DOI:10.14753/SE.2017.2002

The quest for improvement of cardiac resynchronization therapy

Doctoral Dissertation

Eszter Mária Végh MD

Doctoral School of Basic Medicine

Semmelweis University

Supervisor: László Gellér, MD, PhD, associate professor
Official reviewers: Zoltán Járai MD, PhD, honorary professor
András Vereckei MD, PhD, associate professor

Head of the Final Examination Committee:
Anikó Somogyi MD, PhD, professor
Members of the Final Examination Committee:
Lívia Jánoskuti MD, PhD, associate professor
Gábor Duray MD, PhD

Budapest
2016

DOI:10.14753/SE.2017.2002

Table of contents

DOI:10.14753/SE.2017.2002

DOI:10.14753/SE.2017.2002

DOI:10.14753/SE.2017.2002

DOI:10.14753/SE.2017.2002

List of abbreviations

ACE	angiotensin-converting-enzyme,
6MWT	6-minute walk test
AF	atrial fibrillation
ARB	angiotensin II type 1 receptor blocker,
AV	atrio-ventricular
CABG	coronary artery bypass graft,
CI	confidence interval
CMP	cardiomyopathy
CPX	cardiopulmonary exercise testing
CRT	cardiac resynchronization therapy
CS	coronary sinus
ECG	electrocardiogram
HF	heart failure
HFH	heart failure hospitalization
HR	hazard ratio
HTLD	composite endpoint of HF hospitalization, heart transplantation, left ventricular assist device, or death.
ID	intrinsicoid deflection
LBBB	left bundle branch block,
LAD	left axis deviation
LV	left ventricle
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction,
LVIDd	left ventricular internal dimension diastole;
LVIDs	left ventricular internal dimension systole
NYHA	New York Heart Association
OR	odds ratio
PCI	percutaneous coronary intervention
PNS	phrenic nerve stimulation
RBBB	right bundle branch block
RV	right ventricle

DOI:10.14753/SE.2017.2002

TSH thyroid-stimulating hormone

VCG vectrocardiogram

DOI:10.14753/SE.2017.2002

1. Introduction

Since the two decades of clinical application, cardiac resynchronization therapy (CRT) has revolutionized the patient care with heart failure and dyssynchrony. (1-3) It also catalyzed the cooperation among different field of cardiology, including electrophysiology, heart failure and cardiac imaging. (4)

1.1. The cardiac resynchronization therapy

The ventricular myocardium is activated by a electrical waveform, through the His-Purkinje system. In altered electrochemical substrates, conduction gets impaired, that can result uneven and slower electrical propagation, leading to an electrical, subsequently mechanical dyssynchrony. The delayed activation is most often the results of left bundle branch block (LBBB), that results interventricular and intraventricular dyssynchrony. Long-standing cardiac dyssynchrony leads to a pathologic remodeling, causing ventricular dilatation, worsening of systolic and diastolic function. Cardiac resynchronization can be achieved by stimulating the delayed ventricular area, by adding a left ventricular lead to a standard pacemaker or implantable defibrillator system. Traditionally, the left ventricular lead is introduced to the side-branches of the coronary sinus (CS).

Nowadays, CRT is a well-established therapeutic strategy for patients with advanced congestive heart failure (HF) and prolonged QRS complex (5-9). It has been shown to improve cardiac pump function, HF symptoms and quality of life. (10)

CRT reduces mortality and morbidity significantly in this population, but despite its proven clinical value, a significant minority of patients do not derive benefit from CRT; termed “non-responders.” (6, 11-14) The ratio of non-responders ranges from 20-30% (in studies using soft clinical endpoint, as improvement in NYHA class or quality of life) to 30-50%, where echocardiographic reverse remodeling was examined. (15)

Reasons for non-response are likely multifactorial, and part of the explanation may be absence of significant dyssynchrony prior to treatment, or ineffective resynchronization due to suboptimal device programming or lead placement. (16, 17) After the initial learning curve, biventricular devices can be implanted with a success rate >90%,

however the long-term device-related event rate remains higher, than in single- or dual-chamber pacemakers and defibrillators. (18) Futhermore, the implantation of biventricular devices and multiple leads mean considerable costs to the health-care system, therefore the best possible application and patient selection is expected from human and financial point of view.

