INVESTIGATION OF CARDIAC RESYNCHRONIZATION THERAPY AND PATHOMECHANISM OF ATRIAL FIBRILLATION

Doctoral thesis

Dr. Attila Roka

Semmelweis University
Doctoral School of Basic Medicine

Supervisor:
Dr. Bela Merkely, assistant professor in medicine, doctor of MTA

Opponents:
Dr. Jozsef Tenczer, head of cardiology department, doctor of MTA
Dr. Andras Vereckei, assistant professor in medicine, Ph. D.

Examination committee:
President: Dr. Istvan Karadi, professor in medicine, doctor of MTA
Members: Dr. Laszlo Melczer, assistant professor in medicine, Ph. D.
Dr. Zoltan Csanadi, assistant professor, Ph. D.

Budapest
2007

INTRODUCTION

Diseases of the heart are among the leading causes of mortality in the world, they become even more imortant as the ratio of elderly population increases. Most common forms are heart failure and disturbances of the heart rhythm. In addition the increased mortality, heart illnesses have a great affect on the quality of life. Both heart failure and atrial fibrillation (AF) are responsible for huge medical expenses as they require prolonged and expensive treatment.

Link between heart failure and atrial fibrillation

Hemodynamic effects of atrial fibrillation (chronic high heart rate, increased atrial filling pressure, irregular cycle length, absence of atrial contraction and loss of atrioventricular synchrony) may impair ventricular function and provoke heart failure. Similarly, changes during heart failure (increased filling pressures, disturbance of intracellular calcium-metabolism, autonomic and neuroendocrine dysfunction) may significantly increase the risk of AF. In some cases pharmacological or non-pharmacological treatment of one of these processes may beneficially affect the other.

Cardiac resynchronization therapy of heart failure

Intraventricular conduction delay is present in 15-30% of patients with heart failure and may worsen the already impaired mechanical function. Cardiac resynchronization therapy with a biventricular pacemaker is an effective treatment of severe heart failure combined with electromechanical dyssynchrony.
One of the unresolved questions is the high ratio of non-responders, which was detected in 30% of patients in clinical studies. Optimal placement of left ventricular electrode is crucial as it is responsible for the resynchronization. With suboptimal position the therapy can be inefficient. Currently there is no generally accepted method for optimization of left ventricular elelctrode position, there are ongoing

studies with ECG, intracardiac electrogram, electroanatomical mapping, echocardiography, SPECT and invasive hemodynamic measurements.
Most common complication of transvenous left ventricular pacing is the contraction of the diaphragm due to phrenic nerve stimulation. Severity of this complication may preclude continuation of treatment.

Atrial fibrillation

Atrial fibrillation is the most common sustained arrhythmia in the clinical practice. Hypotheses of its pathomechanism started to evolve as early as in the beginning of the XXth century, but there is still no generally accepted global model available. Several aspects of the pathomechanism have been described (multiple reentry, automated foci, electrical and structural remodeling), summation of these can be responsible for the variety of forms appearing in the clinical practice. Studies of atrioventricular conduction have found the role of concealed conduction, but opinions on the randomness of ventricular rate during atrial fibrillation still vary. Numerous experimental models of AF have been developed and utilized, which can be responsible for the conflicting results. Clarification of the pathomechanism, description of individual differences can help to optimize individual treatment.
High ventricular rate during AF can be one of the factors significantly affecting the quality of life. Current therapeutic modalities have multiple side effects, which limit the applicability: beta-blockers and calcium channel antagonists have negative inotropic effect, which can contraindicate them in acute heart failure, while digoxin can be the cause of proarrhythmia and multiple medication interactions.

AIMS

1. MRI can be used to differentiate between viable and scarred myocardium, in addition to the evaluation of heart function. Our aim was to investigate the efficacy of MRI in left ventricular lead placement during cardiac resynchronization therapy.

