Ventricular Evoked Response in Patients with Hypertrophic Obstructive Cardiomyopathy Treated with DDD Pacing

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Objective - *To assess the changes in ventricular evoked responses (VER) produced by the decrease in left ventricular outflow tract gradient (LVOTG) in patients with hypertrophic obstructive cardiomyopathy (HOCM) treated with dual-chamber (DDD) pacing.*

Methods - *A pulse generator Physios CTM (Biotronik, Germany) was implanted in 9 patients with severe drug-refractory HOCM. After implantation, the following conditions were assessed: 1) Baseline evaluation: different AV delay (ranging from 150ms to 50 ms) were sequentially programmed during 5 to 10 minutes, and the LVOTG (as determined by Doppler echocardiography) and VER recorded; 2) standard evaluation, when the best AV delay (resulting in the lowest LVOTG) programmed at the initial evaluation was maintained so that its effect on VER and LVOTG could be assessed during each chronic pacing evaluation.*

Results - *LVOTG decreased after DDD pacing, with a mean value of 59 ± 24 mmHg after dual chamber pacemaker, which was significantly less than the gradient before pacing (98 + 22mmHg). An AV delay >100ms produced a significantly lower decrease in VER depolarization duration (VER_{DD}) when compared to an AV delay £100ms. Linear regression analyses showed a significant correlation between the LVOTG values and the magnitude of VER (r=0.69; p<0.05) in the 9 studied patients.*

Conclusion - *The telemetry obtained intramyocardial electrogram is a sensitive means to assess left ventricular dynamics in patients with HOCM treated with DDD pacing.*

Key words: obstructive hypertrophic cardiomyopathy, DDD pacing intracardiac electrogram

DDD pacing has been recently recognized as an alternative therapy to reduce left ventricular outflow tract gradient (LVOTG) in patients with hypertrophic obstructive cardiomyopathy (HOMC)[1]. Although some controversies still remains[2], most reports show the effectiveness of this technique to reduce (or even to eliminate) LVOTG[3], improve clinical status[4] and to increase survival[5] in patients with HOCM. Doppler echocardiography, a non-invasive examination available in most cardiac clinics, is routinely used to evaluate patients with DDD pacing. Not infrequently, however, it is difficult for the patient to come to the routine evaluation when serial or extra programming are required. An alternative means of evaluating pacing would thus be highly useful.

The summation of action potentials of a group of myocardial fibers around a lead is known as an intramyocardial electrogram (IMEG), a signal which is better recorded when fractally coated intramyocardial leads[7] are used, and which is modified according to the status of myocardial fibers(such as under the influence of inotropic or chronotropic drugs)[8] or inflammatory responses (episodes of rejection after heart transplantation)[9], and recorded with an implantable pacemaker for posterior data processing analysis[10]. The sequential analysis of an IMEG can identify myocardial modifications, and accordingly, it has been used for monitoring rejection in patients post heart transplantation[11]. This system, known as Cardiac Heart Acute Rejection Monitor (CHARM)[9,10] has disclosed substantial prospects for a better management of heart transplant patients.

The aim of this study is to present a novel system of DDD pacing suitable for obtaining intramyocardial electrograms in patients with HOCM in an attempt to correlate possible benefits resulting from the decrease in left ventricular obstruction (as assessed by Doppler echocardiography) with recordings of intracardiac electrogram (recorded as ventricular evoked response - VER).

Methods

From September, 97, to October, 98, nine patients with

HOCM were submitted to an atrioventricular (AV) sequential DDD pacemaker implantation, model Physios (Biotronik, Germany). There were 3 males and 6 females, age ranging from 14 to 63 (mean 59) years. All patients had severe drug-refractory symptoms (syncope, effort angina, and dyspnea). Six of them were in New York Heart Association (NYHA) functional class (FC) II for dyspnea, while the others were in FC III. Current therapy consisted of calcium antagonists and β-blocker or the association of the two. All patients had been under a regular follow-up, with routine Doppler echocardiography, in which a progressive increase in the LVOTG could be observed. Mean LVOTG measured prior to pacemaker implantation was 92±22mmHg. Clinical characteristics of the patients are shown on table I.

