Diagnostic Potential of Intramyocardial Electrograms

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Summary

Advanced pacemaker technology and modern telecommunication technology renders possible the acquisition and worldwide transmission of intramyocardial electrograms (IEGM) to specialized centers. It has been proven during the last decade that IEGMs represent clinically relevant information that cannot be obtained from surface ECGs. A large body of knowledge has been gained concerning rejection monitoring of transplanted hearts where the results can be compared favorably with endomyocardial biopsies. More recent results demonstrate that IEGMs have a challenging potential for risk monitoring. Furthermore IEGMs can be used to adjust the AV interval in patients with cardiomyopathies, e.g. to reduce the left ventricular outflow tract gradient. These advantages of IEGMs together with the service provided by specialized centers that are accessible for every hospital with internet access render possible new insights in cardiology and the realization of multicenter studies.

Key Words

Intramyocardial electrograms, telecardiology, remote ECG analysis, parameter extraction, risk monitoring

Introduction

It has been a long way from the initial research work and the first publications by Einthoven on the electrogram in 1895 (in 1924 Einthoven was distinguished as Nobel Laureate "for his discovery of the mechanism of the electrocardiogram") to the present state of routine diagnostics by computer-assisted ECG evaluation. Frequently during this long period of more than 100 years the impression came up that the diagnostic potential of ECG might be exhausted. But mainly by the advancement of technology and signal processing new diagnostic fields could be opened for ECG assessment.

The availability of implants with broad bandwidth telemetry renders possible the acquisition of intramyocardial electrograms (IEGM) with high signal quality and resolution. The morphology of these IEGMs represents much more information than extracorporeal or surface electrograms. The most serious shortcomings for long-term monitoring of extracorporeal ECGs are the poor reproducibility of the exact electrode position, the relative displacement of the heart against the position of the electrodes during ventilation and due to changes in posture, and the dependence of the transmission impedance between the heart and the skin on different air filling of the lung tissue.

IEGMs have become the key to a new field with challenging and promising applications that attracts the attention of the medical community. The diagnostic potential of this new field is still not completely revealed. There is first evidence, however, that reliable long-term risk monitoring and monitoring of cardiac parameters with hemodynamic relevance by the assessment of electrophysiological signals may be possible. Since the electrodes are permanently fixed either in endomyocardial or epimyocardial position, any relative displacement between the electrodes and the heart is excluded.

Evaluation of IEGMs requires a tailored software for signal and data processing that is different from the software for extracorporeal ECGs. This software must be based on a fundamental understanding of the signal characteristics of IEGMs and must enable the adjustment to individual features, e.g., the position of the electrode or the mode of signal acquisition. In the present phase with a rapid development of new applications it seems to be too early to introduce standardized software for clinical use. However, advanced telecommunication technology can be utilized for the world-wide transmission of ECGs to specialized centers where the signals can be evaluated in accordance with the wishes of the hospital. Such a specialized center can provide additional service to hospitals, e.g., supply complete trend records for patients, make statistical analysis, ensure current data back-up, and support multicenter studies [8,17].

Methods

Data Acquisition and Transmission

IEGMs have been recorded in high-resolution quality during spontaneous heart rhythm as well as during pacing employing a dual chamber pacemaker (Physios CTM 01) with wide-band telemetry (0.33 - 200 Hz) in combination with electrodes provided with fractal coated surface either for epimyocardial or intraventricular position. Electrogram sequences with a duration of one minute have been received with a portable pacemaker programming and data acquisition unit (all pacemaker materials: Biotronik, Berlin, Germany) by inductive coupling. The received data have been digitized with a sampling rate of 667 Hz and resolution of 0.1 mV. After association with clinically relevant information, compression and encryption, the complete data file has subsequently been sent via the Internet to Graz where the central processing station had been established. Transmission required usually less than one minute for a complete data file depending on the location of the center and the time of the day. Transmission has been accomplished either using the File Transfer Protocol (FTP) or e-mail [5].

After adequate processing, the results have been returned to the sending hospital in form of complete records provided to the special wishes of the hospital. Trend curves, remarks and pointers can be supplied in the records.

Data Processing and Signal Analysis

At the processing center (Cortronik, Graz, Austria: http://www.cortronik.co.at) a password secured data bank account has been established for each hospital. Identification of the individual patient is possible with the pacemaker identification code that is heading the transmitted data file. Figure 1 shows all operating and data processing tasks which are necessary for remote IEGM analysis. Routine analyses run completely automatically [10]. During the evaluation of new diagnostic approaches manual analyses is performed to develop appropriate signal processing methods.