2. We aimed to investigate the stimulation characteristics (rheobase, chronaxie) of left ventricle and phrenic nerve, and to avoid phrenic nerve stimulation - the most common complication of cardiac resynchronization therapy - based on the differences.
3. Numerous studies have been performed to analyze temporal characteristics of atrial fibrillation; however, interpretation of the results is difficult due to multiple induction protocols, whose effect on the characteristics of induced arrhythmia has not been elucidated yet. Out aim was to investigate the effect of induction method on the atrial and ventricular rhythm in an experimental study in healthy dogs, during induction and during the induced transient of persisting arrhythmia.
4. RR intervals are irregular in atrial fibrillation if the conduction system is intact; the ventricular rate is affected by multiple factors. The results of experimental and clinical studies on the randomness of RR intervals are conflicting. Our aim was the statistical analysis of RR intervals in atrial fibrillation to identify individually and generally specific parameters of atrial fibrillation.
5. Parasympathetic neurostimulation with temorary electrodes in experimental and clinical studies has been shown to be useful to slow down ventricular heart rate in atrial fibrillation in an acute setting. Our aim was to investigate the efficacy of the stimulation with a chronically implated lead in a patient with biatrial pacemaker to slow down ventricular rate in atrial fibrillation.

METHODS

MRI guided biventricular pacemaker upgrde

Biventricular pacemaker implantation was attempted in a 64-year old patient with old myocardial infarction, chronic atrial fibrillation, severe congestive heart failure, bradycardia, left bundle branch block and intraventricular dyssynhromy. Optimal coronary sinus lead position could not be achieved, so a VVI pacemaker was implanted. As the condiction of the patient did not improve, biventricular upgrade with epicardial left ventricular lead implantation was planned.

A viability and functional study was performed with MRI. After informed consent a 1,5T GE Signa Infinity Echospeed device was used. To prevent heating of the electrode tip due to the altering magnetic field, a FIESTA sequence was utilized. The sequences were edited with MASS 5.0 (Medis) software.

Optimization of left ventricular stimulation pulse

Biventricular pacemaker was implanted in 44 patients (32 male, age 64.6±9.3 years, NYHA III-IV functional stage despite optimal medical treatment, QRS >120 ms, left ventricular ejection fraction ≤35%). Etiology of heart failure was ischemic in 41%, non-ischemic in 59%. Electrodes were implanted with the standard transvenous techique.

Electrophysiological measurements were performed on the first postoperative day in unipolar configuration, pacing impedance was measured with a 3.6 V, 0.4 ms impulse. Left ventricular stimulation threshold was determined with a step-down protocol with VVI 110/min stimulation, the stimulation voltage was decreased at each pulse duration, until the loss of effective stimulation. Phrenic nerve stimulation was measured with a similar protocol in supine position. Clinically relevant phrenic nerve stimulation was determined if

palplable diaphragmatic contractions were apparent in the epigastric region.

Dara from at least 4 threshold measurements were used to calculate the strength-duration curves. Parameters of the curves were determined with linear regression after inverse transformation of data.

Effect of induction method on the characteristics of induced arrhythmia

The experimental study was performed in 6 healthy dogs. Anesthesia was achieved with iv. pentobarbital, then 2-2 epicardial electrodes were fixed to the appendages of the left and right atria after thoracotomy. A 10-polar electrophysiological catheter was placed near the bundle of His via the superior vena cava, the distal pole was located on the right ventricular septum. This electrode was used to simultaneously detect atrial and ventricular signals most proximal to the atrioventricular junction. The signals were recorded with a Biotronik HBV20 device and Biocord software. Identification of atrial and ventricular activation, calculation of A-A (atrial) and V-V (ventricular) intervals were performed with software developed by the author. Intracardiac conduction delay was determined in sinus rhythm using the time elapsed between the atrial and ventricular activation. AF was induced with direct current and 50 Hz current at 4.5 V, for 2-2 minutes in bipolar right and left appendage and biatrial configurations. The protocol was repeated in every dog 3 times in different order. If the AF persisted for 5 minutes, cardioversion was performed with 10 J energy using epicardial paddle electrodes. Next induction was initiated 5 minutes after spontaneous or electrical cardioversion .

Temporal characteristics of atrial and ventricular activation were described using 7 statistical parameters. Areas with good signals (spikes) were analysed, segments with high-amplitude noise due to far-field signals or pacing artifacts (FF/PA) were not included in the analysis as it was impossible to determine the cycle length there.

Instead, the ratio of these areas compared to the total duration of recording was calculated.

