

# **Novel aspects of the non-pharmacological management of tachyarrhythmias in chronic systolic heart failure in adults**

Doctoral thesis

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## 1. Introduction

Arrhythmias are prevalent in patients suffering from chronic systolic heart failure (HF), and their negative impact on mortality and quality of life is significant. Besides the well-established treatment with complex, optimised pharmacological therapy, promising non-pharmacological methods have been emerged in the past decades as frontline therapies: catheter ablation of cardiac arrhythmias and implantation of cardiac electronic devices. Many of them have already been clinically proved to be effective not only in treating and preventing tachyarrhythmias, but also in reducing morbidity and mortality. In the non-pharmacological treatment of supraventricular tachyarrhythmias catheter ablation techniques are impressively effective, therefore they have a primary role over cardiac implantable electronic devices (CIED). Catheter ablation therapy of the common supraventricular arrhythmias in heart failure is not much different from the standard approach. Patients suffering from heart failure can hardly tolerate long sessions and sometimes considerable amount of saline-overload without dyspnoea while lying supine on the table. Therefore every attempt to shorten procedure time without compromising success is welcomed.

Rate control of rapid atrial fibrillation can be achieved by AV-conduction slowing drugs or in drug-refractory cases, by AV-node catheter ablation with prior pacemaker implantation. Instantaneous rate control with pacemaker therapy would be of great importance to prevent or reverse the course of tachycardia-induced cardiomyopathy.

In the non-pharmacological treatment of ventricular arrhythmias both CIEDs and catheter ablation techniques have a firm ground in heart failure. An implantable cardioverter-defibrillator (ICD) has become the standard therapy for patients

with chronic systolic HF at high risk for sudden cardiac death. Therefore it is a reasonable choice for non-hospitalized patients awaiting heart transplantation (HTX). On the downside of ICD therapy are the device-related complications and inappropriate ICD discharges. Defibrillation leads are the most vulnerable part of the ICD system due to their complex design. Fragmentation of these leads during HTX can lead to fragment retention, which can have serious consequences in an immune-compromised patient. Cardiac resynchronisation therapy (CRT) has emerged from the therapeutic options of chronic systolic HF with wide QRS complexes as an effective tool of treatment over the last two decades. Chronic renal failure (CRF) is a condition that worsens the clinical course and mortality of HF. There are growing data in the literature that life expectancy of CRF patients cannot be improved by ICD or CRT-D implantation.

## **2. Objectives**

### ***Instantaneous rate-control of rapid atrial fibrillation with coupled and paired ventricular pacing***

The objective of this study was to compare the acute rate-controlling effects of coupled pacing (CP) and paired pacing (PP) algorithms during atrial fibrillation with rapid ventricular rates in humans in an experimental setting. We also wanted to determine the drive train cycle length resulting in the lowest controlled rate during PP. Safety of the different ventricular pacing algorithms were analysed according to their ability to trigger life-threatening arrhythmias.

### ***Maximum voltage-guided technique for cavotricuspid isthmus ablation during ongoing atrial flutter***

In order to assess the feasibility of the maximum voltage guided technique (MVGTT) during ongoing atrial flutter we compared procedural outcomes in patients undergoing standard anatomical ablation vs. patients with MVGT. The primary endpoints of this prospective randomized study were acute and chronic procedural success, fluoroscopy time, and procedure times. Secondary endpoints were the number of radiofrequency lesions and total radiofrequency application duration.

### ***Defibrillation coil retention during orthotopic heart transplantation***

Surgical removal of the whole ICD system is part of the orthotopic HTX procedure and it is usually carried out without complications. We wanted to explore the incidence and causes of defibrillation lead-related adverse events in our HTX patients who had an ICD implantation while awaiting heart transplantation. We retrospectively collected data on lead retention, conductor fracture, insulation damage, dislodgement, perforation, and lead migration. We compared the incidence of these adverse events according to the type of shock lead.

### ***Cardiac resynchronisation in chronic renal failure***

We aimed to assess the effect of CRF on the long-term clinical outcome and mortality of HF patients who underwent CRT implantation in a single centre. Clinical outcome measures as CRT responder rate, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF),

number of annual hospitalizations, and all-cause mortality were compared between groups with normal and abnormal renal function. We also addressed the question whether the more frequent utilisation of CRT-D over CRT-P could be transformed to a survival advantage in CRF patients.

