 ms if available. Biotronik Dromos DR pacemaker has the following parameters available: 15 ms AV internal (shortest) and DDT mode stimulation (Figure 5).

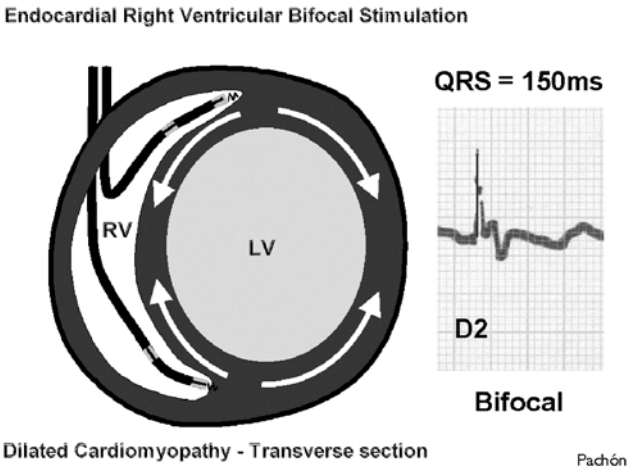

Figure 5. Scheme of the bifocal endocardial right ventricular stimulation resulting a narrow of QRS.

To avoid the risk of pacemaker syndrome (since we are stimulating only the ventricles), we decided to select only patients with formal indication of VVI pacing, that is, chronic atrial fibrillation with AV block. In addition, this model has the benefit of avoiding the undesirable random atrial contractions during the echocardiographic measurements.

Implantation technique

The implantations were done following the classical methodology of the endocardial dual chamber pacemakers. The first lead was preferably positioned far in the apex of the right ventricle. The second lead was positioned in the His bundle area, guided by the H potential and by anatomical elements. In four patients, due to the severe cardiomyopathy the H potential was difficult to locate and, in that case, the lead was positioned in the sub-pulmonary region. This position was easily obtained by entering the pulmonary artery, withdrawing the lead slowly, previously connected to the stimulator, until the ventricular capture was obtained. In that point the lead was firmly tightened using the active screw fixation mechanism. In all cases this lead was bipolar. The R wave, the stimulation threshold and the impedance measurements were obtained by conventional techniques. The first lead ("conventional")

