Recording of Ventricular Propagation Time Using Dual-Chamber Pacemaker Telemetry

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Summary

In 20 heart transplant patients stimulated intramyocardial electrograms have been recorded during the posttransplant period using telemetric pacemakers and two epimyocardial electrodes. Employing one electrode for stimulation and the second electrode for sensing it was possible to measure the propagation time for evoked responses between the location of the two electrodes. Preliminary results show that (1) the propagation time is the same in both directions with some few exceptions, (2) the propagation time is changing during the early posttransplant phase in most patients before it reaches a stable level after some weeks, (3) the propagation time depends on the location of the two electrodes, and (4) the propagation time does not show significant dependence on cardiac rejection events up to grade 2.

Key Words

propagation time, evoked response, intramyocardial electrogram, pacemaker telemetry, heart transplantation

Introduction

The propagation of action potentials along single skeletal muscle cells and peripheral nerve fibers has been investigated in nearly all details. Detailed knowledge has also been provided on the transmission of excitation in neural networks including synaptic signal processing. Considering the heart, the physiological processes of automatic generation and spreading of excitation are fairly well understood. On the contrary, only poor knowledge is available on the spreading of excitation in the cardiac muscle after artificial pacing. It is obvious that the propagation of action potentials along single skeletal muscle cells, i.e. along a „cable" structure, is a too simple model for the three-dimensional spreading in a tissue that contains many cells, fibers, and specialized conduction systems.

The conduction velocity along an excitable cell membrane depends primarily on all impacts that affect the membrane permeability during resting state and the dynamic behavior of each kind of specific ion channels. Those impacts can be related with:

- temperature,
- ion concentrations on both sides of the membrane,
- the performance of active ion transport mechanisms across the membrane,
- substances like hormones, chemicals, drugs and aggressive cells.

Conduction velocity is well defined only for „cable"-like structures. For those structures and constant distance between both electrodes, propagation time is inverse to conduction velocity.

Compared with the skeletal muscle cell, the cardiac muscle cell or myocyte shows significant functional and behavioral peculiarities despite the fact that both

cell types have some similarities, e.g. the striated structure.

- The cardiac muscle cell is rather short and can be compared with a rod 12 - 20 μm in diameter and 60 - 100 μm long[6]. Thus, the cardiac muscle fibers are in reality a series of cardiac muscle cells that are separated by membranes with only a small gap between them. Special structures are embedded at opposite sites of both approaching membranes that are assumed to provide the mechanical coupling of the actin filaments of the two cells. As a consequence, the cardiac muscle fiber can develop mechanical force over its whole length.

- The intercalated discs with their close approach offer an electrical resistance that is many times less than the resistance through the other parts of the cell membrane. It is discussed whether nexuses, i.e. a pseudo-fusion of both membranes with a gap of only few nm between them, are actually short-circuiting both cells. As a consequence, transmission of excitation from one cell to the next in the same fiber is possible. This is the basic mechanism for the spreading of the excitation over the whole fiber after it started in a single cell.

- At certain places where two cells of the same fiber are connected to each other by intercalated discs, one of the cells is additionally connected via a thin branch with a third cell in another muscle fiber. This pathway renders possible the spreading of excitation from one fiber to another.

In summarizing it can be said that the cardiac muscle is a „functional syncytium", i.e. wherever excitation starts in that tissue it can finally reach every other cell that is connected with the system. The transmission between distant cells, however, does not occur on the direct pathway if the cells do not belong to the same fiber. The pattern of all pathways can be rather compared with a three-dimensional latticework.

The objective of the present work has been to investigate whether the propagation time in trans-planted hearts can be utilized for patient monitoring.

