The Ventricular Evoked Response in Patients Paced for Hypertrophic Obstructive Cardiomyopathy-Initial Results

J.R.M. SANT'ANNA, R. PRATI, R. KALIL, P.R. PRATES, I.A. NESRALLA
Instituto de Cardiologia do Rio Grande do Su/ F.U.C., Porto Alegre, Brazil

G. SCHREIER, P. KASTNER, H. HUTTEN
Cortronik GmbH, Graz, Austria

M. SCHALDACH
Department of Biomedical Engineering, University of Erlangen-Nuremberg, Erlangen, Germany

Summary

This study examined a correlation between changes of the ventricular evoked response and the maximum systolic pressure gradient at the left ventricular outflow tract. The beneficial effects of DDD pacing in 9 patients (6 female, 3 male) with hypertrophic obstructive cardiomyopathy (HOCM) were also evaluated. In the course of 20 follow-up, the left ventricular outflow tract pressure gradients (as monitored by echocardiography) and ventricular evoked responses were recorded simultaneously at different atrioventricular intervals. The left ventricular outflow tract pressure gradient decreased from a pre-pacemaker implant value of 98 ± 22 mmHg to 59 ± 24 mmHg ($p < 0.01$). Atrioventricular intervals >100 ms resulted in significantly reduced ventricular evoked response depolarization durations as compared to shorter intervals ($p < 0.05$), indicating a decreasing degree of ventricular capture with increasing atrioventricular intervals. Degrees of ventricular capture < 95% were found to be associated with significantly higher pressure gradient values (71 ± 25 mmHg versus 58 ± 28 mmHg, $p < 0.001$). Regression analysis revealed a significant correlation between the average pressure gradient values and the average magnitude of the ventricular evoked response ($r = 0.69$, $p < 0.05$). The study also indicated that dual-chamber pacing may be an effective therapy to reduce the outflow tract obstruction in HOCM patients.

Key Words

Hypertrophic obstructive cardiomyopathy, pacemaker telemetry, AV interval optimization, intracardiac electrogram, ventricular evoked response

Introduction

Dual-chamber pacing with shortened atrioventricular intervals (AVI) has been accepted as an effective therapy to reduce the left ventricular outflow tract obstruction in patients with hypertrophic obstructive cardiomyopathy (HOCM) [1]. Although one investigation failed to demonstrate such benefit [2], most investigations have demonstrated that pacing reduces or even eliminates the outflow tract obstruction [3], improves the clinical condition [4] or even prolongs survival [5] of patients with HOCM. Doppler echocardiography is used to examine HOCM patients periodically and to help in the adjustment of their pacemakers [6]. Available in most medical centers, this non-invasive technique is expensive, requires special skills and is time-consuming, particularly in case of mulitiple pacemaker adjustments in the same patient. For an improved therapy management, an objective, frequently applicable, low-cost and easy-to-use technique to evaluate the response to DDD pacemaker therapy would be useful. The ultimate solution would be a pacemaker capable of adjusting its pacing parameters automatically to account for different cardiac states under the varying conditions of daily life activities.

A special telemetric dual-chamber pacemaker allows non-invasive recording of intracardiac electrograms (IEGM). The IEGM reflects the electrical activity of the myocardium and contains information about the state of the heart. The ventricular evoked response (VER) is defined as the answer of the myocardium to a pacing stimulus. Fractal coated pacing leads allow the VER to be recorded with the same electrode used to stimulate and to sense the signal [7]. The VER has been shown to reflect changes in the state of the heart, e.g., the influence of inotropic or chronotropic drugs [8] as well as pathological conditions like rejection episodes in patients after heart transplantation [9,10,11].

The objective of this work has been to investigate the behavior of the VER in HOCM patients and to find out whether this signal can be utilized to guide AVI optimization and to monitor the benefits of pacemaker therapy in patients paced for HOCM.

Materials and Methods

Patients

The criteria for inclusion of a patient into the present investigation were:

- diagnosis of HOCM,
- symptoms unresponsive to pharmacological therapy,
- progressive outflow tract obstruction and a maximum systolic pressure gradient at the left ventricular outflow tract (LVOTG) higher than 50 mmHg,
- pacemaker implant at our institution, and
- informed consent to participate in the study.