„Electrophysiological fingerprint" in atrial fibrillation

Data was collected from 23 patients with persistent or permanent AF. Atrioventricular conduction was intact in all cases. Holter ECG (Rozinn) and an electrophysiological measurement system (EP Control, Biotronik) was used to record the data. RR intervals were measured with ms accuracy. Only tracings with at least 10 RR interval distance from a PVC were analysed as the retrograde activation of the AV node can affect the conduction of the consecutive beats. No PVCs or beats with bundle branch block were present in the samples. The length of the tracing was 100 RR intervals to achieve adequte sample size for statistical analysis and number of samples. A total of 249 samples satisfied the above criteria (median 12/patient).

Statistics were calculated with SPSS 10.1 and software developed by us. RR interval analysis was performed in 4 categories: mean, distribution, variability, randomness. Parameters of atrial electrical activity used in experimental studies and descriptors of time series were calculated. We did not focus on the analysis of exclusively independent parameters.

Individual variability was characterized by the ratio of standard deviation and mean of a given parameter (relative standard deviation). General variability was determined by the ratio of standard deviation and mean calculated from all samples for a given parameter. Low variability (stable parameter) was characterized by low relative standard deviation.

Comparison of samples was performed with software developed by us. A sample was randomly chosen and five others, which contained one sample from the same patient as of the first sample. Parameters of the first sample were used to find the most identical sample from the other five. The ratio of successful identification of the two

samples from the same patient was calculated from 10000 comparisons.

Parasympathetic neurostimulation with implanted coronary sinus lead

A biatrial pacemaker (Logos DS, Biotronik) implantation was performed in 2000 in a 46-year old patient due to sinus bradycardia, intraatrial conduction block and paroxysmal atrial fibrillation with rapid ventricular rate. Left atrium was stimulated with a coronary sinus lead (Corox LA 65 BP, Biotronik). The right atrial lead was placed into the right atrial appendage (PX 53 JBP, Biotronik). Pacemaker generator replacement was performed in 2003 due to battery depletion. The patient was in atrial fibrillation on the day of procedure. After obtaining informed consent, stimulation of the parasympathetic nerves of the AV node was attempted with the implanted coronary sinus lead and an external pulse generator (ERA 300, Biotronik).

High frequency electrical stimulation was used (200, 500, 800, 1000/min: 3, 8, 13 and 17 Hz) for 10-10 seconds at 4, 6 and 8 V with 1 ms pulse duration. Each protocol was used 3 times, with 1 minute resting period between each stimulation. 8 and 17 Hz stimulation was repeated after 1 mg iv. atropine was administered. RR intervals were measured for 10 seconds before and during each stimulation.

RESULTS

MRI guided biventricular pacemaker upgrde

Pacemaker spikes were not detected during the MRI study using VVI 30/min stimulation, there were no RR intervals longer than 2 s. Stimulation threshold remained unchanged, device or lead malfunction was not detected. The right ventricular lead did not affect the interpretation of the results. An extremly dilated left ventricle (EDV 408.4 ml), severely decreased left ventricular function (EF 22%), normal stroke volume (SV 88.8 ml) and severe left ventricular hypertrohy was detected (MM 245 g). Six segments were viable (2-4 mm of wall thickening during systole and the absence of delayed contrast pooling): anteroseptal, inferoseptal and lateral in the mid and apical portions of the left ventricle. The other 10 segments were akinetic.

The border of the lateral and apical region was determined to be the position of the epicardial left ventricular electrode, 3 cm from the diaphragmatic surface, where a wall thickening of 4 mm was measured and delayed contrast poolong was not present. An intraventricular delay of 140 ms was detected between the septum and the selected position by measuring the time of wall thickening.

Epicardial left ventricular lead (Elox, Biotronik) was implanted from anterolateral mini thoracotomy. Left ventricular signal was 9.1 mV, the stimulation threshold was 0.9 V at 0.5 ms pulse delay. Spontaneous intraventricular conduction delay was 120 ms. A dual-chamber pacemaker was implanted (Logos DS, Biotronik), the mode was set to DDD 70/min with 0 ms interventricular delay. QRS duration decreased from 160 ms to 120 ms with biventricular stimulation. Improving contraction pattern, decrease of mitral regurgitation was proven by echocardiography.