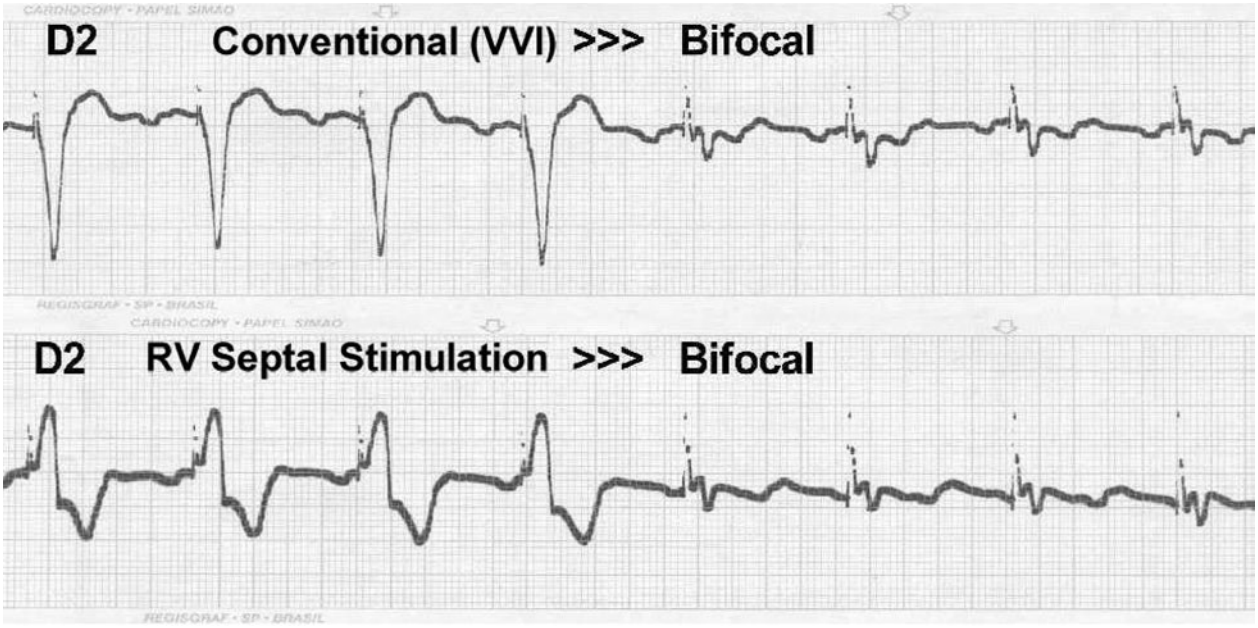

Figure 6. Impact of the right ventricular bifocal stimulation in the QRS narrowing. In this example the QRS width decreased from 240 ms with conventional pacing to 150 ms with bifocal stimulation. After 8 days the hemodynamic improvement provided conditions for cardioversion of chronic atrial fibrillation.

was connected to the ventricular output and the second lead("septal") to the atrial output in the pacemaker.

Programming the generator
After surgery the generators were programmed to the DDT mode for bifocal stimulation with an AV interval of 15ms. Pacing was programmed in unipolar, sensing in bipolar mode. The stimulation rates were selected between 60 and 65 ppm, according to individual clinical performance. Hysteresis was not programmed as all the patients presented with ventricular arrhythmia.

Programming the generator during echocardiographic evaluation
Maintaining the same stimulation rate and strictly the same patient position, the generators were programmed to VVI mode (classic conventional pacing), "AAI mode" (septal pacing) and "DDT mode" with an AV interval of 15 ms (bifocal pacing). Measurements were taken 5 minutes after mode change.

Narrowing the QRS
With bifocal stimulation the mean duration of the QRS was 151 ms (SD = 10.2) in other words, 61 ms narrower in relation to the mean QRS duration at conventional pacing (212 ms, SD = 19.2) (Figure 6 and Figure 7). This proved to be statistically significant, p = 0.003. Septal pacing alone also showed a more narrow QRS than conventional pacing, however, without statistical significance (Table 2).

Echocardiographic Parameters
Comparing conventional with the bifocal stimulation, all echocardiographic parameters presented significant improvement (Table 1 and 2). On average, the ejection fraction increased by 6.8% (p = 0.002), and the cardiac output increased by 0.6 l/min (p = 0.01). (Figure 8) In

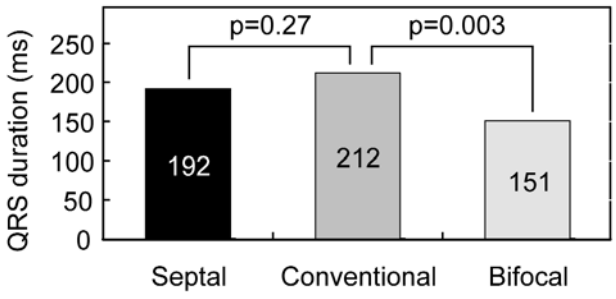

Figure 7. Graphic representation of the QRS duration changes according to the stimulation type. Significant narrowing of QRS is verified with the endocardial right ventricular bifocal stimulation.