IEGM sequences can contain different kinds of events, e.g., paced beats, fusion beats of different expression and spontaneous beats. To consider the different origins of excitation and electrophysiologic effects careful classification is necessary in order to obtain averaged beats with reliable and well-structured morphology. Especially fusion beats can occur frequently in patients with high spontaneous heart rate and must not be considered for averaging the ventricular evoked response (VER) signals.

Results

Data Transmission

Up to now, the central processing station has received about 25,000 IEGM sequences from 279 patients from 14 hospitals worldwide. No problems have been observed that have caused erroneous data transmission. Acceptance in the hospital is strongly affected by the operational convenience offered to the users in the hospital. Special support by the processing center is required in cases where the hospitals are protected by advanced firewall systems or if special software systems are employed. Another problem has been the use of different protocols for patient management in the hospitals. In the past, all those problems could be solved to the satisfaction of the hospitals.

Prognostic value of epimyocardial electrograms in heart transplants [13]

The CHARM (Computerized Heart Allograft Recipient Monitoring) system has been established about 8 years ago [1-4,12,14,19]. The original objective has been rejection monitoring in heart transplant patients. It has been proven that parameters extracted from the VER that is monitored under standardized conditions provide valuable information on rejection episodes as well as on significant infection. The maximum slewrate of the repolarization phase (VER_Tslew) indicates absence of relevant rejection (negative predictive value > 98%) and/or cardiac dysfunction. The ECG is frequently used to monitor functional disorders caused by bacterial endocarditis [20]. The duration of the VER corrected to the pacing rate (VER_DURc) is prolonged during infection [18]. To evaluate the prognostic value of VER recordings the parameters of the most recent IEGM examination have been observed in