After 6 months of resynchronization the functional stage improved to NYHA II, the patient did not require any additional hospitalizations. The stimulation threshold and signal remained stable: 0.8 V and 9.3

mV. The left ventricular end-diastolic and end-systolic diameters decreased (62 and 54 mm, respectively), the left ventricular ejection fraction improved to 26%.

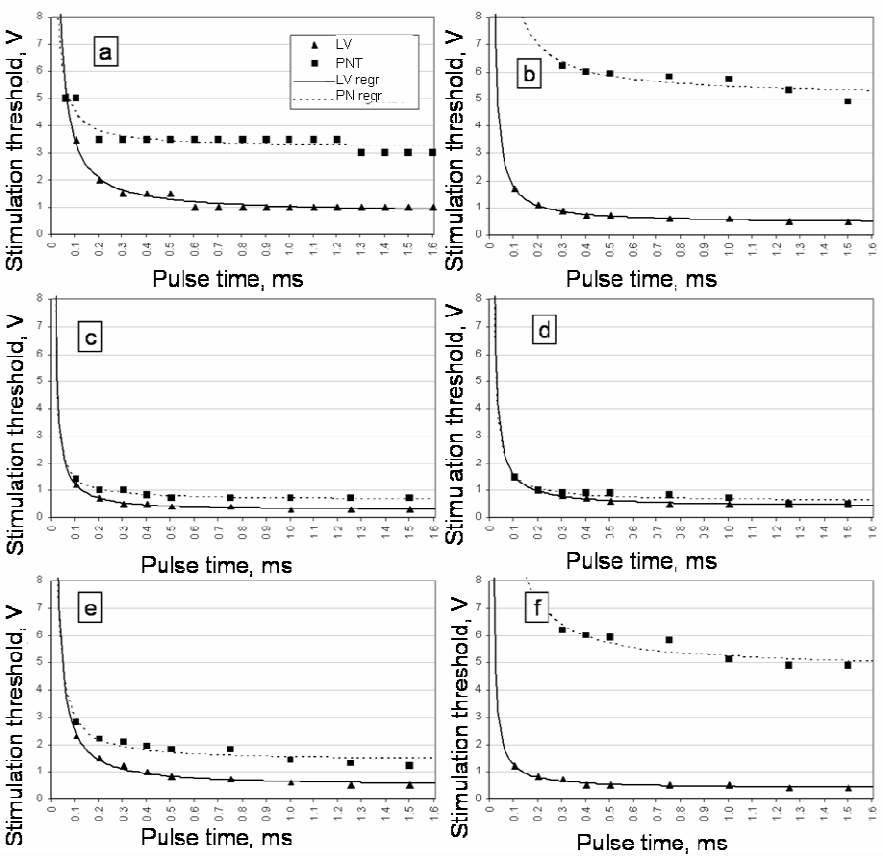
Optimization of left ventricular stimulation pulse

Left ventricular impedance was 617±130 Ohm, the rheobase was 0.84±0.73 V. The regression coefficient showed a good correlation (r^2=0.953±0.007, $p<0.05$ in each patient). No clinical or implantation factor affected significantly these parameters. There was a weak, but significant correlation between left ventricular impedance and left ventricular rheobase.

Phrenic nerve stimulation was found in 6 patients (14%). The rheobase was 2.59±2.01 V, the chronaxie 104±43 ms, the regression coefficient was high (r^2=0.850±0.083, $p<0.05$ in each patient). As the chronaxie point of the phrenic nerve stimulation was lower than the left ventricle (104±18 vs. 333±33 ms, $p<0.05$), the stimulation characteristics of the two structures show a greater difference at longer pulse delay (Graph 1). Using stimulation at 1.5 ms pulse duration and twice threshold, phrenic nerve stimulation appeared only in one patient compared to three patients at the factory setting of 0.4 ms.

Risk of phrenic nerve stimulation was significanty affected only by distal electrode position (p=0.032, OR=6.44, 95% CI 1.008-41.18), while rheobase and chronaxie was not affected by any clinical parameter.

There was no difference in the energy of the stimulation pulse using pulse duration at chronaxie point, 0.4 ms, 0.5 ms or 1.5 ms (p=0.275).