Between September 1997 and October 1998, 9 patients (6 female, 3 male) met the inclusion criteria. Age at implant was 47 ± 15 years (range: 14 - 63). Prior to pacemaker therapy, the patients presented symptoms such as syncope, dyspnea, angina and tiredness during exercise that were unresponsive to pharmacological therapy (β-blockers, calcium antagonists). All patients had periodical medical and echocardiographic evaluations and a progressive increase in LVOTG had been identified.

Pacemaker implantation

Dual-chamber pacemakers with wide-band IEGM telemetry (0.3 - 200 Hz) and fractal coated ventricular (TIR 60 BP or LX 60 BP, BIOTRONIK) and atrial (YB 60 BP or LX 60 BP, BIOTRONIK) electrodes were implanted using the transvenous approach. The ventricular lead was positioned near the right ventricular apex, as far as possible from the tricuspid valve. The atrial lead was positioned in the left atrial appendix. Electrophysiologic evaluation was performed, and the patients were asked to perform respiratory maneuvers to ensure adequate fixation of the electrodes. Subsequently, the electrodes were fixed in the venous access and connected to the pulse generator (Physios CTM 01, BIOTRONIK) which was introduced into the subcutaneous tissue and the incision was sutured. Prior to implantation, the pulse generator was programmed to the VVI mode with a pacing frequency of 40 or 50 ppm, to achieve inhibition. Hospital discharge occurred two days after pacemaker implantation and medication prescriptions were maintained.

Follow-up

Each follow-up consisted of clinical and echocardiographic evaluations, pacemaker programming and IEGM recordings at different AVI. The investigator, technique and time of the day were the same for each patient.

The first follow-up occurred 10 to 12 days after implantation. The pacemaker was programmed to the DDD mode and to a pacing frequency high enough to achieve AV sequential pacing. Further evaluations have been scheduled in monthly intervals during the first six postoperative months and in extended intervals (three to six months) thereafter. Additional evaluations were performed when necessary to verify the pacemaker program or to adjust medication.

During each follow-up, the pacemaker was successively programmed to various AVI with at least one value out of each of the following three AVI classes:

1. Short: < 100 ms (50/75 ms),
2. Medium: 100 ms,
3. Long: > 100 ms (120/150 ms).

To reach steady state conditions, the IEGM was recorded five to ten minutes after each AVI modification for a period of one minute using the appropriate pacemaker programming and IEGM recording system (SWD/SWM 1000, BIOTRONIK). Parallel to IEGM acquisition, the LVOTG was evaluated and registered by echocardiography. At the end of each follow-up, the pacemaker was programmed with the AVI associated with the lowest LVOTG. This setting was maintained until the next evaluation.

Signal analysis

Figure 1 illustrates the IEGM processing concept used in the present and earlier studies [9,18]. After IEGM recording the signals were sent via the Internet to the IEGM analysis center in Graz, Austria, for processing. Signal analysis was performed automatically and provided averaged, representative VER as well as para-