### **3. Methods**

#### ***Instantaneous rate-control of rapid atrial fibrillation with coupled and paired ventricular pacing***

Sixteen consenting patients (12 males), scheduled for elective pulmonary vein isolation because of paroxysmal or persistent atrial fibrillation, were enrolled into this prospective, single-centre study at the Hungarian Institute of Cardiology. All patients had spontaneous atrial fibrillation during the procedure as we only selected those patients from the paroxysmal group who had an ongoing episode in order to avoid burst-induction of atrial fibrillation on the table. Electrophysiological studies were performed in the post-anaesthetic, non-sedated state. The procedure was done right before pulmonary vein isolation. Standard 5 Fr quadripolar electrophysiological catheters were introduced under fluoroscopic guidance into the right ventricular apex (RVA) and high right atrium (HRA) via the right femoral approach. An arterial line was inserted into the right radial artery for monitoring arterial blood pressure and mechanical pulse rate (MPR). Surface electrogram, intracardiac electrograms from the RVA and HRA, and arterial pressure were monitored and recorded simultaneously and continuously. The distal pairs of the RVA electrode were used to stimulate the right ventricle and the proximal pairs to sense spontaneous ventricular signals. The pacing protocol was generated using a four-channel Radionics stimulator. The pulse output was set as

5 V at 2 ms. Following the measurement of the ventricular effective refractory period (ERP) by ventricular extrastimulus testing, CP or PP was applied in random order in each patient. During CP a coupling interval (CI) of ERP plus 20 ms was used following a sensed ventricular event. To maintain the steady hemodynamic effects of pacing, stimulation protocols were delivered for 3 minutes. PP was started with a basic cycle length of 500 ms followed by an extrastimulus with a CI of ERP plus 20 ms. The drive train was then changed at 50 ms increments. Stimulation protocols were separated by 5-minute breaks. The MPR was recorded for 3 minutes at each increment until the lowest regular MPR frequency was reached. The MPR was analysed under steady-state conditions for all protocols during the last minute. Irregularity index of the pulse cycle length (CL) was defined as the ratio of  $(CL_{\max} - CL_{\min}) / CL_{\max} > 0.10$ . Proarrhythmic effects were characterized by the number of premature ventricular complexes (PVCs) and/or ventricular tachycardia.

### ***Maximum voltage-guided technique for cavotricuspid isthmus ablation during ongoing atrial flutter***

Twenty patients were recruited into this single-centre, prospective, randomized study after having their consent obtained. The presence of cavotricuspid isthmus (CTI) dependent atrial flutter was proven by the atrial activation sequence and concealed entrainment mapping from the CTI during the electrophysiological evaluation, with a difference in tachycardia cycle length and post-pacing interval of less than 30 milliseconds. Patients with prior CTI ablation were excluded from the study. The study patients were randomized into two groups. In group I (ten patients) CTI block was achieved with a complete, continuous anatomical ablation line

using standard ablation technique. After completion of the line without termination of the flutter or without achievement of bidirectional block another line was performed usually at a more anterior location. Mapping for gaps were only performed if the second anatomical line was still unsuccessful. In group II (ten patients) the CTI was mapped, and peak-to-peak bipolar atrial electrogram amplitudes were measured continuously, and the application points were guided by the highest amplitude potentials on the CTI sequentially until bidirectional isthmus block was reached.

In both groups standard pacing manoeuvres were used to verify bidirectional isthmus block after the termination of the atrial flutter. Cross over to another group was not allowed in this study. All procedures were performed during a fasting state, using local anaesthesia. A 20-pole catheter was advanced to the right atrium, and positioned around the tricuspid annulus. An octopolar catheter was positioned in the coronary sinus and a quadripolar catheter in the RVA. All patients received full anticoagulation during the ablation procedure (heparine 100 IU/kg) following the local protocol. An 8 mm tip ablation catheter was used in all cases (Blazer, Boston Scientific). Radiofrequency energy was delivered for 60 s at each application point. Maximum power was set to 70 W, maximum temperature to 65°C in all patients regardless whether they were randomized to groups I or II. Procedural success was determined as the termination of the atrial flutter and achievement of a bidirectional CTI block. The primary endpoints of the study were procedure time, fluoroscopy time, radiofrequency application numbers, and total radiofrequency time. For group II the maximum bipolar atrial signal was determined as target. For group I, after the ablation procedure atrial bipolar signal amplitudes were measured off line at all ablation spots. Follow-up visits were scheduled at 3 and 6 months after the ablation procedure.