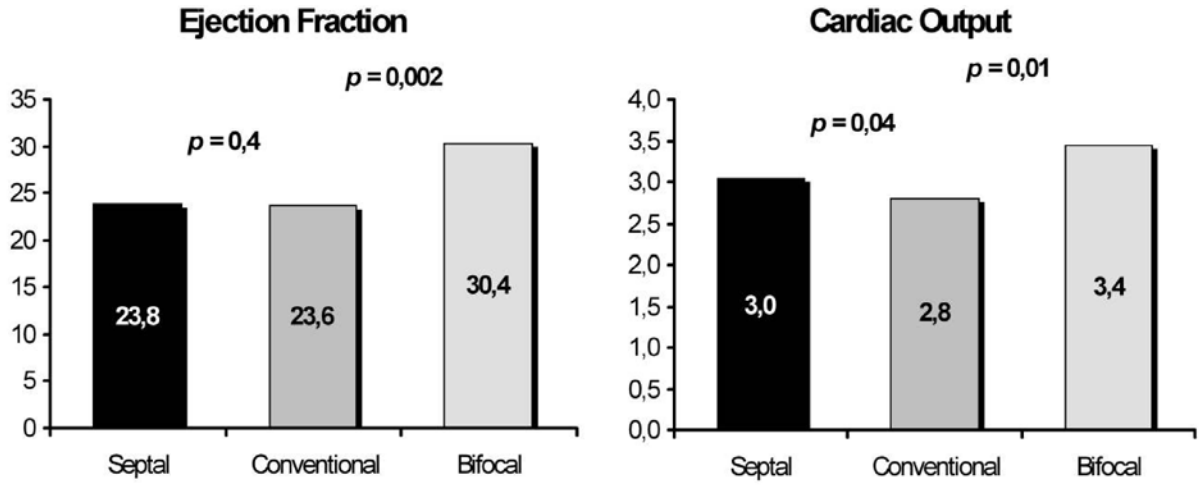

Figure 8. Comparison of the ejection fraction and of the cardiac output in the 3 stimulation modes.

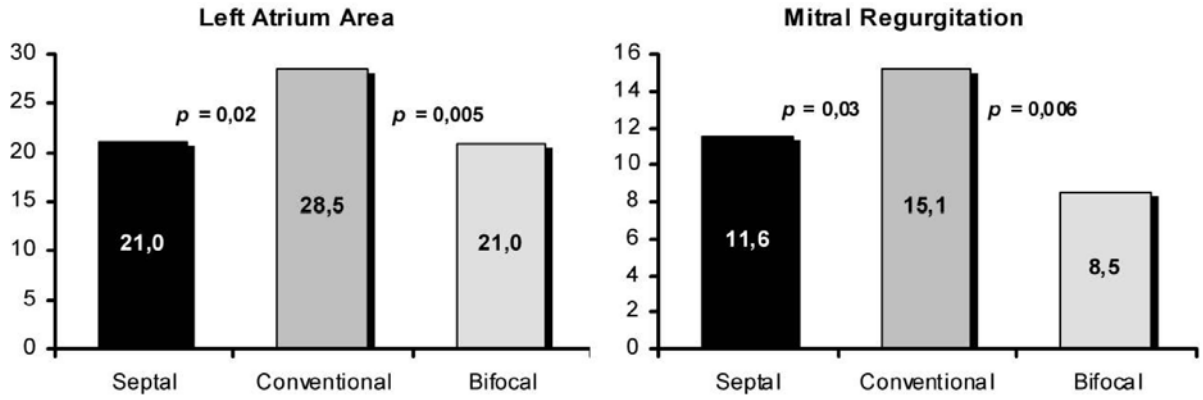

Figure 9. Comparison of the left atrial area and of the area of mitral regurgitation measured by the bidimensional echocardiography with Doppler in 3 stimulation modes.

the same way, there was a significant reduction in left atrial size (average 7.5 cm^2 ($p = 0.004$)) due to an evident reduction in the degree of functional mitral regurgitation. (Figure 9) The regurgitation area was reduced by a mean of 7.4 cm^2 ($p = 0.006$). The dynamic analysis in the bidimensional mode also showed clear improvement in contractility and more synergism. We believe, that this is the reason for mitral function improvement. (Figure 10)

Clinical evaluation

In short term (mean follow-up of 5.6 ± 1.1 months) there was a significant clinical improvement in all cases with improvements from NYHA class III and IV to class II. (Figure 11) The long term clinical follow up will be very important to evaluate the chronic outcome.

Conclusion

In this group of patients with severe dilated cardiomyopathy and functional mitral regurgitation, the conventional VVI pacing mode was the worst. Echocardiographic and clinical evaluation during different stimulation mode tests proved, that bifocal stimulation, which was easily obtained in the right ventricle, was significantly superior to monofocal pacing (Figure 12) A good and evident "intra-ventricular resynchronization" with better contractility caused by a significant QRS duration reduction was achieved. The implantation technique was simple and did not cause any increase in the surgical risk. Finally, considering that AV synchrony contributes significantly to improving heart failure, the stimulation method shown in Figure 13 should be bene-