DDD pacemaker lead was transvenously implanted under local anesthesia. Briefly, after venous puncture (cephalic or subclavian vein), atrial and ventricular leads were advanced up to the right atrium (RA) under fluoroscopy. The ventricular lead (TIR 60 BP or LX 60 BP/ Biotronik, Germany) was positioned far from the tricuspid valve at the right ventricular apex. The atrial lead (YP 60 BP or JP 60 BP/ Biotronik, Germany) was positioned inside the right atrial appendage. Electrophysiologic measurements were performed and proper lead insertion was undertaken after respiratory maneuvers. The leads were thus firmly fixed at the site of venous access and connected to a DDD pulse generator Physios CMT (Biotronik, Germany), the generator inserted into a subcutaneous pouch at the subpectoral region and the incision was closed. During implantation, the generator was programmed to VVI mode to a basic rate of 40 or 50 beats per minute, in order to assure it would remain inhibited. Patients were discharged from hospital on the second day after the surgery; cardiovascular medication was unchanged.

DDD mode was programmed on the 10th to 12th day of pacemaker implantation, with an adequate pulse frequency capable of consistently capturing the atrium and maintaining a short AV delay, in order to obtain the lowest possible gradient (as recorded by Doppler echocardiography).

After programming the pacemaker, the IMEG was recorded by telemetry as VER, that is, the initial intracavitary electrogram subsequent to pacemaker stimulation of the ventricle. At the same time, LVOTG was evaluated and recorded by Doppler echocardiography. The evaluation procedures used were twofold: pacing evaluation: pacemaker was successively programmed to all AV delays available, whether long (150 to 120ms), medium (100ms) or short (<100ms, usually 75 or 50ms) during 5 to 10 minutes; chronic evaluation - the AV delay producing the lowest LVOTG was used for the final pacing programming and maintained for the following monthly evaluations. During each evaluation, the LVOTG and the VER were recorded with the previously programmed AV delay. If during that evaluation a new AV delay was considered to be more appropriate, it would be maintained for chronic pacing.

A specific software in a portable laptop base was used to program the pacemaker and record the electric signals, with each signal acquisition lasting for one minute. After adequate signals were recorded, they were sent to the central data processing site in Graz, Austria, via the Internet, along with the recordings of the corresponding LVOTG. The methodology used to analyze the VER has already been published elsewhere [12,13] (fig. 1).

Signal analyses were automatically performed, with average and representative recordings of VER, as well as the parameters related to each recording. The representative parameters were VER depolarization duration (VER_{DD}), and the negative VER area (VER_{NA}) (fig. 2). Analyses of the signals were sent back in 24 hours (fig. 3).

Monthly evaluations were performed up to the 6th month of pacemaker implantation, followed by a 6-month interval evaluation. Each evaluation consisted of clinical examination, Doppler echocardiography, pacemaker programming to different AV delays and VER recordings, as previously remarked. The way to obtain the signal and the time of the examination was preserved for each patient, to maintain the same interval between the ingestion of medication and the exam. In case of complications associated with clinical deterioration, inadequate medication or pacemaker dysfunction, additional evaluations could be undertaken. The reason for the extra evaluation and any management modifications were invariably recorded.

LVOTG values obtained at the initial pacing program-

| Table I - Clinical characteristics of 9 patients with hypertrophic obstructive cardiomyopathy (HOCM) during pacemaker implantation, and the maximum left ventricular outflow tract gradient, prior to and after pacemaker programming to DDD mode during the final evaluation (LVOTG)						
Sex	Age	Main symptom	Medication	LVOTG (mmHg)		
				Initial	After procedure	Final
Female	41	Angina	Propranolol	124	76	45
Male	47	Dyspnea	Atenolol, disopyramide	117	81	46
Female	63	Dyspnea	Propranolol, disopiramide	83	44	14
Female	59	Fatigue	Atenolol, disopyramide	121	100	77
Female	63	Fatigue	Propranolol	64	32	11
Male	14	Dizziness	Verapamil	105	74	-
Female	44	Fatigue	Propranolol, verapamil	90	46	27
Male	44	Angina	Atenolol	70	29	-
Female	51	Dizziness	Propranolol, verapamil	110	53	-
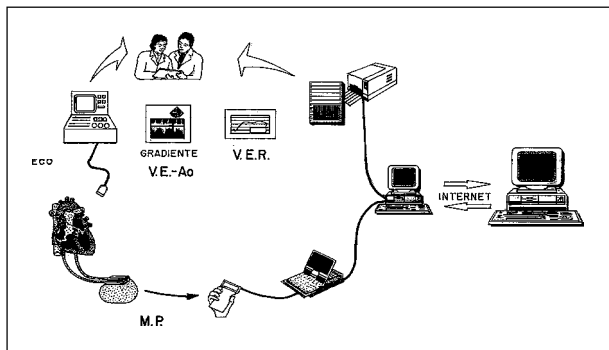
Fig. 1 - Procedures used during the study: Doppler echocardiography to record maximum left ventricular outflow tract gradient (LVOTG) and the acquisition, recording and analyzing intramyocardial electrogram, as ventricular evoked response (VER).