### ***Defibrillation coil retention during orthotopic heart transplantation***

We conducted a single-centre, retrospective study, and reviewed all the medical and surgical reports of 117 patients who underwent HTX in the Erasmus MC in Rotterdam, between March 2005 and May 2011. We further analyzed data of those 84 patients (72%) who had an ICD (n=53) or cardiac resynchronization therapy with defibrillator (CRT-D) implantation (n=31) prior to HTX. We determined the time from ICD implantation to HTX, the duration of the transplant procedure, the type and manufacturer of defibrillation leads, and the defibrillator lead-related adverse events (AEs). AEs were defined as lead fragment retention, lead perforation of cardiac chambers, evidence of conductor fracture on X-ray or as a sudden impedance rise, insulation failure, and macrodislodgement of the lead. All patients were closely followed after HTX as a routine part of their clinical management. No patient was lost to follow-up.

### ***Cardiac resynchronisation in chronic renal failure***

Clinical and echocardiographic data of 60 consecutive patients who underwent pacemaker-only biventricular device (CRT-P) or CRT-D implantation were analysed in this retrospective study. Implantations were done between May 2005 and October 2006 in the Hungarian Institute of Cardiology. We assumed the existence of CRF if serum creatinine concentration was  $>130 \mu\text{mol/L}$  on at least two separate days. Patients with both ischemic and non-ischemic dilated cardiomyopathy were included. Patient selection for CRT-P or



CRT-D implantation had been performed according to the guideline in operation at the time of implantation. Patients received optimal pharmacological therapy of chronic HF before selection to CRT. The following baseline characteristics were recorded: age, gender, NYHA functional class, history of ischemic cardiomyopathy, diabetes, CRF, anaemia, atrial fibrillation, LVEF, presence of a permanent pacemaker, proportion of CRT-D at implantation, and annual hospitalisation rate prior to implantation. LVEF was calculated from the apical window of 2D-mode echocardiography using the modified Simpson's rule. Available hospital records and outpatient follow-up documents were reviewed. Data on change in NYHA functional class and change in LVEF were collected at a mean post-implantation period of  $9.6 \pm 3.0$  months. Improvement of one or more NYHA class was considered as a positive response to CRT. Data on all-cause mortality and the annual number of postoperative hospitalisations due to HF had been collected for 36 months. Seven patients were lost to follow-up, so 53 completed the whole course of the study.

## 4. Results

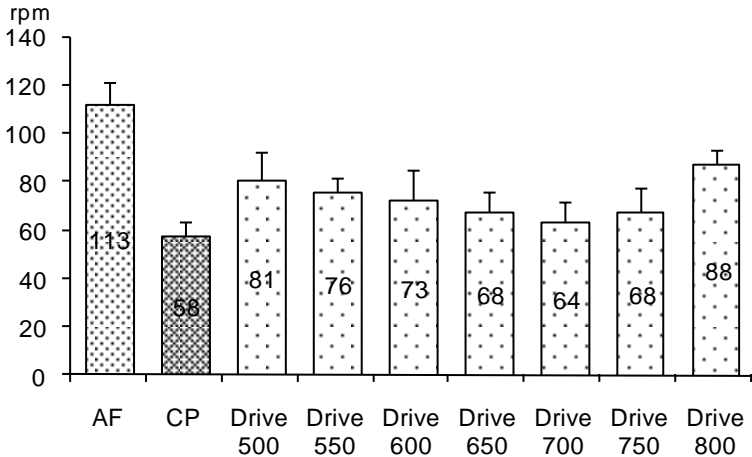
### *Instantaneous rate-control of rapid atrial fibrillation with coupled and paired ventricular pacing*

Results with the coupled pacing protocol

Successful MPR control was achieved in all patients using CP. The MPR significantly decreased from baseline ( $113 \pm 9$  vs.  $58 \pm 4$ /min;  $P < 0.001$ ) (Figure 1). The controlled rhythm remained irregular, as the pulse CL ranged between  $896 \pm 24$  and  $1452 \pm 67$  ms, and the index of irregularity at baseline and

during CP was 0.43 and 0.38, respectively. Neither PVCs nor ventricular tachycardia occurred during CP.