The successful CRT can be forwarded by the following factors:

- improved patient selection,
- optimal lead positioning,
- therapy optimization, and
- multidisciplinary postoperative care.

According to the recent European guidelines, CRT is indicated for patients with heart failure and wide QRS complex (Table 1). A QRS duration ≥150 ms is a strong predictor of CRT response, while values between 120 and 150 ms require further evidence. (19, 20) More recently, LBBB morphology of the QRS complex has been shown to be the strongest predictor of CRT response. (8, 21-26) However, definition of LBBB pattern is drawing increased attention: conventionally - and in major clinical trials (MADIT-CRT (8), REVERSE (27)) - it is defined as QRS duration of 121-130 ms, negative QRS in V1 lead and absence of Q wave in V5-6, I and aVL. Clincal guideline of ESC suggest stricter criteria, while definition of Strauss and colleagues require mid-QRS notching or slurring in two or more contiguous lead of V1, V2, V5, V6, I or aVL, as well. Recently, two studies has demonstrated, that refinement of criteria can predict better response, compared to the conventional ones. (25, 28) A relation was also found between the presence of notching or slurring and the mechanical LBBB pattern in 2D longitudinal strain echocardiography.

In patients with RBBB pattern or intraventricular conduction disturbances, the benefits of CRT could not be verified in MADIT-CRT and RAFT trials, or even worse outcomes were found, except for cases with a favourable lead placement. (29)

Table 1. ESC guidelines for CRTv(30)

CRT is indicated (class I)

- Sinus rhythm, LBBB with a QRS duration >150 ms, and NYHA class II, III, and ambulatory IV (evidence level A)
- Sinus rhythm, LBBB with a QRS duration 120–150 ms, and NYHA class II, III, and ambulatory IV (evidence level B)
- Conventional pacemaker, high percentage right ventricular pacing, and NYHA class III and ambulatory IV (evidence level B)

CRT should be considered (class IIa)

- Sinus rhythm, non-LBBB with a QRS duration >150 ms, and NYHA class II, III, and ambulatory IV (evidence level B)
- Chronic atrial fibrillation, a QRS duration ≥120 ms, NYHA class III and ambulatory IV, and near to 100% biventricular pacing guaranteed or concomitant atrioventricular junction ablation (evidence level B)
- Chronic atrial fibrillation with uncontrolled heart rate in candidates for atrioventricular junction ablation (evidence level B)
- Conventional pacemaker indication and expected high percentage of ventricular pacing (evidence level B)

CRT can be considered (class IIb)

- Sinus rhythm, non-LBBB with a QRS duration 120–150 ms, and NYHA class II, III, and ambulatory IV (evidence level B)

CRT is not recommended (class III)

- Sinus rhythm, QRS duration <120 ms, and NYHA class II, III, and ambulatory IV (evidence level B)

All patients should have chronic heart failure and a left ventricular ejection fraction ≤35% despite adequate medical treatment. Abbreviations: CRT, cardiac resynchronization therapy; LBBB, left bundle branch block.

Whether the presence of mechanical dyssynchrony has a predictive value, has been debated extensively in the past years. After promising single-center studies, in PROSPECT trial, echocardiography-based mechanical dyssynchrony indices failed to improve the patient selection. (13) The disappointing outcomes can be partly explained

by the usage of tissue Doppler and M-mode techniques, that might be improved by speckle tracking methods. (31) However, patients with mechanical dyssynchrony and narrow QRS did not benefit from CRT, according to EchoCRT trial. (32)

Ischaemic etiology of cardiomyopathy occurs in more than half of CRT patients. Major trials have confirmed, that these patients has non-inferior outcome, compared to the non-ischaemic etiology. (8, 33) Although, presence of scarring can affect the response to CRT, as extensive scarring can diminish the viable tissue that can be recruited by the resynchronization, and pacing in the scar tissue can be ineffective. Therefore, nuclear imaging and cardiac MRI can be helpful in prediction of the outcome of CRT. (34, 35)