ming were recorded and analyzed with a Student t test in order to identify the degree of difference significance.

To identify the influence of AV delay on the ventricular depolarization duration (VER_{DD}), mean values of VER_{DD} were grouped together according to AV delay classification. A paired Student t test was used to assess the difference among the distinct AV delay groups (short, medium and long). Linear regression analyses was used to test the correlation between the magnitude of VER and the degree of LVOT obstruction. P values <0.05 were considered to be of statistical significance.

Results

Pacemakers were programmed to DDD mode, at a rate of 70 to 75 beats per minute and an AV delay ranging from 50 to 100ms, resulting in a decrease in LVOTG from 98 ± 22 mmHg to 59 ± 24mmHg (p<0.05). During this period, 20 evaluations were performed in 9 patients, yet 3 patients had only one evaluation performed. In the former, LVOTG measured during the final evaluation showed a value even lower than that recorded at the initial pacing evaluation (table I).
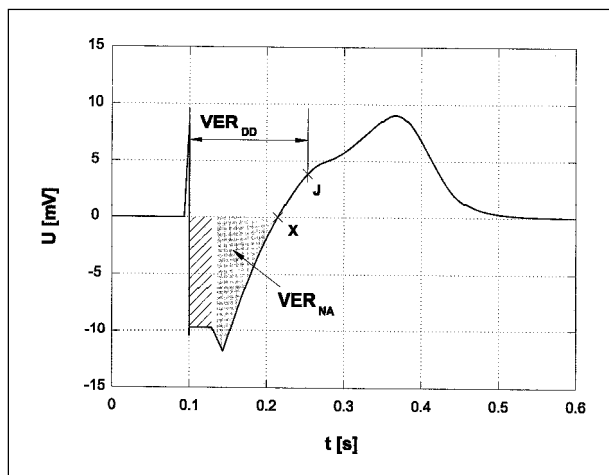
During the 20 follow-up evaluations, it was observed that long AV delays (such as 120 and 150ms) were associated with higher LVOTG than medium (100ms) or short (75 and 50ms) AV delays. Accordingly, VER_{DD} also displayed modifications in most evaluations, since it showed a decrease with long AV delays compared to medium or short AV delays (fig. 4).

Linear regression analyses showed a significant correlation between LVOTG and VER_{NA} (r=0.69, p<0.05) (fig. 5).

It should be remarked that during chronic evaluations, patients with reduced LVOTG due to chronic stimulation (LVOTG <30mmHg), and those in whom AV delay modification did not decrease left ventricular obstruction, VER changes were insignificant.

Discussion

It has been reported that fractally coated leads result in better IMEG signals [7]. The sensitivity of a fractally coated lead, along with proper filtration and amplification of action potential around myocardial fibers allow a better defined electric signal which can be recorded with an implantable pacemaker [10]. The intrinsic cardiac signal is called a spontaneous action potential, whereas the one resulting from a pacemaker is called evoked action potential. When it is originated in the ventricle it is called ventricular evoked potential (VER). These electrical signals can show modifications in myocardial fibers resulting from inotropic drugs or chronotropic interventions [13,14].

In transplanted hearts with acute graft rejection confirmed by endomyocardial biopsy, a correlation has been shown between the IMEG and the degree of inflammatory process. IMEG has thus been accepted as an alternative means to grade severity of rejection episodes [14]. A system called CHARM, consisting of a DDD pacemaker, a programmer, computers and a central analyzing site (transmitted via the Internet) is presently under clinical use. This system is likely to offer a rapid, non-invasive and accurate means of detecting acute rejection in heart transplant patients [11], thus permitting a more effective treatment of these episodes.