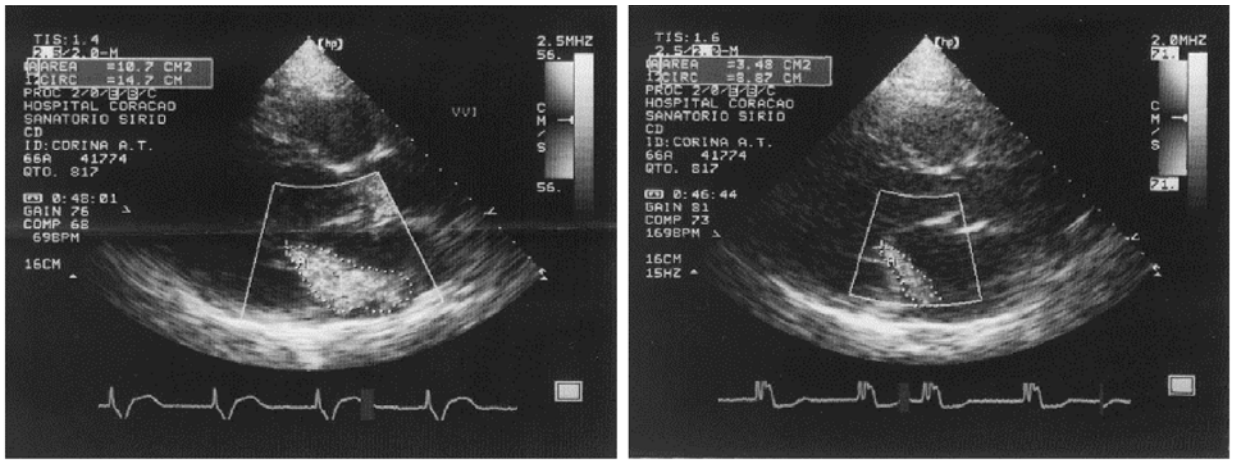

Figure 10. Bidimensional echocardiogram showing significant reduction of the functional mitral regurgitation with the right ventricular bifocal stimulation.

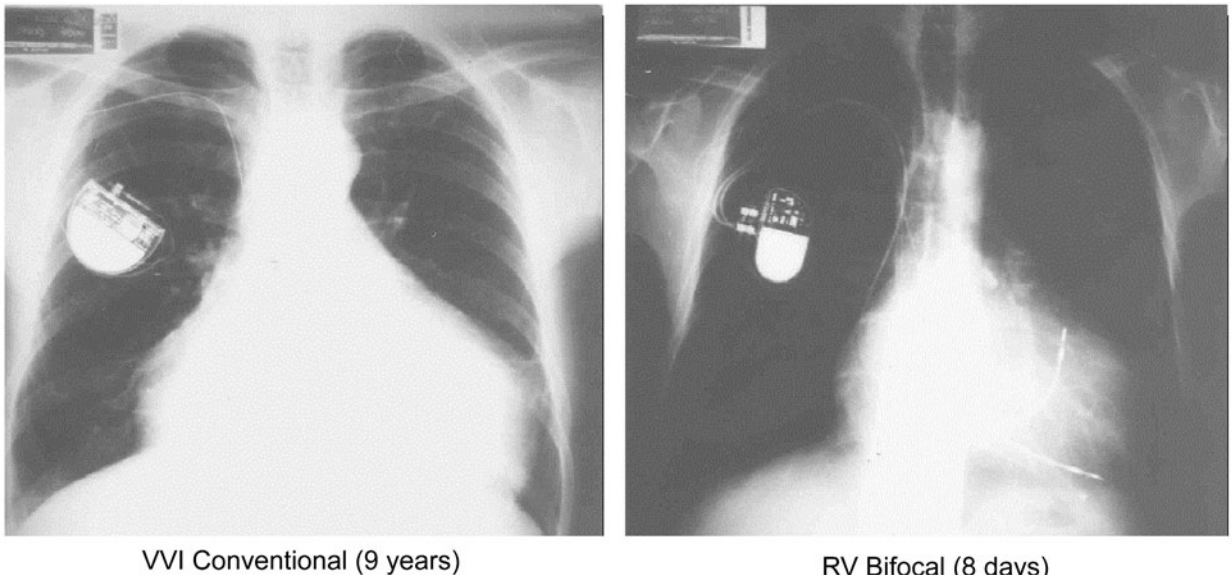

Figure 11. Thorax X-rays obtained in the same patient, the first with nine years of evolution with conventional ventricular pacing and the second, after 8 days of bifocal ventricular stimulation. There was an evident reduction in heart size. In this case the old VVI pacemaker was changed due to battery depletion and replaced by a bifocal system.

ficial in cases with severe dilated cardiomyopathy, functional mitral insufficiency and AV block in the absence of atrial fibrillation.