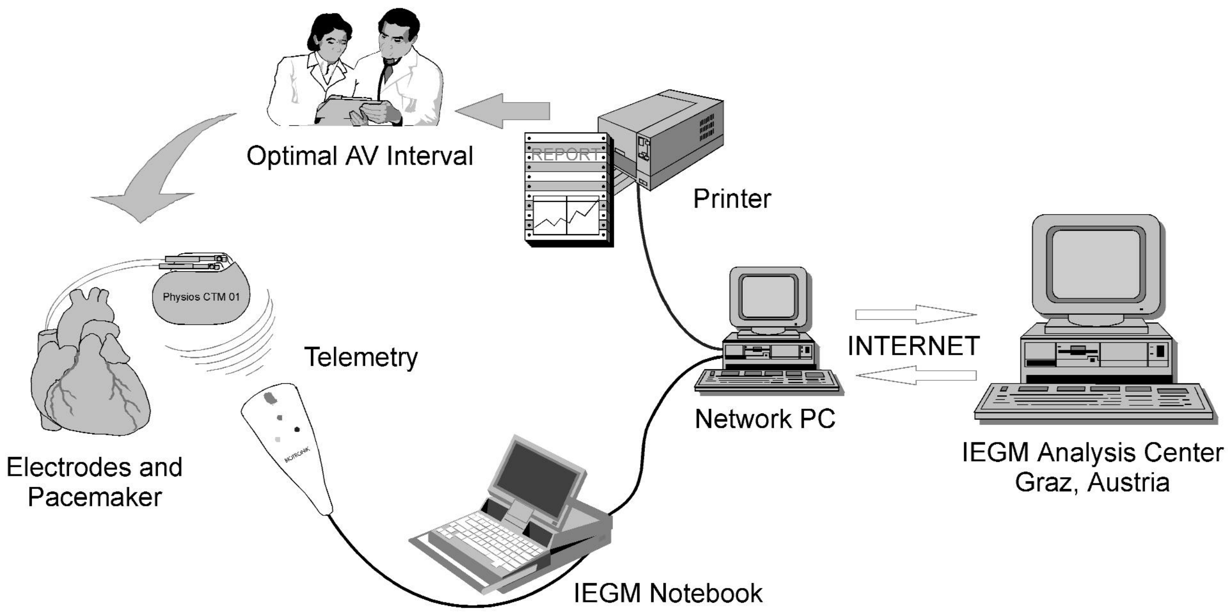

Figure 1. Concept of intracardiac electrogram (IEGM) acquisition, transmission and analysis.

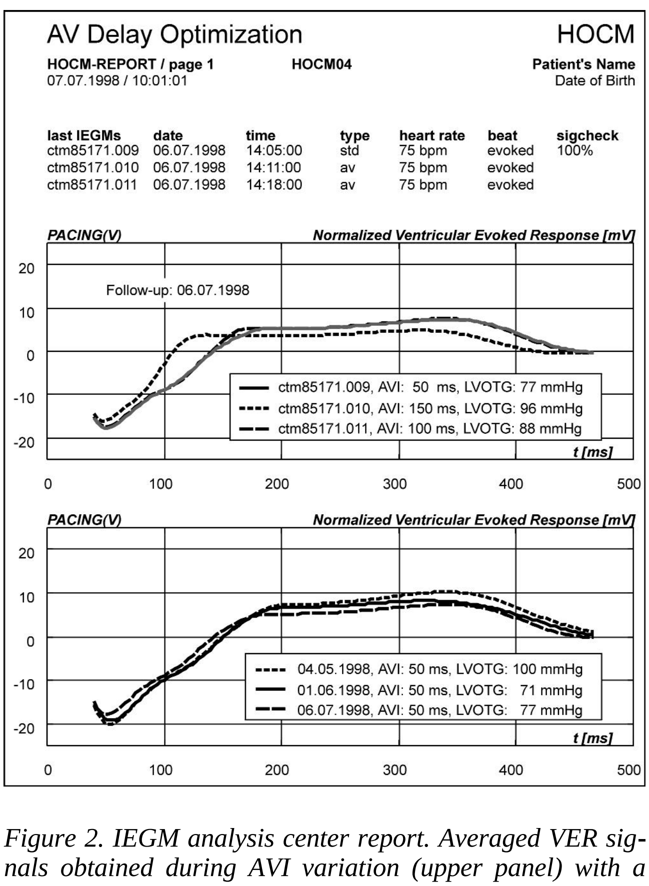

Figure 2. IEGM analysis center report. Averaged VER signals obtained during AVI variation (upper panel) with a distinct AVI influence on LVOTG values and VER signal morphology. Averaged VER signals obtained for the standard pacemaker settings during subsequent follow-up (lower panel), also indicating VER changes.

meters extracted from each recording. Analysis results became available within 24 hours and consisted of a report protocol containing the averaged VER signals as displayed in Figure 2. The definitions of the VER parameters important to the present study - the VER depolarization duration (VER_{DD}) and the VER negative area (VER_{NA}) - are displayed in Figure 3.