Considering the Physios pacemaker is capable of recording IMEG, and the recorded signals can be subse-
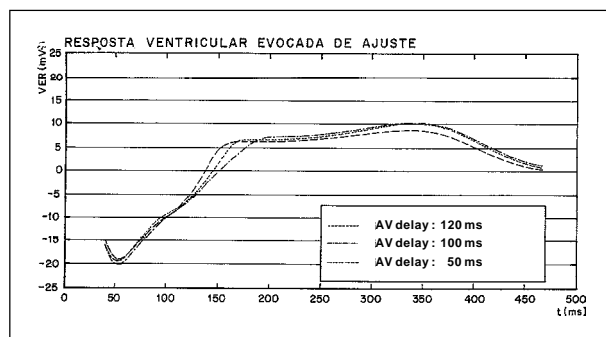

Fig. 2 - Variables used to assess modifications on ventricular evoked response: VER_{DD}, representing duration of ventricular repolarization, VER_{NA}, representing signal magnitude.

Fig. 3 - Variations on ventricular evoked response (VER) and on left ventricular outflow tract gradient (LVOTG) recorded during acute modifications of AV delay.
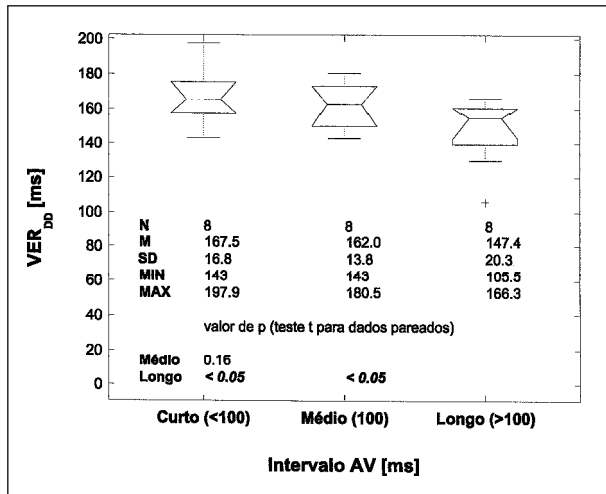
Fig. 4 - Mean value of VER_{DD} for distinct AV delays, observed in 8 initial evaluations (or acute evaluations). Please note that ventricular depolarization period (VER_{DD}) was significantly increased for a shorter AV delay (<100ms), when compared with a medium AV delay (100ms) or a longer one (>100ms).
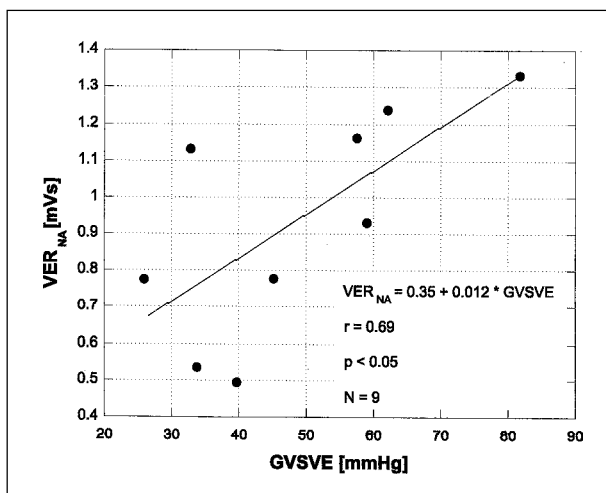

Fig. 5 - Graph showing the significant correlation between VER magnitude (VER_{NA}) and maximum left ventricular outflow tract gradient (LVOTG).

quently analyzed, we attempted to use this pacemaker in a disease that required the use of a universal pacemaker, and further, changes in pacing programming, for instance AV delay or heart rate modifications, were likely to produce changes in myocardial conditions, such as left ventricular overload and hypertrophy. Since HOCM is a disease in which sequential pacing can reduce LVOTG [1,3-5], it was chosen as an suitable indication to examine this system. The benefit of cardiac stimulation in HOCM can be effectively shown by Doppler echocardiography [6], a non-invasive method also used for pacemaker programming and monitoring LVOTG changes.