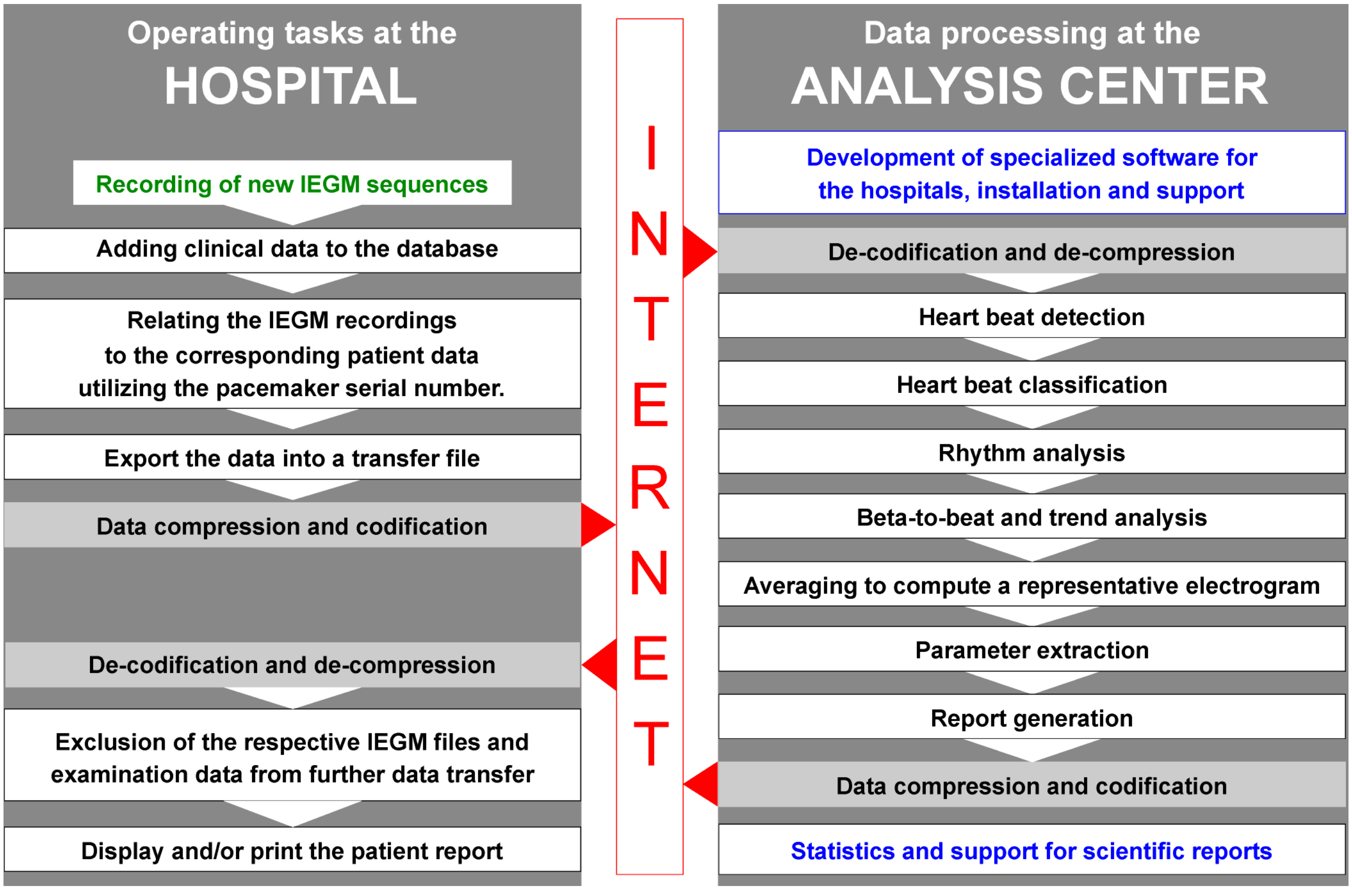

Figure 1. Flowchart of the operating and data processing tasks which are necessary for remote IEGM analysis: The left hand side shows the main steps performed at the hospital and the right hand side contains the subsequently executed steps at the analysis center. Both sides are connected via the Internet which provides worldwide accessibility.

consecutive heart transplant recipients in the University of Graz - Heart Transplant Program [12]. Survivors, who were alive at the time of data analysis, showed significantly higher VER_Tslew values as compared to the patients who died. No significant differences between both groups were found regarding to the VER_DURc. The deaths associated with higher VER_Tslew values were not related to cardiac dysfunction. The results of this study showed, that persistently low VER_Tslew values are strongly associated with a cardiac dysfunction and, subsequently, fatal outcome after HTX.

AV-Adjustment for Patients with Cardiomyopathies [16]
Dual chamber pacing with shortened atrioventricular interval (AVI) has gained acceptance as an effective therapy to reduce the left ventricular outflow tract obstruction in patients suffering from hypertrophic obstructive cardiomyopathy (HOCM) [15]. Doppler echocardiography is currently used to measure the maximum systolic pressure gradient of the left ventricular outflow tract (LVOTG) and to adjust the AVI accordingly. This study has been performed to find out whether there is a significant correlation between the parameters extracted from the VER and the LVOTG in such patients.
Nine patients with severe HOCM, as indicated by LVOTG values higher than 50 mmHg before pacemaker implantation, were included in the study. In the course of 20 follow-ups the LVOTG and the VER were registered simultaneously at different AVIs. The AVI resulting in the lowest LVOTG was maintained until the next evaluation. The VER recordings were sent to Graz, Austria, for automatic signal processing in order to extract the VER depolarization duration (VER_{DD}) as a measure of the degree of ventricular capture (DVC).

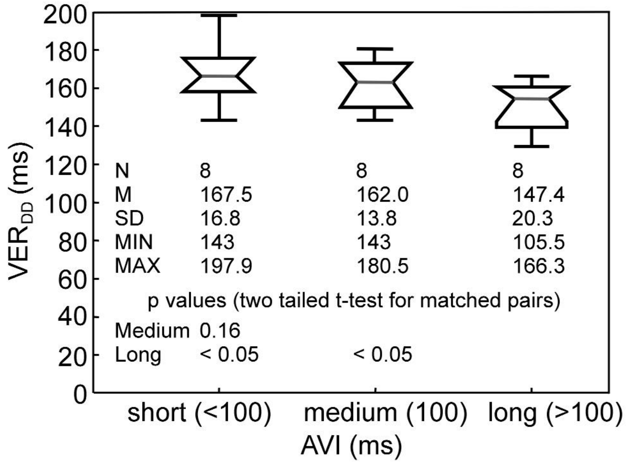

Figure 2. Statistics on the VER depolarization duration (VER_{DD}) versus the AV interval (AVI), indicating significantly lower VER_{DD} values for long AVIs as compared to short and medium AVIs [16].