**Figure 1** The rate controlling effect of CP and PP at different drive trains



CP resulted in a significant reduction of the mean MPR. During PP all drive trains resulted in significantly lower pulse rates compared to baseline, and the lowest MPR was achieved at a ventricular drive train of 700 ms. Abbreviations: AF: baseline pulse rate during atrial fibrillation, rpm: rate per minute, Drive: drive trains with respective cycle lengths

#### Results with the paired pacing protocol

With different drive trains PP resulted in different regular MPRs (range  $64 \pm 6$  –  $88 \pm 4$ /min). Increasing the drive train by 50 ms resulted in significantly lower MPR values as compared with the baseline (Figure 1). The lowest MPR achieved was found at the 700 ms drive train. With drive trains > 700 ms an increase in MPR was observed due to the occurrence of intercalated, spontaneously conducted atrial fibrillation beats.

Continuous MPR control was only achieved in seven patients, while PP caused premature beats in nine patients (56%) [mean 7 (range 1–72) PVCs per patient], resulting in failure of continuous MPR control. In these patients PP was regarded unsuccessful. No ventricular tachycardia was observed during PP.

The lowest MPR achieved by PP was significantly higher than in the CP group ( $64\pm 6$  vs.  $58\pm 4$  /min;  $p<0.05$ ). Neither death nor any life-threatening complication occurred during the study.

### ***Maximum voltage-guided technique for cavotricuspid isthmus ablation during ongoing atrial flutter***

In all primary and secondary endpoints the MVGT was superior to the anatomical approach as shown in Table 1. In all patients, atrial flutter was terminated during ablation. However, termination resulted in complete block in only 45% of the patients. In this regard there was no difference between group I and group II (42 vs 48%, respectively). At the end of the ablation procedure bidirectional isthmus block was achieved in all cases. Procedure time was shorter in group II. Significantly less fluoroscopy was used in group II, less application needed for complete bidirectional isthmus block, and radiofrequency application duration was also shorter in group II. There were no major complications related to the procedures. Minor complications such as groin haematoma were not different between the groups.

Atrial bipolar signal amplitudes of each ablation sites were assessed. There was no difference between the maximum atrial bipolar amplitudes in groups I and II. During the median

follow-up of  $8.4 \pm 2.4$  months, 1–1 recurrences of atrial flutter were detected in each group and redo procedures were performed successfully (not included into the ablation results). The occurrence of atrial fibrillation was not statistically different between the groups (group I 25% vs group II 34%).

**Table 1** Baseline characteristics and results of flutter patients treated with the MVG method or with conventional linear anatomical ablation

	<b>Group I</b> <i>(anatomical line)</i>	<b>Group II</b> <i>(MVG)</i>	<b>p</b>
<b>Age (years)</b>	60.6	58.7	NS
<b>Gender (F/M)</b>	3/7	2/8	NS
<b>Procedure time (min)</b>	107±40	47±6,2	0.01
<b>Fluoroscopy time (min)</b>	22.6±10.6	12.1±3.8	0.01
<b>RF numbers</b>	27.1±21.5	5.9±2.4	0.001
<b>RF time (sec)</b>	1370±1120	375±180	0.001
<b>Mapping amplitude (mV)</b>	1.76±0.61	1.82±0.58	NS