In the present study, a potential correlation between VER amplitude and morphology modification and variations of maximum LVOTG was assessed, not only during the initial evaluation (acute AV delay modifications) but also during chronic evaluations (an AV delay maintained for a long period).

No ethical considerations hindered the present investigation, since: 1) the parameters used to program the DDD pacemaker were not distinct from those currently used for HOCM therapy; 2) implantation technique and follow-up were not unlike the usual; 3) echocardiographic evaluations were undertaken in shorter intervals than the usual, resulting in a more adequate pacing programming; 4) the acquisition of VER was accomplished by telemetry, which does not offer any risks for the patient.

The methodology used for obtaining IMEG is highly sensitive, considering that the electrical signals represent the action potentials of myocardial cells [8]. VER can be influenced by various acute or chronic cardiac interventions [8,10,13], and these influences must be minimized during the study. A strict protocol was thus followed, including continuing drug therapy administered (or registering any modifications), the same time and place for echocardiographic examination, and whenever possible, the same group of investigators.

VER was the only IMEG used, from two available forms. Patients with HOCM require atrial and ventricular pacing in order to obtain optimum hemodynamic benefits; using spontaneous action potential would result in loss of ventricular stimulation and consequently, LVOTG changes. Using VER permits a predetermined frequency to be used when obtaining the signal, thus eliminating one the variables capable of changing IMEG morphology [13,16,17].

During initial evaluation, AV delay variation resulted in a decrease in LVOTG in most patients. The signal (and the LVOTG) was obtained 5 minutes after pacemaker programming. At first it was decided to prolong the interval during signal programming and acquisition to 10 minutes, assuming that in some patients the lead might be situated further from the right ventricular apex, left or interventricular septum, and consequently the hemodynamic benefit determined by AV delay modification (that is, the decrease in LVOTG) would take longer to influence right ventricular dynamics. Against that hypothesis is the idea that VER would translate global modifications on left ventricular geometry thus reflecting instantaneous left ventricular dynamics, even when the lead is distant from that chamber. Prolonging adjustment periods has not disclosed any variations among the comparable signals, and they have further increased evaluation time, so that a 5 minute time after programming the pacemaker is considered satisfactory for obtaining VER.

The selection of the adequate AV delay during follow-up evaluations was modified along the study, but the criteria used to define long (150 or 120ms) medium (100) or short value (75 or 50ms) was always maintained. On the other hand, it was noted that a lengthy echocardiographic examination (resulting from a complete comprehensive study, followed by repeated generator programming and LVOTG evaluations and VER recordings) caused discomfort for the patient and was not practical, since they could induce result variations. Alternatively, minor variations of AV delay, mainly ranging from 100ms to 75ms and from 75ms to 50ms resulted in insignificant changes in LVOTG, and conse-

quently on VER. Thus, higher ranges of AV delay changes (such as from 150ms, 100ms and 50ms) resulted in more marked changes of LVOTG (as predictable from the accuracy of the evaluation method) and VER.

VER modifications due to AV delay modifications showed 2 distinct patterns: 1) they were particularly striking in patients in whom a decrease in AV delay resulted in a significant reduction of LVOTG. The corresponding VER showed a higher duration of depolarization, as seen in figure 4; 2) small variations in LVOTG, as shown in patients with a very favorable response to DDD pacing and who previously presented a maximum systolic gradient of 30 mmHg, resulted in minor VER modifications.

Theses findings support the idea that the VER_{DD} can be used to help select optimum AV delay (AV delay producing the lowest LVOTG).

Serial evaluations along the study have shown that a progressive decrease in LVOTG occurred in all patients. Similarly, AV delay variation, patients who showed marked modification in LVOTG also disclosed important modification in VER. In one of the patients, it was observed that an inotropic-negative drug (calcium antagonist) resulted

in a higher decrease in LVOTG, together with a modification in VER.

The correlation observed between the LVOTG and the magnitude of electrical activity of the heart (determined by the VER_{NA}) can have several explanations, yet to be proven. A modification in left ventricular shape or a decrease in wall stress due to the decrease in interventricular pressure might be a possible explanation, however these hypothesis were not assessed in the present study.