Methods

Monitoring

Unipolar intramyocardial electrograms were obtained using dual-chamber pacemakers with extended bandwidth capability of 0,3 - 200 Hz (Physios CTM 01), and fractally coated epimyocardial electrodes (ELC 54-UP). The first electrode (E1) was always placed at the right ventricular outflow tract and has been connected to the ventricular channel of the pacemaker. The second electrode (E2) was implanted either at the right ventricle with a distance of about 4 cm to E1 or somewhere else at the left ventricle, thus not presenting the same or comparable distances between both leads E1 and E2. In the course of each rejection monitoring session sequences of intramyo-cardial electrograms were recorded from the spontaneously beating as well as from the paced heart. Sequences that have been obtained using one electrode for stimulation and the second electrode for sensing are designated VERX. The recordings were telemetrically received and sampled with 667 Hz, thus resulting in a temporal resolution of 1.5 ms. The digitized signals have been stored in the special data acquisition unit (SWD 1000, all appliances so far: BIOTRONIK, Berlin, Germany). For signal analysis the electrogram sequences have been

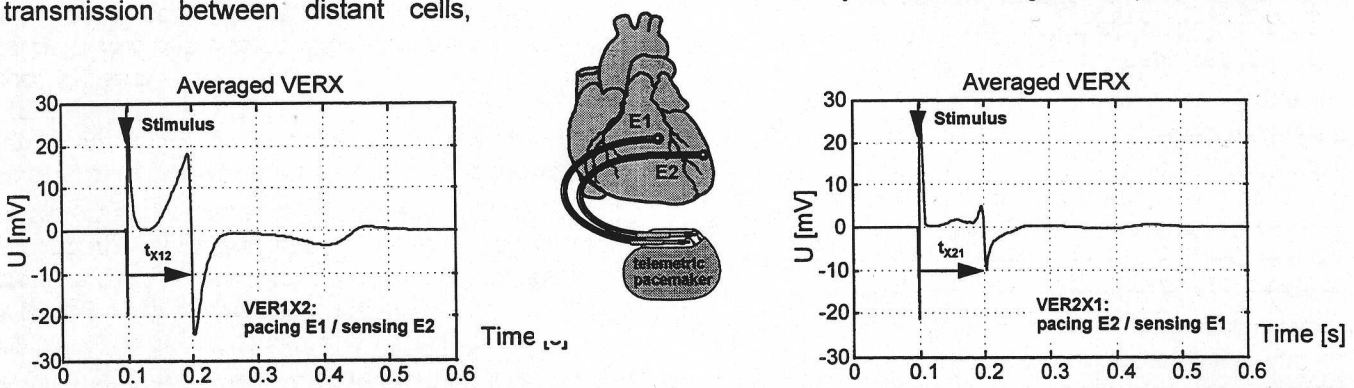

Figure 1. *Recording of intramyocardial electrograms with telemetric pacemakers and two ventricular electrodes - one is used for stimulation and the other is used for sensing. The propagation time (t_X) is defined as the time from the stimulus to the steepest downslope of the signal.*

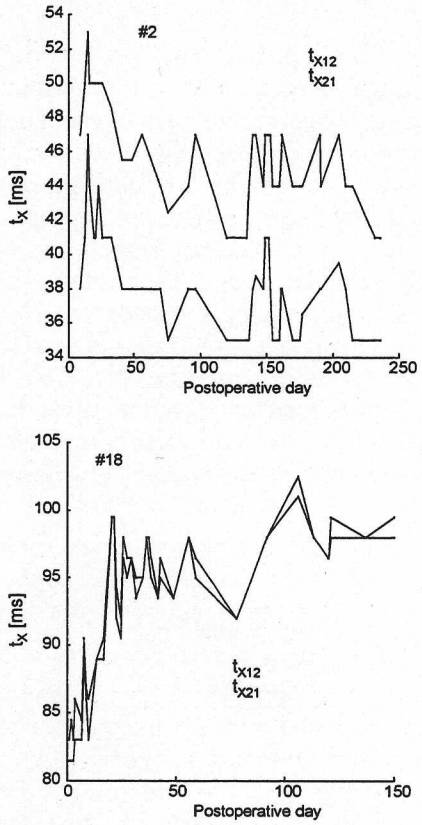

Figure 2. *Examples for the postoperative time course of the propagation times t_{X12} and t_{X21} for the patients #2 (top) and #18 (bottom).*

transmitted via the Internet to the central processing station[5].