RF: radiofrequency

***Defibrillation coil retention during orthotopic heart transplantation***

No lead-related AEs occurred in the single-coil group, while a total of eleven (22%) ICD lead-related AEs were documented in the dual-coil group immediately after HTX. All of the AEs were retained proximal coil fragments of ICD leads. No other kind of defibrillator lead problems occurred post-transplantation. There was no significant difference in the dual-coil cohort with or without fragment retention regarding age,

gender, ischemic aetiology, lead age, or the duration of HTX procedure. Nine different heart surgeons were involved in the HTX procedures, all with ample clinical experience in this field. There was no difference in the distribution of surgeons according to the presence or absence of lead retention. The proportion of manufacturers in the dual-coil group was: St Jude Medical 41%, Medtronic 26%, Guidant 23%, and Biotronik 10%. There was no fragment retention among the Biotronik leads in our patients. The fragmented defibrillation leads came from the St. Jude Medical Riata family in the majority of cases (7/11 = 64%, 43% of all St Jude Medical dual-coil leads); whereas the Medtronic Sprint (2/11 = 18%, 20% of all Medtronic dual-coil leads) and CPI-Guidant families (2/11 = 18%, 22% of all Guidant dual-coil leads) were represented in the other four cases. Except three patients, the ICD extraction procedures of those eleven transplantations were considered complete removals at the time of the transplant procedure, and in eight cases only the postoperative chest X-ray or CT-scan revealed the retained proximal defibrillation coil fragments in the body. On follow-up, one coil fragment migrated into the pericardial space, another into the right atrium causing perforation of the interatrial septum. The latter patient died of multi-organ failure 3 months after HTX.

Four patients died in the retention group. Of the 40 patients without retention in the dual-coil group, and of the 33 patients in the single-coil group also four-four patients died, but the small numbers and absence of any direct, unequivocal relation of the deaths to the retained fragments made any comparison meaningless.

### ***Cardiac resynchronisation in chronic renal failure***

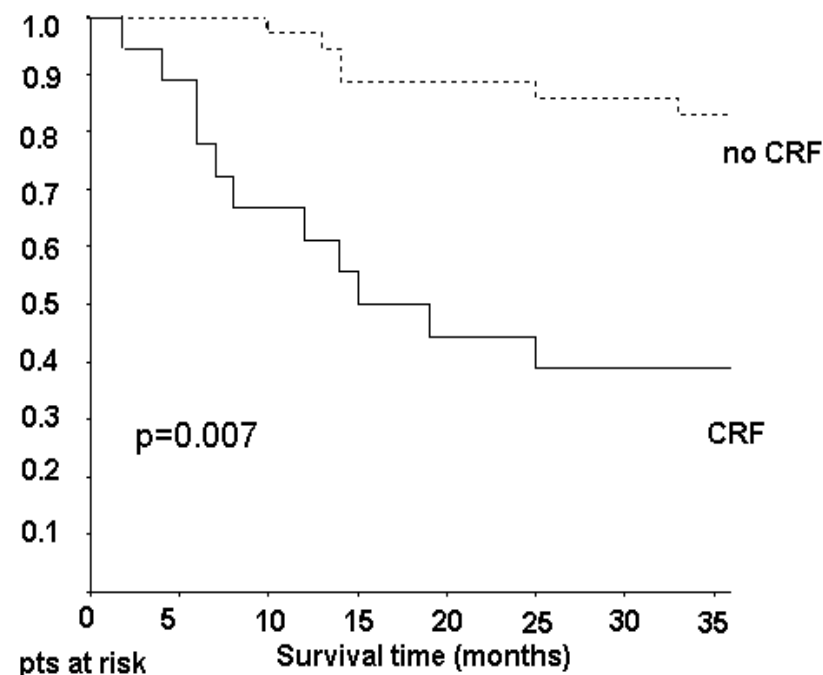
The worse clinical condition of the CRF group was marked by the advanced NYHA class ( $3.1 \pm 0.5$  vs.  $2.6 \pm 0.6$   $p=0.01$ ), more

hospitalisations ( $3.4 \pm 2.4$  vs.  $1.7 \pm 1.1$   $p=0.005$ ), and a previous need for more conventional pacemaker implantations (27 vs. 5%  $p=0.015$ ). Significantly more patients received a defibrillator (i.e. CRT-D) in the CRF group (73 vs. 45%  $p=0.035$ ). CRT resulted in significant clinical improvement in both groups in terms of reduction of NYHA class and in reduction of the annual number of hospitalisations. Although there was a tendency towards an improvement in LVEF, this variable did not reach significance.