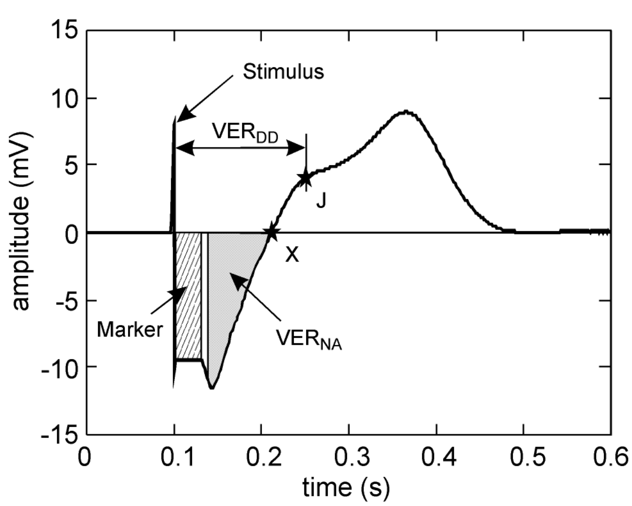

Figure 3. Parameters extracted from the VER. VER_{NA} serves as a measure of the VER magnitude; VER_{DD}, the DVC.

Patient#	Gender	Age (a)	Follow-up	Symptoms	Medication	LVOTG (mmHg) Before	After	Last
1	F	41	3	A, T	Pr	124	76	53
2	M	47	4	D	At, Dis	117	81	47
3	F	63	4	D	Pr, Dis	83	44	17
4	F	59	3	T, S	Dis	121	100	77
5	F	63	1	T, D	Pr	64	32	NA
6	M	14	1	T, A	Ver	105	74	NA
7	F	44	2	T, A	Pr, Ver	90	46	22
8	M	41	1	A, T	At	70	29	NA
9	F	51	1	A, T	Pr, Ver	110	53	NA
M ± SD		47 ± 15	2.2 ± 1.3			98 ± 22*	59 ± 24*	

*Table 1. Basic statistics of all patients. Symptoms: A = angina, D = dyspnea, S = syncope, T = tiredness; Medication: At = atenolol, Dis = disopyramide, Pr = propanolol, Ver = verapamil; LVOTG before and after pacemaker implantation and the value at the most recent follow-up, NA = not yet available; * p < 0.01 (two-tailed Wilcoxon test for matched pairs); M ± SD = mean ± standard deviation.*

Statistics

Influence of the AVI on the VER_{DD}

To assess the influence of the AVI on the depolarization duration of the VER (as measured by the VER_{DD}), the average VER_{DD} absolute values were grouped according to the associated AVI classes. Differences between the AVI groups "Short," "Medium," and "Long" were tested using the two-tailed t-test for matched pairs.

Degree of ventricular capture

The degree of ventricular capture (DVC) has been defined for each recording using the following ratio:

$DVC = VER_{DD}/VER_{DD}max$;

that is as the percentage of the current VER_{DD} value in relation to the highest VER_{DD} value obtained for the respective patient and follow-up. Accordingly, a 100% DVC corresponds to 100% ventricular capture.

Influence of the degree of ventricular capture on the LVOTG

The LVOTG values associated with full ventricular capture (DVC > 95%) were compared to those associated with DVC ≤ 95%. The differences between both groups were tested using the two-tailed t-test for matched pairs.

Correlation between LVOTG and the VER magnitude

To check for an overall correlation between the magnitude of the VER and the degree of outflow tract obstruction, linear regression analysis between the VER_{NA} (as a measure of the magnitude of the VER) and the LVOTG (as a measure of outflow tract obstruction) was performed using the average LVOTG and VER_{NA} values of all recordings with full ventricular capture of each patient as observation pairs. Statistically significant were p-values < 0.05.

Results

In the course of the initial follow-up, the pacemakers were programmed to a pacing frequency of 70 to 75 ppm and an AVI of 50 to 100 ms. This resulted in a significant reduction of the outflow tract obstruction in all patients with a decrease of the LVOTG from a pre-implant value of 98 ± 22 (64 - 124) mmHg to 59 + 24 (29 - 100) mmHg ($p < 0.01$).

Up to now, a total of 20 follow-up checks have been performed in all nine patients. Four patients have attended only one follow-up visit. In the remaining five patients, however, the LVOTG values measured during the last evaluation show a further decrease as compared to the first evaluation after pacemaker implantation. Table 1 shows the demographics and statistics for the entire patient group.