Signal Analysis

The usual signal analysis consisted of signal processing and parameter extraction. Signal processing was performed in the following steps:

- event detection,
- event classification,
- averaging of all events assigned to the same class.

The extracted parameter was the propagation time (t_X), i.e. the time interval between the application of the stimulus at the one electrode and the arrival of the excitation at the other electrode. As can be seen from Figure 1, the typical shape of the evoked response following the cross-talking of the stimulus shows a slow upward deflection, then a rapid downward deflection, and finally again a slow upward-deflection. A more detailed consideration reveals that the first upward deflection is caused by the spreading of the excitation in tissue that is „seen" by the electrode, although this tissue is distant from the electrode. This deflection increases when the excitation is spreading on more cells and/or approaching. The excitation passes beneath the recording electrode at the instant of the rapid downward deflection[7]. The following upward deflection is again representing the spreading in tissue distant of the recording electrode. Consequently, the time interval between the stimulus and the steepest slope of the rapid downward deflection was identified as propagation time (t_X).

Statistics

For all recording pairs of each individual patient the correlation coefficient (r) was calculated using linear regression analysis between the t_X values obtained from both electrodes (t_{X12}: stimulation with E1 and recording with E2; t_{X21}: vice versa). All consecutive transplants with two epimyocardial electrodes placed on the ventricles and with more than 5 observations were included.

Results

Figure 2 shows examples of the courses of the propagation time within a period of 240 days and 150 days, respectively after transplantation. In patient #18 (Figure 2, bottom) the propagation time in both direction is nearly identical both in the absolute value and in the time course. In the early postoperative phase, the propagation time is about 81 ms and reaches a rather stable level of about 100 ms after 25 days. In contrast to this behavior is the time course illustrated in Figure 2, top. In the first few days after transplantation the propagation time shows a short increase, followed by a steady decrease before a rather stable level is reached after about 50 days. In this patient, both time courses reveal again a similar behavior although the propagation times in both directions have a nearly constant difference of about 9 ms, i.e. much more than can be explained by the temporal resolution.

Figure 3 shows the results of regression analysis for those two patients. For patient #18 (Figure 3, bottom) the propagation times in both directions are approximately identical over the whole range from 81 ms to 103 ms (r = 0.9858). For patient #2 (Figure 3, top) the nearly constant difference in the propagation times causes a distinct deviation from the line of identity.

Table 1 presents the results of the regression analysis for all 20 patients. In 11 patients the second electrode was positioned at the right ventricle, in 8 patients at

the left ventricle, and in one patient at the apex.

For the patients with the second electrode at the right ventricle the mean propagation times are ${}_{M}t_{X12}$ = 46,6 ms (range: 38 - 53 ms) and ${}_{M}t_{X21}$ = 49,1 ms (range: 41 - 56 ms), respectively. For patients with the second electrode at the left ventricular wall in a not-defined position, the mean propagation times are ${}_{M}t_{X12}$ = 86,7 ms (range: 56 - 124 ms); and ${}_{M}t_{X21}$ = 86,7 ms (range: 56 - 126 ms), respectively. Employing the two tailed Wilcoxon test for matched pairs, p values of 0.021 and 0.686 were obtained for the right and left ventricular positions, respectively. This indicates statistically significant difference between ${}_{M}t_{X12}$ and ${}_{M}t_{X21}$ for right ventricular positions only.