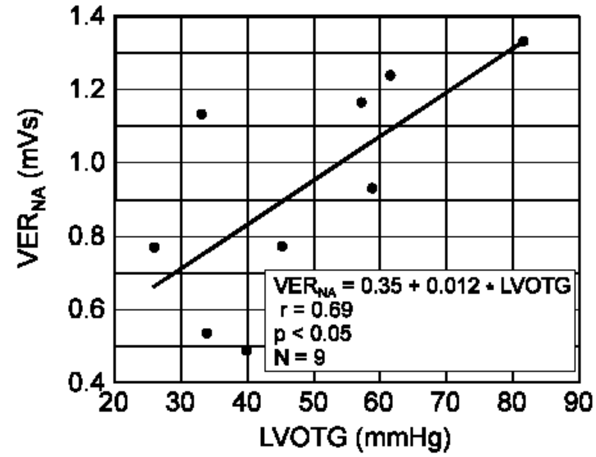

Figure 3. Linear regression analysis between the left ventricular outflow tract gradient (LVOTG) and the magnitude of the VER, as measured by the area under the negative signal part (VER_{NA}), revealing a significant correlation between hemodynamics and electrical activity [16].

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. The LVOTG decreased from a pre-pacemaker implant value of 98 ± 22 mmHg to 59 ± 24 mmHg ($p < 0.01$). AVIs > 100 ms resulted in significantly reduced VER_{DD} as compared to shorter AVIs ($p < 0.05$), indicating a decreasing DVC for increasing AVIs (Figure 2). PM settings resulting in a DVC < 95% (full ventricular capture = 100%) were found to be associated with significantly higher LVOTG values (71 ± 25 mmHg versus 58 ± 28 mmHg, $p < 0.001$). Linear regression analysis revealed a significant overall correlation ($r = 0.69$, $p < 0.05$) between the LVOTG and the VER_{NA} values (Figure 3).

Dual-chamber pacing is an effective therapy to reduce the outflow tract obstruction in HOCM patients. Changes in hemodynamics are accompanied by distinct VER changes in such patients. The method can be used to noninvasively assess the DVC in order to find a favorable AVI and to minimize the LVOTG.

Hemodynamic Assessment

It is generally accepted that the ECG represents the electrophysiological processes in the heart, mainly the process of excitation, spreading of depolarization and the repolarization. Recent results obtained from IEGMs have proven that the electrophysiological signal also contains information on hemodynamic parameters like enddiastolic volume and stroke volume. From a theoretical point of view it follows that the geometry of the heart and the filling conditions are of significant influence on well-defined features of IEGMs. The depolarization phase corresponds to the enddiastolic shape of the heart, which can be assumed to be fairly constant during this phase. In general, lower depolarization signal amplitudes are to be expected in case of higher enddiastolic volumes and vice versa. If this applies, one would expect higher amplitudes for beats with shorter coupling intervals if associated with an incomplete filling pattern. The aim of this study was to test this hypothesis.

After recording of IEGMs during spontaneous heart rhythm remote signal analysis was performed automatically. Heartbeat classification provided a group of regular heartbeats characterized by similar signal morphologies, i.e., high correlation coefficients to each other. The following parameters were extracted and statistically compared:

- RR_{min}: shortest single RR interval of all regular heartbeats within an IEGM sequence of one minute duration,