Figure 2 shows an example of the protocol report of patient 4 after three follow-up. The upper panel displays the averaged VER as obtained for three different AVI, indicating shorter VER_{DD} values for longer AVI. The VER_{DD} values were obtained for all three classes of AVI, except in patient 3 (AVI > 100 ms always resulted in ventricular inhibition in this patient). Overall, long AVI were found to be associated with significantly decreased VER_{DD} values if compared with short and medium AVI (Figure 4).

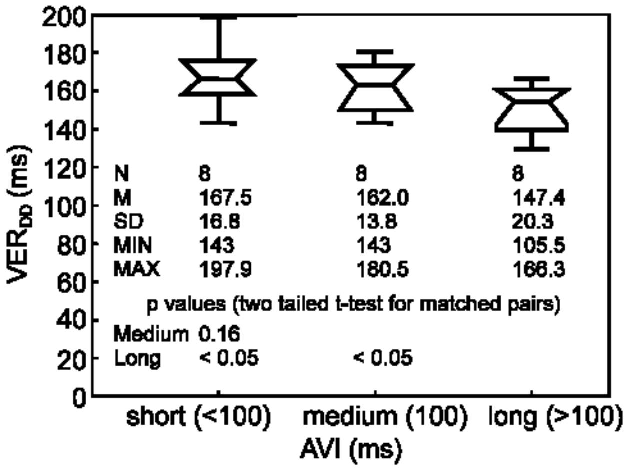

Figure 4. Statistics on VER_{DD} vs. AVI, indicating significantly lower VER_{DD} values for long AVIs as compared with short and medium AVIs.

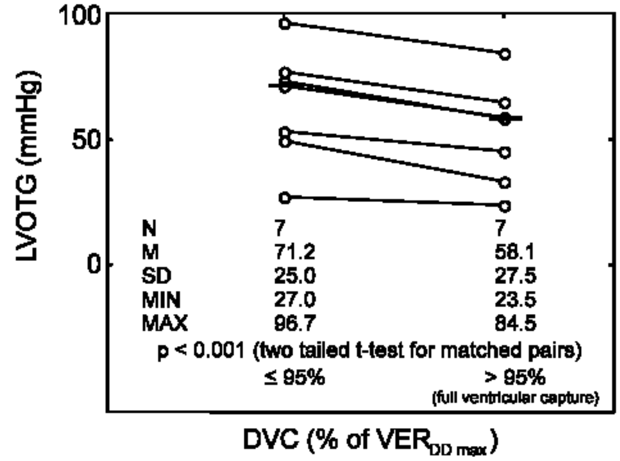

Figure 5. LVOTG values grouped according to DVC, indicating significantly lower LVOTG values in cases of full ventricular capture (DVC > 95%).

In two patients (patients 3 and 8), ventricular capture was always complete (DVC > 95%). Comparison of the LVOTG values with/without full ventricular capture in the remaining seven patients revealed significantly lower LVOTG values in case of full ventricular cap-ture ($p < 0.001$) (Figure 5).

Linear regression analysis revealed a significant overall correlation ($r = 0.69$, $p < 0.05$) between the LVOTG and the VER_{NA} values (Figure 6).

Discussion

Dual-chamber pacing with shortened AVI has been accepted as an effective therapy to consistently reduce the left ventricular outflow tract obstruction in patients with HOCM [1,3-5,16].

Full ventricular capture is necessary for this therapy to be effective, i.e., excitation of the whole ventricular myocardium has to occur exclusively from the apex via the pacing lead. Currently, the pacing effect on the heart is determined by Doppler echocardiography [6], a non-invasive technique used to adjust (program) the pacemaker and to monitor modifications of the obstruction and mitral valve function.

Before this investigation, 11 patients with HOCM had already been supplied with DDD (10 patients) or VVI pacemakers (one patient) at our institution. These patients presented similar preoperative characteristics compared to those patients included in the present investigation [12]. Having gained basic experience with this therapy concept, we decided to use telemetric pacemakers to look for a correlation between hemodynamics and the VER, both in terms of chronic DDD pacing and in terms of acute changes due to modifications of the AVI.

Implanting the telemetric pacemaker for the purpose of the study presented no ethical concerns. This pacemaker is fully equivalent to other pacemakers used in patients with HOCM, and the non-invasive, telemetric IEGM recording procedure does not present any discomfort or risk to the patients.