The overall clinical response rate of the whole study population to CRT after  $9.6 \pm 3.0$  months was 76%, and 63 % vs. 84% in CRF vs. non-CRF patients, respectively. The effect of CRT on the response rate, on the change of NYHA class, on the improvement in LVEF and on the annual rate of hospitalisations did not differ significantly among the groups with or without CRF.

During the 36-month long follow-up period seven patients were lost to follow-up, all of them were dropped out after the initial six months of the study. Among the remaining 53 patients 18 deaths occurred, resulting in an all-cause mortality rate of 34%. The ratio of CRT-P/CRT-D was 1:1 among the deceased. Thirteen patients died due to end-stage HF, two died due to ventricular fibrillation resistant to multiple ICD therapy, one died in lung cancer, one in acute renal failure, and we lost one patient in multi-organ failure of septic origin 12 months after CRT-D implantation. There were no procedure related deaths. According to the Kaplan-Meier tests for survival, all-cause mortality was significantly higher in CRF patients (61 vs. 17%  $p<0.01$ ). (Figure 2).

**Figure 2** Kaplan-Meier survival function curves of patients suffering from chronic renal failure over the three-year long follow-up period



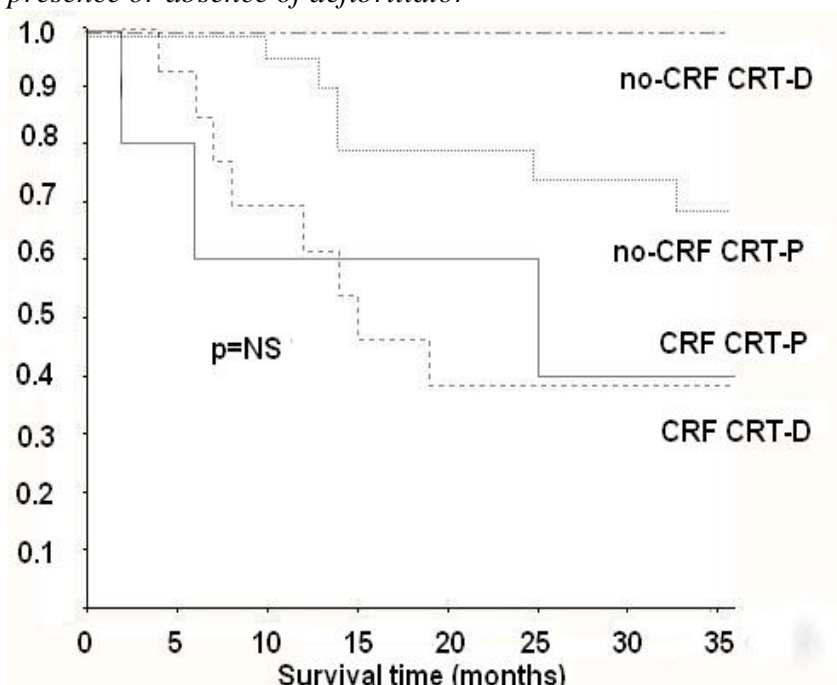
pts at risk	0	5	10	15	20	25	30	35
CRF	18	16	12	9	8	7	7	7
non	35	35	34	31	31	30	30	29

Patients with normal renal function had a significantly better survival over the 3-year long follow-up period. P value represents log-rank test result. CRF: patients with chronic renal failure, no CRF: patients with normal renal function.

Mortality data were also compared on the basis of the type of device implanted (CRT-P or CRT-D). The survival of CRT-D patients showed a clearly significant difference in favour of patients with normal renal function. When comparing the

presence or absence of a defibrillator (CRT-D), the survival curves of CRF patients run along a similar course without any significant difference (Figure 3). Univariate analysis revealed that the presence of atrial fibrillation, anaemia, CRF, and the number of preoperative hospitalisations proved to be as significant crude predictors of death (Table 2).

**Figure 3** Kaplan-Meier survival function curves of CRT patients with and without renal failure with regard to the presence or absence of defibrillator



The difference in survival of CRT-D patients with or without CRF was clearly significant, favouring patients with normal renal function.