Pat.	E	N	FU	${}_{M}t_{X12}$	${}_{M}t_{X21}$	r	p<
#			days	[ms]	[ms]		
1	R	50	523	44	43	0.684	0.0001
2	R	29	201	38	47	0.848	0.0001
3	R	45	573	50	53	0.694	0.0001
4	R	39	556	47	50	0.885	0.0001
5	R	29	485	53	53	0.940	0.0001
6	R	42	499	47	49	0.315	0.05
7	R	10	28	53	56	0.888	0.001
8	R	37	406	41	43	0.856	0.0001
9	L	47	358	56	56	0.912	0.0001
10	L	37	347	89	86	0.973	0.0001
11	L	28	326	124	126	0.944	0.0001
12	R	20	70	40	41	0.963	0.0001
13	R	42	294	53	53	0.835	0.0001
14	R	30	282	47	52	0.754	0.0001
15	L	38	185	98	98	0.847	0.0001
16	A	32	182	79	87	0.947	0.0001
17	L	26	154	103	106	0.121	0.6
18	L	36	149	95	95	0.986	0.0001
19	L	31	105	65	65	0.958	0.0001
20	L	16	62	64	62	0.960	0.0001

Table 1. *Patient number (#), electrode position code (E - R = right ventricle, A = apex, L = left ventricle), number of observations (N), follow-up range (FU) = days between the first and the last observation, medians of the propagation times for both electrodes (${}_{M}t_{X12}$, ${}_{M}t_{X21}$), correlation coefficients (r) between t_{X12}, and t_{X21}, and error levels (p) for r.*

Discussion

It has been shown in previous studies that pacemaker telemetry is a useful method to record intramyocardial electrograms for noninvasive patient monitoring after heart transplantation[1,3,4]. Up to now, the influence of specific pathological effects on cardiac conduction properties has not been in the focus of such studies. These preliminary results do not completely reveal the processes of excitation propagation after pacing. The results primarily emphasize the potential of this new methodological approach for further studies. However, until now, no evidence can be provided that the propagation times monitor rejection episodes up to grade 2, according to the grading system of the International Society for Heart and Lung Transplantation[2].

In most patients and during the whole observation period, the propagation times in both directions are nearly identical. This result supports the hypothesis

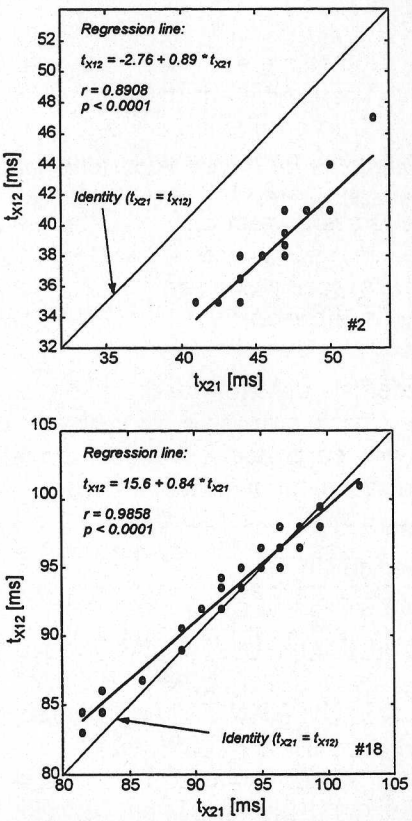

Figure 3. *Regression analysis for the patients #2 (top) and #18 (bottom), indicating significant correlation with respect to the propagation times as obtained in both directions, t_{X12} and t_{X21}, respectively.*

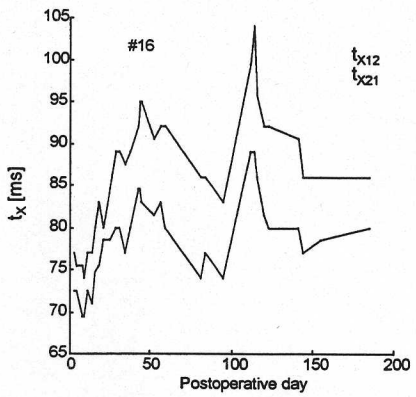

Figure 4. *Example for the postoperative time course of the propagation times t_{X12} and t_{X21} for patient #16 with E2 being located at the apex. The marked differences in both directions can be seen.*

that in theses cases the excitation has been transmitted on the same pathway between the two electrodes. Since this result is not surprising, the exceptions have to be considered.