In early studies of resychronization it was demonstrated, that pacing of the left ventricular free wall can change haemodynamics. (2) Initially, possible lead positions were based on anatomy, however the subsequent studies did not confirm a specific location. Singh and colleagues suggested to avoid apical positions, (36) but other studies showed no difference in outcome, based on apical or basal lead position. (37) Similarly, the benefit of posterolateral pacing site over the anterior wall was debated. (37, 38) Apparently, a personalized lead positioning strategy is required to achieve optimal resynchronization, that can be facilitated by speckle tracking imaging or by monitoring left ventricular electrical delay during implantation. (39, 40) With novel technological developments, multipole leads and endocardial pacing opportunities provide new alternatives for even more effective resynchronization, with finding the optimal pacing site or transfer multisite pacing.

After the implantation and during follow-up, adjusting of the RV and LV pacing can optimize the ventricular filling, inter- and intraventricular resynchronization. In single-center studies, optimization has improved haemodynamic function and clinical response. (41, 42) However, randomized clinical trials could not serve with unambiguous evidences for echocardiography-based optimization. Besides, the procedure requires multiple, skilled operators from different fields, that is logistically challenging and costy in everyday clinical practice. In canine models, vectorcardiography facilitated optimization, that translated into acute haemodynamic improvement. (43) The novel electrogram-based, vendor-specific AdaptiveCRT algorithm was associated with superior results in terms of outcome, in patients whose LV fusion was optimized. (44)

In order to achieve the electrical and mechanical remodeling, effective biventricular pacing is required. It was shown, that >95% of the heart beats should be biventricular paced, to reach the benefits of CRT. Loss of capture is often observed in patients with atrial fibrillation, that can result suboptimal therapy response in this group of patients. In this patient group, atrioventricular nodal ablation can increase the therapy response rate to the level of patients in sinus rhythm. (45)

The postoperative care of CRT patients is not well studied yet, however a multidisciplinary approach was associated with improved clinical outcomes and reduced number of hard clinical endpoints, in a single-center experience study. (4) Another study has demonstrated, that during a comprehensive protocol-driven evaluation most of the non-responders had an identifiable reason for suboptimal response, as inadequate device settings (47%), suboptimal mechanical treatment (32%), arrhythmias (32%), inappropriate lead position (21%) or lack of baseline dyssynchrony (9%). After multidisciplinary recommendations device settings and/or medical therapy modifications resulted fewer adverse events in this group. (46) Furthermore, early risk stratification can help to point out those patients, who need a more frequent follow-up at device, heart failure or internal medicine specialists.

With my colleagues, I intended to investigate this complex process from patient selection to post-operative care and contribute to improved care with the following projects:

1.2. PR interval

Atrioventricular dyssynchrony with resulting impaired left ventricular filling is common in patients with wide QRS complex on ECG, and especially in the setting of concomitant prolonged PR interval with AV block I. (47-49). Mechanistically, correction of the prolonged PR interval by CRT pacing should have a positive effect on ventricular filling in diastole “on top of“ the resynchronization of ventricular contraction during systole. On the other hand, a prolonged PR interval can also be a marker of more advanced heart disease and therefore associated with a poorer prognosis (49). There is conflicting evidence regarding the clinical outcomes in CRT for patients with prolonged PR interval (50-53).

1.3. Electrocardiography based score for risk stratification

QRS duration and morphology reflect the electrical timing and activation sequence of the ventricles, hence it is intuitive to evaluate the effect of CRT using pacing-induced changes in ECG findings, since reversal of the electrical pathology indicates a potentially good effect of the treatment. Consequently, an easy to use ECG-based algorithm for optimization of pacemaker lead placement and immediate prediction of response and clinical outcome would be a valuable tool.

1.4. Vectorcardiography-based T-wave area in prediction of therapy

The QRS complex reflects the sequence of electrical activation, that is: depolarization, throughout the ventricular wall. While this activation sequence is clearly central to electrical dyssynchrony, it ignores the importance of the equally vital repolarization phase of the myocardium. We hypothesized that the T-wave may provide additional information, since it is reflective of the plateau and repolarization phases of the myocardial action potential. These phases are determined by the activity of many ion channels, including those that regulate intracellular calcium concentrations, that mediate contraction and relaxation.