The telemetric pacemaker system used in the present investigation has already been used in a number of previous investigations. These studies demonstrated the

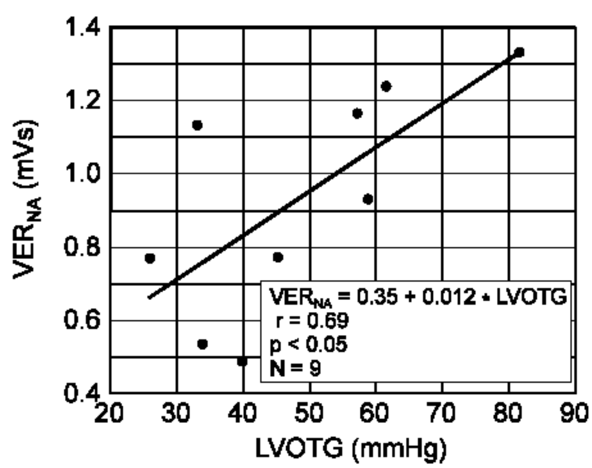

Figure 6. Linear regression analysis between LVOTG and VER_{NA} revealing a significant correlation between hemodynamics and electrical activity.

reliability and reproducibility of this non-invasive IEGM recording technique [7,8,10,13,14]. A correlation was established between the VER and the inflammatory response of transplanted hearts to rejection [9] as confirmed by endomyocardial biopsy - the standard method to diagnose and quantify the severity of rejection episodes [15].
Recently a system called Computerized Heart Acute Rejection Monitor (CHARM) was developed to offer a fast, precise and non-invasive diagnosis of acute rejection episodes in transplanted hearts [11]. The IEGM from the implanted telemetric pacemaker are processed at a central IEGM analysis center. The availability of this versatile monitoring system based on IEGM motivated us to investigate whether this concept can be utilized to monitor HOCM patients as well.
Previous studies revealed that the IEGM is sensitive to a number of acute and chronic influences on the heart [17]. To maximize reproducibility, recordings should be performed under as standardized conditions as possible. Therefore, the investigator and time of day for evaluation were the same for each patient.
Initially, we performed recordings with different periods of time between pacemaker programming and VER recording to find out how long one should wait to reach steady state conditions. Since recordings after 5 and 10 minutes did not differ significantly, we concluded that 5 minutes is a reasonable period of time between an intervention and VER signal acquisition.
The VER changes due to AVI modifications presented two different patterns:

1. They were particularly pronounced in patients where the AVI shortening resulted in an appreciable reduction of the LVOTG. The corresponding VER showed longer depolarization duration as indicated by the example in Figure 2, upper panel. This is assumed to be caused by a higher DVC.
2. On the other hand, small modifications of LVOTG values, as observed in patients with a very favorable response to DDD pacing and already presenting a LVOTG near 30 mmHg, were accompanied by only minimal changes of the associated VERs. In two of those patients (patients 3 and 8) AVI variations changed neither the DVC nor the LVOTG significantly.

These results further support the notion that to obtain a favorable LVOTG, the AVI should be chosen such as to achieve a high DVC. Our results indicate that the VER parameter VER_{DD} can be utilized to achieve this goal.
Successive evaluations in the course of the study indicated a progressive reduction of the LVOTG values in most patients. Similar to AVI variation, patients presenting pronounced changes of the LVOTG values over time exhibited markedly changed VER signals (Figure 2, lower panel). In a single patient we also observed that a negative inotropic intervention (prescription of calcium channel blocker) resulted in a further decrease of the LVOTG as well as a change of the VER.
The overall correlation between the degree of hypertrophy (as measured by the LVOTG) and the magnitude of the electrical activity of the heart (as measured by the VER_{NA}) may be explained by the general assumption that increasing hypertrophy means increased myocardial mass and/or increasing wall thickness and, therefore, increased VER signal magnitude.
Though the study currently comprises a small number of patients and follow-up only, the results indicate a sensitivity of the VER to hemodynamic changes caused by AVI variations. If this can be confirmed in a larger number of patients, noninvasive VER recordings using pacemaker telemetry may become a reliable and easy-to-use tool for optimizing the AVI and monitoring the success of DDD pacing as a therapy for HOCM.