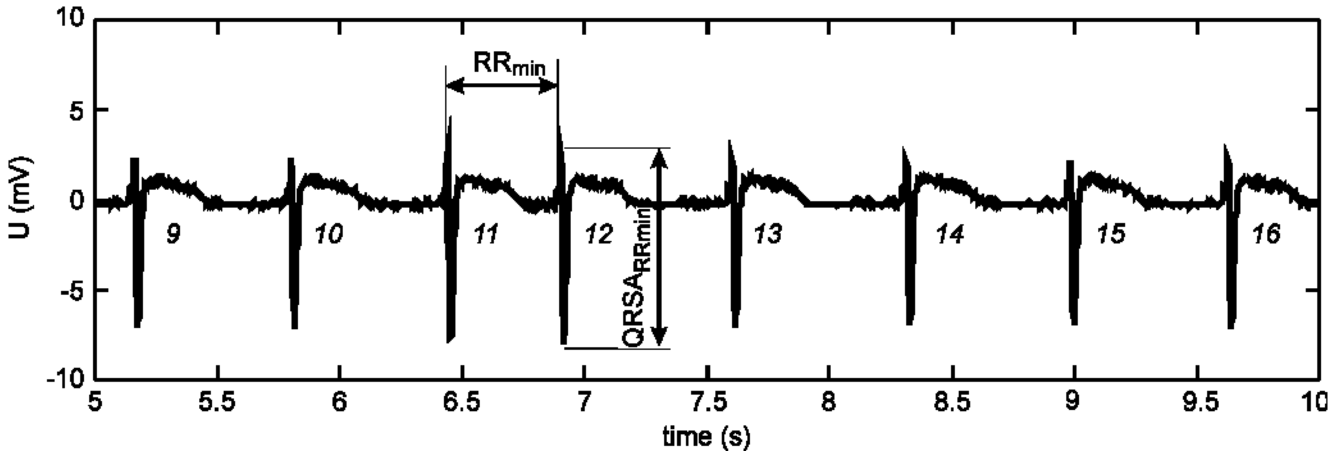

Figure 4. Section of an IEGM recording showing a premature QRS complex with normal contour (heartbeat #12) as well as the definitions of the parameters automatically extracted by signal analysis [7].

- A_{RRmin_rel}: Ratio of the QRS amplitudes of the heartbeats following and preceding the shortest RR interval.

Figure 4 shows an example of an IEGM recording including a premature QRS complex with normal contour as well as the definitions of the parameters. All spontaneous and undisturbed recordings from all patients of the University of Graz - Heart transplant program have been analyzed. The inclusion criteria for statistical analysis was met for recordings which showed at least one heartbeat of regular signal morphology with a short RR interval ($RR_{min} < 0.95\ RR_{mean}$). Since a change of the excitation pattern would by itself change the contour of the QRS complex, the analysis has to be restricted to beats with regular morphology in order to maintain the comparability for the QRS amplitudes. For all recordings the two tailed U-test was performed to assess the correlation between the RRmin and A_{RRmin_rel}.

A total of 400 recordings from 71 patients met the inclusion criteria. Figure 5 shows the results of the statistics, revealing significant difference of A_{RRmin_rel} between groups with RR_{min} lower than 0.55 s and all other groups.

In the course of our previous studies a number of observations indicated the distinct influence of the hemodynamic state, particularly enddiastolic volume and diameters, on IEGMs. In an experimental context, the influence of ventricular volumes on the QRS amplitude of IEGMs has already been investigated, indicating a distinct inverse relationship between both parameters [11]. The present study utilized an indirect approach based on volume changes caused by short RR intervals and, consequently, diminished ventricular filling.

The hypothesis of observing higher QRS amplitudes in smaller, less filled hearts assumes that the electrical activity is increased due to

a) diminished distance between the lead point and the center of gravity of the myocardium, and
b) thicker myocardial walls; increased source density.

Though both effects go parallel to each other for intramyocardial lead positions, they may opposite and partially cancel out each other for lead positions on the body surface which do not follow the movement of the heart.

The results show that short RR intervals have a significant influence on the amplitude of the following QRS complex, even in case of constant signal morphology, i.e., constant excitation spreading over the ventricular myocardium. Therefore, the QRS amplitude of IEGMs reflects changing filling conditions of the heart and contains hemodynamic information. It can be assumed that premature beats have significant effect on the hemodynamic efficiency of the heart in a short period following the premature beat [6,7].

Most recent results of a study on the correlation between parameters extracted from the VER and the stroke volume sustain the distinct impact of hemodynamic changes on IEGMs [9].

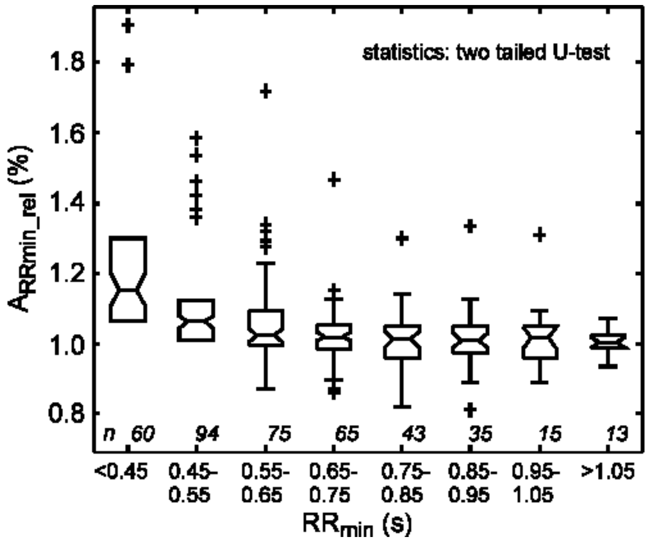

Figure 5. The boxplots show a significant difference of A_{RRmin_rel} between groups with RR_{min} lower than 0.55 s and all other groups [7].