In order to explore the predictive value of the T-wave, we retrospectively investigated the electrocardiograms from a large cohort of CRT patients. For more comprehensive analysis of the T-wave, ECG signals were converted into vectorcardiograms (VCG). The advantage of the VCG is that it contains three-dimensional information of the electrical forces within the heart and might provide more valuable information than the one-dimensional ECG.

1.5. T-wave area in prediction of outcome

Then we examined whether the T-wave area in LBBB patients also predicts the long-term clinical outcome to CRT. In order to do so, we extended the patient group from the previous study with CRT patients with known clinical follow-up of at least 3 years. This potential predictive value was also compared to other relevant electrocardiographic parameters.

1.6. Hyponatremia

Hyponatremia is a common electrolyte abnormality, seen in approximately 20% of patients with HF and it has been particularly demonstrated to be of much prognostic significance in HF population. (54-57) However, there is a paucity of data looking at how serum sodium levels impact patients who receive CRT.

1.7. Hypothyroidism

Notably, hypothyroidism is a frequent comorbid condition for patients with HF, but to our knowledge has not been previously specifically evaluated for its impact on CRT response. Persistent subclinical hypothyroidism has been associated with the development of HF in patients with and without underlying heart disease. (58, 59) The Health, Aging, Body Composition population based study showed that participants with TSH ≥ 7μU/mL had 3 times higher HF events than euthyroid patients (60).The Cardiovascular Health Study showed a greater incidence of HF events among participants >65 years of age with TSH ≥ 10 μU/mL (58). However, there are also studies with contradictory findings where no relationship was established between hypothyroidism and cardiovascular risk. (61, 62) The prevalence of hypothyroidism in HF patients has been reported from 7% for overt hypothyroidism to 14% for subclinical hypothyroidism. (58, 63) Guidelines from the American College of Cardiology recommend workup for all cases of HF to include screening with thyrotropin levels. (64)

1.8. Device measured physical activity

For effective clinical management of heart failure patients living with CRT, early risk-stratification to identify potential non-response, and also finding simple and reliable method to evaluate the functional status is important. Although 6-minute walk test (6MWD) and cardiopulmonary exercise testing (CPX) have been shown to provide prognostic information for all-cause hospitalization and mortality in HF population, (65-69) they have significant limitations both logistically and in their reproducibility. (70) Of note, both of these tests can only be performed periodically, and are thereby reflective of the clinical status of the patient only at that particular point in time. More

recently, data derived from implantable devices have gained considerable attention as risk stratifying measures. (71-73) Most contemporary devices have the ability of measuring daily physical activity via sensors incorporated within the device. The activity information can thereby be acquired on a daily basis over prolonged periods of time. (74) Despite the ease of acquiring this information, there are limited data examining the relationship of device-based physical activity measures and clinical response to CRT.

1.9. Coronary sinus side branch stenting

Despite continuous technical developments in the last few years, implantation of a CRT system may be challenging. The success rate of coronary sinus (CS) lead positioning is 88-96% in previous clinical studies, (75-78) but even in the recently published MADIT CRT trial, 7.5 % of the CS lead implantations were unsuccessful. (79) During follow-up, 5-10 % of patients require re-operation because of CS lead dysfunction. [76, 77, 79-81]

Stent implantation, which anchors the CS electrode to the wall of the coronary sinus side branch, may increase the stability of the lead. A more stable CS lead position may increase implantation success rates and decrease the number of postoperative complications. The procedure was described in a previous single center observational study of our working group and in case reports. (82-85) In this study, long-term follow-up results of coronary sinus stenting are reported in a larger patient population.