Conclusion

In accordance with previous studies, the present results confirmed that dual-chamber pacing is an effective therapy to reduce the outflow tract obstruction in patients suffering from HOCM. The distinct impact of the AVI on the LVOTG emphasizes the importance of programming an appropriate AVI to obtain full ventricular capture. Noninvasive VER recording using telemetric pacemakers is a well-standardized, easy-to-use and reliable method which can be utilized to assess the degree of ventricular capture and to guide AVI optimization.
Further research based on longer follow-up periods is necessary to find out whether the correlation between the magnitude of the VER and the severity of outflow tract obstruction as obtained in this study can be utilized to monitor the long-term benefits of DDD pacing in HOCM patients.

Acknowledgments

Many thanks to Mr. Dirceu Stona and the engineers Mr. Flávio Menegola and Mr. Carlos Nunes for maintaining the IEGM data acquisition.

References

[1] Futterman LG, Lemberg L. New indications for dual-chamber pacing: Hypertrophic and dilated cardiomyopathy. Am J Critical Care. 1995;4(1):82-87.

[2] Nishnamura RA, Tursty JM, Hayes DL, Ilstrup DM, Larson DR, Hayes SN, Allison TG, Tajik AJ. Dual-chamber pacing for hypertrophic obstructive cardiomyopathy: A randomized, double-blind, crossover study. J Am Coll Cardiol. 1997;29:345-351.

[3] Sadoul N, Simon JP, de Chillou C, Isaaz K, Brunz JF, Beurrier D, Dodinot B, Aliot E. Long-term dual-chamber pacing improves hemodynamic function in patients with obstructive hypertrophic cardiomyopathy. Pacing Clin Electrophysiol. 1993;16(5):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(6):2149-2161.

[5] Fananapzir 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(6):2731-2742.

[6] Shah PM, Gramiak R, Adelman AG, Wigle ED. Echocardiographic assessment of the effects of surgery and propranolol on the dynamics of outflow obstruction in hypertrophic subaortic stenosis. Circulation. 1972;45:516-521.

[7] Lang V, Merkely B, Geller L, Ströbel JP, Fazekas L, Juhasz-Nagy A, Schaldach M. Monitoring cellular electrical activity-Monophasic action potential and ventricular evoked response. Prog Biomed Res. 1997;2:11-16.

[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, et al. CHARM-Computerized heart acute rejection monitoring. Biomed Tech (Berl). 1996;41:35-40.

[10] Auer T, Schreier G, et al. Paced epimyocardial electrograms for noninvasive rejection monitoring after heart transplantation. J Heart Lung Transplant. 1996;15:993-998.

[11] Schreier G, Kastner P, Hutten H, Grasser B, Schaffellner S, Iberer F, Tscheliessnigg KH, Schaldach M. Noninvasive patient monitoring after heart transplantation-New methodological aspects. Prog Biomed Res. 1997;2:73-79.

[12] Sant'Anna JRM. Tratamento da miocardiopatia hipertrófica obstrutiva: uma opção não farmacológica. Palestra proferida no simpósio Avanços na Eletroterapia do Coração. 8o. Congresso de Cardiologia do RGS, Caxias do Sul . R.S. 21 de novembro de 1997.

[13] Hutten H, Schaldach M. Automatic pacing becomes a technical reality. Biomed Tech (Berl). 1996;41(2):1-11.

[14] Brofman P, Costa I, et al. Cardiac transplant monitoring trough intramyocardial electrogram analysis. In: EUROPACE '97. Vardas P (ed). Bologna: Monduzzi Editore; 1997:219-223.

[15] Billingham ME, Cary NRB, et al. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Heart rejection study group. J Heart Transplant. 1990;9:587-593.

[16] Yuzvinkevich SA, Federov VV, Krutikov AN, Domashenko AA, Khirmanov VN, Schaldach M. Clinical experience with dual-chamber pacing in patients with hypertrophic obstructive cardiomyopathy. Prog Biomed Res. 1997;2:31-40.

[17] Grasser B, Iberer F, et al. Influences on intramyocardial electrograms for rejection monitoring after HTX. Proceedings of CARDIOSTIM '98 (Nice, France), June 1998:166.

[18] Schreier G, Hutten H, et al. Remote intramyocardial electrogram analysis for non-invasive rejection monitoring after heart transplantation. Med Biol Eng Comput. 1996;34:205-206.