Critical considerations

To obtain definitive information, the number of patients for this study was reduced. However, each patient was his own control, which allows results from a smaller number of cases. Our initial objective consisted in finding trends and study models that can be useful in new extensive projects. We believe that the positive point of this study was the proposed model. This model used the VVIR mode without harming the patient as all patients had chronic atrial fibrillation. In this way and without any technical barrier, we could make use of the dual chamber pacemaker to obtain undoubtful and safe long term information for multisite ventricular pacing. The patients took benefit from a safer way of pacing by stimulating two areas in the

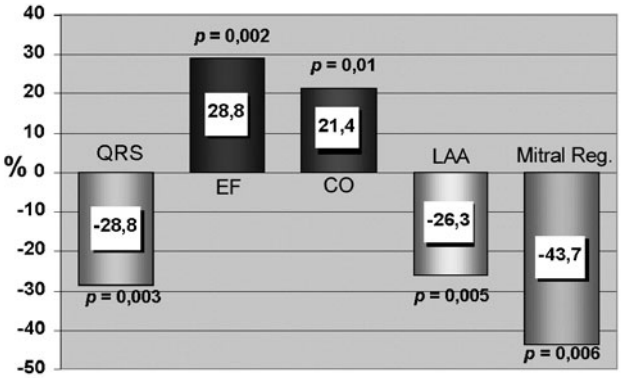

Figure 12. Graphic representation in percentile modifications of the studied parameters, comparing conventional with bifocal stimulation. EF: ejection fraction; CO: cardiac output; LAA: left atrium area.

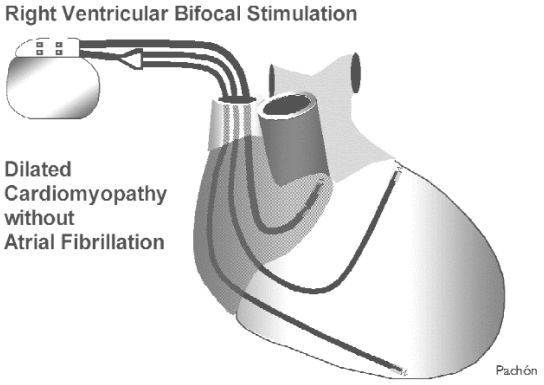

Figure 13. Stimulation suggested by the authors to take advantage of the benefit of the bifocal right ventricular endocardial pacing in patient without atrial fibrillation. In the ventricles may be used unipolar leads, of the new generation, much finer than the current ones.

same chamber. Furthermore, the narrowing of the QRS proved us of pacing in a more physiologic way. In fact, these arguments convinced us to introduce this system into our clinical practice for cases of AV nodal ablation and refractory atrial tachyarrhythmia. In case of exit block in one lead there will always be a backup lead. The main aspect, however, is that this model allows us to evaluate the 3 stimulation modes in the same patient eliminating all inter-individual variables, solving the problem of obtaining equivalent pt control groups. The comparison of echocardiographic variables, changing the ventricular stimulation mode only by non-invasive programming and without any change in pt's position, heart frequency, respiratory frequency, physical activity, venous return, sympathetic tone or psychological condition, comprises a valuable method capable to evaluate minimum hemodynamic modifications. Another critical aspect is the control only by echocardiogram in the acute phase. This is justified by the fact that our initial objective was to find clear and immediate evidences that justified the accomplishment of a larger number of implants without any patient damage. The patients are being followed up to evaluate the long term benefit. Right ventricular bifocal stimulation seems to be a very good alternative to the technically much more difficult left sided multisite pacing.

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