DOI:10.14753/SE.2017.2002

2. The aims of our studies

- We assessed the relationship between PR interval duration and outcomes in patients undergoing CRT.
- We searched for novel predictors based on 12-lead ECG, registered before and after biventricular pacing. Our aim was to establish a simple score for early risk stratification and therapy optimization.
- Based on vectorcardiographic analyses, we compared the different depolarization and repolarization parameters to the established ECG predictor of QRS duration. We also investigated the potential predictive values of these repolarization parameters within different QRS morphologies, in terms of therapy response and long-term clinical outcome.
- We examined the effect of pre- and postoperative hyponatremia on HF patients receiving CRT, and the influence of CRT on this electrolyte abnormality and consequently clinical outcomes.
- We determined how hypothyroidism in patients with HF impacted response to CRT.
- We investigated the prognostic value of device-measured physical activity data as compared to a one-time 6MWT in predicting clinical response to CRT.
- We observed the effectiveness, safety and long-term outcome of stent implantation to anchor the lead to the wall of the CS side branch.

DOI:10.14753/SE.2017.2002

3. Methods

3.1. Study population of the therapy prediction projects

The questions regarding the prediction of therapy response and oucome were examined in the CRT patient register of the Massachusetts General Hospital (MGH). These patients who met established indications (New York Heart Association class III/IV symptoms, left ventricular ejection fraction <35% and QRS duration >120 ms) or had QRS<120ms with significant mechanical dyssynchrony), underwent CRT implantation, between 2004 and 2010. (86-88) The patient population consisted of 569 consecutive cases.

The right ventricular (RV) lead was implanted at the RV apex or septum, and the right atrial lead was placed at the right atrial appendage. LV leads were positioned in the most favorable available anatomic branch of the coronary sinus (CS) that resulted adequate lead stability with acceptable pacing parameters, without diaphragmatic stimulation, preferentially in a lateral or posterolateral vein branch of the coronary sinus.

The patients were prospectively followed according to a standardized protocol in a multidisciplinary clinic, including evaluation by electrophysiologists, heart failure specialists and echocardiography imaging specialists (4). Echocardiographic optimization was completed at 1-month follow-up. Atrio-ventricular delay was determined with monitoring the mitral inflow during gradual shortening of the delay, until maximal separation of A and E waves was obtained, without truncation of the A wave. For optimal VV delay, different RV and LV preexitation values were set, while the maximal velocity time integral was measured. Echo-optimization was uniformly performed after October 2005, and 380 of the total 491 patients in the study population underwent the echo-optimization process. The results in the remainder of the patients were similar to those of the entire population, and echo-optimization did not impact the results of the studies.

Clinical events including heart failure hospitalizations, heart transplantation, left ventricular assist devices (LVAD) and mortality were recorded and crosschecked with the social security death index. HF hospitalization was defined as necessity of inpatient admission due to acute cardiac decompensation, symptoms of shortness of breath, signs

of congestion on the chest radiograph, peripheral oedema, or relieve of shortness of breath after intravenous medical therapy. Transthoracic echocardiography was performed in a standardized manner. For assessment of left ventricular ejection fraction Simpson's biplane method of disks was applied. CRT response was defined as at least 10% improvement of LVEF at the six-month follow-up, compared to baseline. Patients who received a heart transplant or an LVAD prior to the six-month follow-up were categorized as non-responders. The primary endpoint was a composite of all-cause death, heart transplantation, placement of left ventricular assist device (LVAD), and heart failure hospitalization. The project was approved by the Partners Institutional Review Board and Ethics Committee and was conducted in accordance with the Declaration of Helsinki.

3.2. Echocardiography

Transthoracic echocardiography was performed at baseline and at 6-months clinical follow-up. The images were taken by Philips iE33 (Eindhoven, The Netherlands), SONOS 5500/7500 (Andover, MA, USA) and General Electric Vivid 7 (GE, Milwaukee, WI) ultrasound machines. CRT response was defined as absolute increase in LVEF of ≥5% after 6-months of CRT, determined using the biplane method of discs (modified Simpson's method).

3.3. ECG registration

Before CRT implantation and during follow-up visits, supine 12-lead ECGs were recorded digitally by a MAC 5500 ECG Machine (GE Healthcare, Waukesha, WI, USA) at a paper speed of 25 mm/s and a frequency of 250 Hz. All ECGs were stored digitally as PDF files in the MUSE Cardiology Information system (GE Medical System).