P represents log-rank test result between CRT-P and CRT-D patients suffering from CRF



*Table 2 Univariate analysis of the crude predictors of excess mortality in the CRF group*

	<b>HR</b>	<b>95% CI</b>	<b>P</b>
<b>atrial fibrillation</b>	2.85	1.07-7.43	0.033
<b>CRF</b>	5.30	1.94-14.4	0.001
<b>anaemia</b>	4.58	1.58-13.2	0.004
<b>prehosp#</b>	1.55	1.27-1.88	0.001

HR: hazard ratio, CI: confidence interval, CRF: chronic renal failure, prehosp# : annual number of hospitalisations before implantation

## **5. Conclusions**

1. We can conclude that both CP and PP promptly and feasibly reduce the pulse rate during rapidly conducting atrial fibrillation.
2. PP has the advantage of achieving different target heart rates with different drive trains.
3. We have demonstrated first that CP has a more pronounced and more effective rate-slowing effect.
4. No life-threatening arrhythmia occurred during the study. CP seems to be less proarrhythmic regarding the number of triggered PVCs.
5. Our results proved it first that the MVGT is a feasible method even during ongoing isthmus-dependent atrial flutter. Previous works showed similar results only during coronary sinus pacing, when the arrhythmia was not present at the time of the procedure.
6. Our data confirm that the MVGT is an effective technique to considerably decrease procedure, fluoroscopy, and radiofrequency application times making it an appealing technique for heart failure patients, as well.
7. Our group was the first in demonstrating that defibrillation lead fragment retention is a clinically relevant problem during orthotopic HTX, as 22 % of patients with dual-coil defibrillator lead shown retained fragments in the vasculature.

8. No single-coil defibrillator lead removal resulted in fragment retention.

9. The majority of cases came from the Riata dual-coil shock lead family.

10. The use of single-coil defibrillation leads in candidates to HTX is highly recommended to prevent such complications.

11. Patients with dual-coil defibrillation leads need extra awareness from the surgeon during HTX and lead explantation, as the ICD lead must be cut between the coils and never through the proximal coil. All explanted materials should be thoroughly checked for completeness.

12. Patients suffering from CRF have a positive short-term clinical response to CRT with improvement in NYHA functional class and a decrease in the number of hospitalisations, but their survival benefit is strongly questionable on the long run.

13. In our study even the significantly higher CRT-D implantation rate in CRF patients could not abolish this unfavourable outcome.

14. Predictors of an excess mortality were the presence of atrial fibrillation, anaemia, more hospitalizations pre-implantation, and the presence of CRF at baseline.

## **Publications related to my thesis**

**Abraham P**, Caliskan K, Szili-Torok T. (2012) High incidence of unexpected defibrillation coil retention during orthotopic heart transplantation. *J Heart Lung Transplant*, 8: 909-911.

**IF: 5.112**

**Ábrahám P**, Földesi Cs, Kardos A, Mihálcz A, Temesvári A, Bálint H, Szili-Török T. (2014) Renal failure confers higher mortality despite more frequent defibrillator implantation in patients with cardiac resynchronisation. *Card Hung*, 44: 155-160.

Bauernfeind T, Kardos A, Foldesi C, Mihalcz A, **Abraham P**, Szili-Torok T. (2007) Assessment of the maximum voltage-guided technique for cavotricuspid isthmus ablation during ongoing atrial flutter. *J Interv Card Electrophysiol*, 19: 195-199. **IF:1.246**

Kardos A, **Abraham P**, Mihalcz A, Foldesi Cs, Szili-Torok T. (2012) Coupled pacing controls rapid heart rates better than paired pacing during atrial fibrillation. *Europace*, 14: 481-485.

**IF: 2.765**

## **Publications not related to my thesis**

**Abraham P**, Abkenari LD, Peters EC, Szili-Torok T. (2013) Feasibility of remote magnetic navigation for epicardial ablation. *Neth Heart J*, 21: 391-395. **IF: 2.263**

Kis Z, Földesi C, Pál M, Som Z, Csillik A, **Ábrahám P**, Temesvári A, Fontos G, Szatmári A, Andréka P, Kardos A. (2013) Percutan bal pitvari fülcsezárás dabigatrannal való fülcsethrombus feloldását követően. *Orv Hetil*, 154: 262-265.