In few cases, e.g. patient #17, the two propagation times are distinctly different in single measurements (with an increase of about 32 ms in t_{X12}). Possible causes might be temporary changes in the excitability of tissue that become effective only if the excitation arrives at this tissue from one direction, or temporary threshold variations in the vicinity of the stimulus electrode, thus leading to a restriction in the volume of the tissue that is depolarized by the stimulus („region of early capture").

In some patients a permanent difference between both propagation times can be observed (i.e. over the whole observation period, patient #2). These results support the assumption that in those patients the pathways for excitation spreading are not identical but depend on the location of the stimulating electrode.

Two possible effects may account for these findings:

(1) Differences between the conduction times in both directions may be associated with a different participation of a specialized conduction tissue. In patients with both electrodes at the right ventricle, E1 can be assumed to be not very far from the right bundle branch, whereas E2 can be assumed to lie in a region where the specialized conduction tissue has already been split into Purkinje fibers. Both parts of the specialized conduction system may interact differently with the approaching excitation wavefront initiated by the stimulus. Due to its thickness the bundle of His and the right bundle branch may be excited quickly and, subsequently, accelerate the excitation spreading towards the apex. The thin Purkinje fibers, on the other hand, may not be able to significantly affect the way the excitation passes towards E1.

Considering the cases with one electrode located at the left ventricle, the objective for future studies is to reveal whether parts of the specialized conduction system are utilized for excitation transmission from one ventricle to the other.

(2) The slightly but significantly smaller t_{X12} values in the patient subgroup with both electrodes at the right ventricle may be associated with the position of the pacemaker case in the left epigastric region. This causes E2 to lie between E1 and the pacemaker case in those patients. Therefore, the „region of early capture" during stimulation at E1 is supposed to extend more towards E2 than it does towards E1 during stimulation at E2. Hence, propagation from E1 towards E2 may face a shorter distance compared to the vice versa situation.

Both of the hypotheses presented above are compatible with the large differences between t_{X12} and t_{X21} observed in patient #16, the single patient with E2 located at the apex (Figure 4).

A rather surprising result is the finding that the propagation times show a time course before they stabilize about 25 - 50 days after transplantation. Further studies have to investigate whether these time courses represent influences on the membrane excitability or the adjustment in the geometrical size of the heart after transplantation. There is some evidence for the last assumption, e.g. that cardiac dilatation will increase the effective length of the transmission pathway between both electrodes.

Conclusion

Preliminary results show that (1) the propagation time is similar in both directions with some few exceptions, (2) the propagation time is changing during the early postoperative phase in most patients before it reaches a stable level after some weeks, (3) the propagation time depends on the location of the two electrodes, and (4) the propagation time does not show significant dependence on cardiac rejection events up to grade 2.

The measurement of propagation times in cardiac muscle utilizing dual-chamber pacemakers with extended bandwidth telemetry and signal processing opens a new challenging field for future studies.

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] 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

[3] Grasser B, Schreier G, et al. Noninvasive monitoring of rejection therapy based on intramyocardial electrograms after orthotopic heart transplantation. Transplant. Proc. 1996;28:3276-3277

[4] Hutten H, Schreier G, et al. Der Herzschrittmacher als Brücke zum kardialen Telemonitoring. Biomedizinische Technik 1996;41:158-165

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

[6] Streeter DD jr. Gross morphology and fiber geometry of the heart. In: Berne RM, Sperelakis N, Geiger SR (eds.): The Cardiovascular System, Section 2, in the series: Handbook of Physiology, Bethesda, American Physiological Society 1979: p. 62

[7] Witkowski FX, Kavanagh KM, et al. Epicardial cardiac source-field behavior. IEEE Trans. Biomed. Eng. 1995;42:552-558