Graph 1. Strength-duration relationship of left ventricular and phrenic nerve stimulation in patients with diaphragm contractions. Dark squares and triangles represent the stimulation threshold at a given pulse time. Stimulation with twice threshold at 1.5 ms pulse time caused phrenic nerve stimulation only in patient „d", while with the factory setting of 0.4 patients „c", „d", and „e" experienced phrenic nerve stimulation.

Effect of induction method on the characteristics of induced arrhythmia

High quality electrograms were recorded with the atrial and ventricular electrodes. Each induction method was 100% efficient: AF started instantly during induction. The induction method did not affect the amount of FF/PA on the atrial channel during the induction ($p=0.839$) or during the induced transient or persistent arrhythmia ($p=0.76$). Similarly, there was no difference on the ventricular channel ($p=0.136$ during induction, $p=0.241$ during induced arrhythmia). Neither the induction method nor the order of induction affected the duration of the induced arrhythmia ($p=0.25$, and $p=0.818$). Five atrial parameters (71%), but no ventricular parameters were significantly affected by the induction method. Neither the atrial nor the ventricular parameters were affected after ceasing the induction, during the induced arrhythmia. The order of the induction did not have a significant effect on the parameters during the induction or during the induced arrhythmia ($p>0.05$ for each parameter) (Table 1).

There was a significant difference between dogs in the amount of atrial FF/PA during the induction and after ceasing it ($p<0.001$ in each case). Ventricular FF/PA was affected by the induction method during stimulation ($p=0.012$), but not after ceasing it, during the induced arrhythmia ($p=0.574$). There was a significant difference in the duration of arrhythmia between the dogs ($p<0.001$).

Using the identification number of dogs as a factor there was a significant difference in 5 atrial (71%) and all 7 ventricular (100%) parameters during the induction and also during the induced arrhythmia (Table 2).

There was a significant difference in the intracardiac atrioventricular delay between the dogs ($p<0.0001$), the averege delay was 119.9±19.8 ms. The delay did not correlate with any atrial parameters during the induction, but there was a significant correlation with all

ventricular parameters. There was a significant correlation with 5 atrial (71%) and 5 ventricular (71%) parameters after ceasing the induction, during the induced arrhythmia.

Parameters	Induction		Persistent or transient AF	
	Atrium	Ventricle	Atrium	Ventricle
Arithmetic mean	$P = .078$	$P = .972$	$P = .785$	$P = .357$
Median	$P = .013$*	$P = .906$	$P = .478$	$P = .309$
5th Percentile	$P = .006$*	$P = .788$	$P = .282$	$P = .251$
95th Percentile	$P = .005$*	$P = .984$	$P = .865$	$P = .458$
Range, 5th-95th percentile	$P < .001$*	$P = .794$	$P = .262$	$P = .892$
SD	$P < .001$*	$P = .435$	$P = .079$	$P = .858$
Minimum value	$P = .883$	$P = .654$	$P = .615$	$P = .425$
No. of significantly affected parameters	5	0	0	0

Table 1. Effect of the induction method on atrial and ventricular parameters. Kruskal-Wallis test

Parameters	Induction		Persistent or transient AF	
	Atrium	Ventricle	Atrium	Ventricle
Arithmetic mean	$P = .058$	$P < .001$*	$P = .003$*	$P < .001$*
Median	$P = .009$*	$P < .001$*	$P = .001$*	$P < .001$*
5th Percentile	$P = .199$	$P < .001$*	$P = .114$	$P < .001$*
95th Percentile	$P = .005$*	$P < .001$*	$P < .001$*	$P < .001$*
Range, 5th-95th percentile	$P = .015$*	$P < .001$*	$P = .015$*	$P = .003$*
SD	$P = .014$*	$P < .001$*	$P = .021$*	$P < .001$*
Minimum value	$P < .001$*	$P < .001$*	$P = .189$	$P < .001$*
No. of significantly affected parameters	5	7	5	7

Table 2. Effect of individual differences (dog number) on atrial and ventricular parameters. Kruskal-Wallis test

„Electrophysiological fingerprint" in atrial fibrillation

There were generally stable parameters in all categories except randomness. The stability of parameters of mean, distribution and variability was similar, while parameters of randomness showed great variability. Individually stable parameters were found also among those describing the variability, distribution and mean of RR intervals. There were no individually stable parameters among those describing the randomness.