Although the present study is limited due to the small number of patients and evaluations, our findings suggest that VER is sensitive enough means to detect hemodynamic changes resulting from AV delay modifications in patients with HOCM. In case these findings are confirmed by larger studies, non-invasive recordings of VER through pacemaker telemetry could become a useful method of programming optimum AV delay and monitoring DDD pacing as a therapy in patients with HOCM.

Acknowledgment

References

1. Futterman LG, Lemberg L. New indications for dual chamber pacing: hypertrophic and dilated cardiomyopathy. Amer J Critical Care 1995; 4: 82-7

2. Nishnamura RA, Tursty JM, Hayes DL, et al. Dual-chamber pacing for hypertrophic obstructive cardiomyopathy: a randomized, doble-blind, crossover study. J Am Coll Cardiol 1997; 29: 345-41.

3. Sadoul N, Simon JP, de Chillou C, et al. Long-term dual-chamber pacing improves hemodynamic function in patients with obstructive hypertrophic cardiomyopathy. PACE 1993; 16(5-parte 2): 1120.

4. Fazanapazir L, Cannon RO, Tripodi D, Panza JA. Impact of dual-chamber permanent pacing in patients with obstructive hypertrophic cardiomyopathy with symptoms refractory to verapamil and beta-adrenergic blocker therapy. Circulation 1992; 85: 2149-61.

5. Fananapazir L, Epstein ND, Curiel RV, Panza JA, Tripodi D, McAreavey D. Long-term results of dual-chamber (DDD) pacing in obstructive hypertrophic cardiomyopathy. Circulation 1994; 90: 2731-42 .

6. Shah PM, Gramiak R, Adelman AG, Wigle ED. Echocardiographic assessesment of the effects of surgery and propranolol on the dynamics of outlow obstruction in hupertrophic subaortic stenosis. Circulation 1972;45:516- 21.

7. Wetzig, T, Fröhlich R, Bolz A, et al. Messung und Analyse monophasischer Aktionspotentiale mittels fracktal beschichteter Elektroden - Teil II. Biomed Technik 1995; 40: 160-7.

8. Yan S, Blomström-Lundqvist C, Olsson SB. Monophasic action potentials: Concepts to practical applications. J Cardiovasc Electrophysiol 1994;3:287-308.

9. Hutten H, Schreier G, Auer T, Iberer F, Tscheliessnigg KH, Schaldach M. Analysis of epimyocardial ECGs from transplanted hearts. Biotronik Review 1994; 5: 1-3.

10. Auer T, Schreier G, Hutten H, Tscheliessnigg KH, Iberer F, Schaldach M. Analysis of the ventricular evoked response for use in cardiac transplanting monitoring. Cardiac Pacing. Anais do EUROPACE 97 - 7ᵗʰ Sympsium on Cardiac Pacing. (Atenas, Grécia). Bolonha. Itália: Monduzzi Editore SPA, 1995: 495-9.

11. Brofman PRS, Lucchese FA, Leães PE, et al. Monitoração não-invasiva do paciente após tranplante cardíaco: Novos aspectos metodológicos. Progress in Biomedical Research 1997; 2(supl. B): 69-75.

12. Hutten H, Schaldach M. Automatic pacing becames a technical reality. Biomedizinische Technik 1996; 41: 1-11.

13. Wetzig T, Bolz A, Hardt R, et al. Validation of monophasic action potentials for detecting neurohomral influences using special DDD-pacemakers. Biotronik Review 1995; 6: 1-3.

14. Eick RET, Whalley, DW, Rasmussen HH. Connections: Heart disease, cellular electrophysiology, and ion channels. FASEB-Journal 1992; 5: 2568-80.

15. Billing ME (chaiman da International Society for Heart Transplantation). A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart Rejection Group Study. J Heart Transplantation 1990; 9: 587-93.

16. Hardman SMC, Young GE, Walker T, Biggs WA, Seed MIM, Noble A. A multielectrode catheter for simulanous pacing and registration of endocardial monophasic action potential. Erop JCPE 1991; 2: 75-82.

17. Schereier G, Hutten H. Remote intramyocardial electrogram analysis for noninvasive monitoring after heart transplantation. Med Biol Eng Comput 1996; 34: 205-6.