Conclusion

IEGMs represent information on cardiac activity and performance that cannot be gained from extracorporeal ECGs. These signals render possible methodologically new diagnostic and therapeutic approaches. Excellent long-term reproducibility combined with high-resolution signal acquisition and careful signal analysis provide reliable information for transplant recipient monitoring, risk monitoring, hemodynamic monitoring and adjustment of hemodynamically effective parameters. This new approach combined with worldwide signal transmission using advanced telecommunication technology and the service, provided by specialized computer centers, has opened the door to modern telecardiology.

References

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

[2] Bourge R, Eisen H, et al. Noninvasive rejection monitoring of cardiac transplants using high resolution intramyocardial electrograms. PACE 1998; 21: 2338-2344.

[3] Eisen H. Noninvasive detection of cardiac transplant rejection using electronic monitoring. Curr Opin Cardiol. 1999; 4: 151-54.

[4] Grasser B, Iberer F, et al. Intramyocardial electrogram variability in the monitoring of graft rejection after heart transplantation. PACE 1998; 21: 2345-2349.

[5] Hutten H, Schreier G, Kastner P: Transmission of cardiac electrograms by Internet for computer-assisted signal processing. In: Vardas PE (Ed): EUROPACE'97. Bologna, Monduzzi Editore: 1997, 341-345.

[6] Hutten H, Kastner P, et al. Hemodynamic assessment by evaluation of intramyocardial electrograms. 41Proc. 20th Ann. Int. Conf. IEEE-EMBS. 1998; 20-I/6: 395-398.

[7] Hutten H, Schreier G, et al. Correlation between amplitudes and RR interval of premature QRS complexes from intramyocardial electrograms. Proc. 20th Ann. Int. Conf. IEEE-EMBS. 1998; 20-I/6: 167-169.

[8] Hutten H. Telemonitoring and computerized assessment of intramyocardial electrograms. Proc. 4th Asian-Pacific Conf. on Med. & Biol. Eng. 1999; 38-41.

[9] Kastner P, Schreier G, et al. Correlation between paced epimyocardial electrograms and stroke volume in heart transplants. Proc. 21th Ann. Int. Conf. IEEE-EMBS, Atlanta. 1999; (in press).

[10] Kastner P, Schreier G, et al. The Cardiac Telemonitoring System in Clinical Practice - Preliminary Results of a Multicenter Study. Proc. EMBEC'99, Vienna, Med Biol Eng Comput. 1999; (in press).

[11] Lekven J, Chatterjee K, et al. Pronounced dependence of ventricular endocardial QRS potentials on ventricular volume. Brit Heart J. 1978; 40: 891-901.

[12] Iberer F, Grasser B, et al. Introducing a new clinical method for noninvasive rejection monitoring after heart transplantation to clinical practice: The analysis of paced intramyocardial electrograms. Transp Proc. 1998; 30: 895-899.

[13] Iberer F, Grasser B, et al. The prognostic value of epimyocardial electrograms after heart transplantation. PACE 1999; 22 Suppl. 6 Part II, A 180.

[14] Mahaux V, Demoulin JC et al. Computerized heart rejection monitoring using high resolution pacemaker telemetry. Prog Biomed Res. 1999; 4: 225-227.

[15] Nishnamura R A, Tursty J M, et al. Dual- chamber pacing for hypertrophic obstructive cardiomyopathy: a randomized, double-blind, crossover study. J Am Coll Cardiol 1997; 29: 345-41.

[16] Sant'Anna JRM, Prati R et al. The ventricular evoked response in patients paced for hypertrophic obstructive cardiomyopathy - Initial results. Prog Biomed Res. 1998; 4: 237-243.

[17] Schaldach M, Hutten H. Telecardiology - Optimizing the diagnostic and therapeutic efficacy of the next implant generation. Prog Biomed Res. 1998; 3: 1-4.

[18] Schreier G, Kastner P, et al. The influence of infectious disease on the ventricular evoked response from heart transplants. Proc. 19th Ann. Int. Conf. IEEE-EMBS. 1997; 169-171.

[19] Schreier G. Intramyocardiale Elektrogramme zur nichtinvasiven Abstoßungsüberwachung nach Herztransplantation. Fachverlag Schiele & Schön, Berlin 1998.

[20] Shevchenko YL. Infective Endocarditis: From Despair to Hope. Spetsialnaya Literatura, Saint-Petersburg 1997.