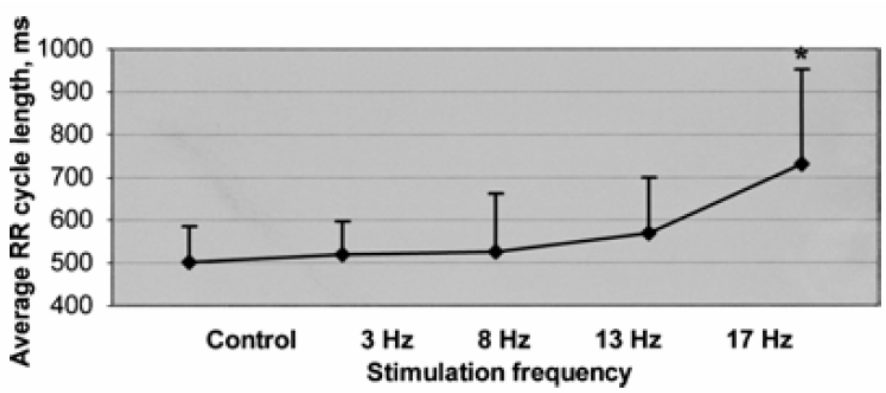
„Fingerprint procedure" was repeated 6 times in each idenification test. The success ratio was 58.04%±0.51% at best using the first quartile value in the formula. Using any other parameters yielded significantly weaker success ratio.

The most successful combination of parameters used together was determined using iteration: using n parameters in the formula, the $n+1^{th}$ parameter was selected as the one which increased the success ratio the most. The formula was expanded up to 50 parameters, the whole procedure was repeated 6 times, repeated use of a parameter was allowed. The success ratio increased up to 11 iterations (72.87±0.40%), then no significant increase was observed. There were no parameters of randomness in the most successful formulae.

Parasympathetic neurostimulation with implanted coronary sinus lead

A left atrial stimulation threshold of 4.4 V was measured at 0.5 ms pulse delay on the day of generator replacement. Incresing the stimulation voltage up to 10 V did not cause ventricular capture. Stimulation with 4 V or 6 V at 3, 8, 13 and 17 Hz, and with 8V at 3, 8 and 13 Hz did not affect the RR intervals significantly. Stimulation with 8 V at 17 Hz significantly increased the RR intervals 1-2 seconds after beginning stimulation (484±79 ms vs. 732±218 ms, $p< 0.05$) (Graph 2). The longest RR interval detected during stimulation was 1700 ms. There was a significant correlation between the

frequency and the cycle length of RR intervals with 8V stimulation (Pearson r=0.838, p<0.05).



Graph 2. 8 V, 17 Hz stimulation significantly increased the average duration of RR intervals (p<0.05, ANOVA)

Negative dromotropic effect was sustained during the 30 seconds of stimulation and ceased immediately after the termination of stimulation. Atropine 1 mg iv. prevented the negative dromotropic effect of stimulation at 8 V, 17 Hz (control RR 456±60 ms, during stimulation 444±72, p=ns). Ventricular stimulation was not detected and the patient did not complain of chest pain or diaphragmatic contractions. Mean arterial blood pressure assessed by non-invasive blood pressure measurement did not change during the parasympathetic neurostimulation (control: 94.4±3.6 Hgmm vs. 93.7±3.9 Hgmm during stimulation, p=ns). There were no other side effects or complications.

CONCLUSION

1. MRI is an applicable method to determine the position of the left ventricular electrode during biventricular pacemaker upgrade. The method used did not cause malfunction of the implanted device.
2. Phrenic nerve stimulation can be avoided by using longer pulse time, based on the difference in the chronaxie values of myocardium and motor nerve. The stimulation energy did not increase significantly with longer pulse delay.
3. The electrophysiological parameters of the induced arrhythmia are affected by the method used to induce atrial fibrillation, which should be considered when evaluating the results.
4. Individually specific characteristics can be found in the RR intervals during atrial fibrillation, which can be used to differentiate between samples of different patients.
5. Chronically implanted lead can be successfully and efficiently used to acutely decrease the ventricular rate during atrial fibrillation by parasympathetic neurostimulation of the AV node.

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