3.4. Statistical analysis

The statistical analysis was performed using IBM SPSS statistics software version 21 (SPSS Inc, Chicago, Illinois). Continuous and discrete variables are presented as mean±standard deviation (SD) and counts (percentages), respectively. Normality was examined by Shapiro-Wilk test. Linear correlations were evaluated by Pearson's correlation or Kendall's tau coefficient when appropriate. Comparison between different

patient groups was performed using either one-way ANOVA (continuous variables) or the χ^2 test (discrete variables), and Fisher's exact test in the case of cell sizes of less than five. Follow-up paired comparisons were made using the Tukey test. The classification performance of electrical parameters in identifying CRT response was evaluated by odds ratios (OR) calculated using logistic regression models. The likelihood ratio test was used for comparison of the goodness-of-fit of hierarchical models.

The Kaplan-Meier estimator of survival function was used to evaluate the associations between variables and reaching the primary or secondary endpoints. The log-rank test was used to determine probability values. The predictive performance of electrical parameters in predicting CRT response was evaluated by the Cox proportional hazard regression analyses and tested using the Wald-test. The Cox regression models were fitted for covariates ($p<0.10$, if not signed differently), where a backward stepwise selection approach was used. A two-sided p-value <0.05 was considered statistically significant.

3.5. Project-specific methods

3.5.1. PR interval

Patients with atrial or ventricular pacing at baseline, atrial fibrillation at baseline, or missing ECG within one year prior to implantation were excluded from analysis.

All ECGs were performed within one year prior to implantation. ECGs recorded at the closest date to implantation date were preferred for use in the analysis. PR interval was defined as the interval from onset of the P-wave deflection to the junction with the QRS complex. The PR intervals were measured automatically by the ECG machine and subsequently verified manually. Based on the intrinsic PR interval measurements, patients were divided into two cohorts: <200 ms and ≥ 200 ms, in accordance with previous studies. (52)

3.5.1.1. Statistical analysis of the substudy

Clinically relevant baseline covariates were entered into the Cox proportional hazard model at a p value of less than 0.05, and remained in the model if the associated p value

was less than 0.05. Receiver operating curves analysis was performed using the Youden index to identify optimal cut-off value of PR interval measurement for predicting outcomes after the CRT implantation. Based on the results of the ROC analysis, the PR interval was dichotomized with a cutoff value of 200 ms.

3.5.2. ECG-based risk stratification score

3.5.2.1. ECG measurements

The measurements on the ECGs were made with CardioCaliper 3.3 (Iconico Inc., New York, NY, USA). CardioCaliper is publicly available and was used in combination with an on-screen digital view of a pdf file with the ECGs in normal size (100%) and with a time-resolution of 25mm/s. The program shows a caliper on top of the pdf ECG image, and allows a detailed and accurate on-screen assessment of elapsed time and voltage. QRS duration was measured on native ECGs from the earliest deflection in any lead of the QRS to the last offset of the QRS wave in any lead (Figure 1A). On paced ECG the start point was uniformly the first ventricular pacing spike (Figure 1B). Among the different leads, the longest duration value was chosen. The summed QRS amplitude was determined in lead V1 by taking the voltage of the maximal R wave and the absolute value of the voltage of the Q or S wave from the baseline and summing them in unit of millivolt (Figure 1D and E). The intrinsicoid deflection (ID) onset was defined as the time from the earliest onset of the QRS morphology in leadV1 to the point where the maximum deflection toward baseline was registered, or immediately after the peak of the R wave, as previously described (Figure 1C) (89). QRS duration and ID onset were registered in milliseconds (msec). The 1-month ECGs obtained for this study were recorded before the optimization process. After the echo-based optimization, additional ECG was not obtained routinely. However, in order evaluate the stability over time of the measured parameters of the score, we also examined the ECGs recorded at the 6-month visits (i.e. after echo optimization at the previous visit). Those parameters showed very high correlations with the 1-month values and no significant changes were noted.

DOI:10.14753/SE.2017.2002

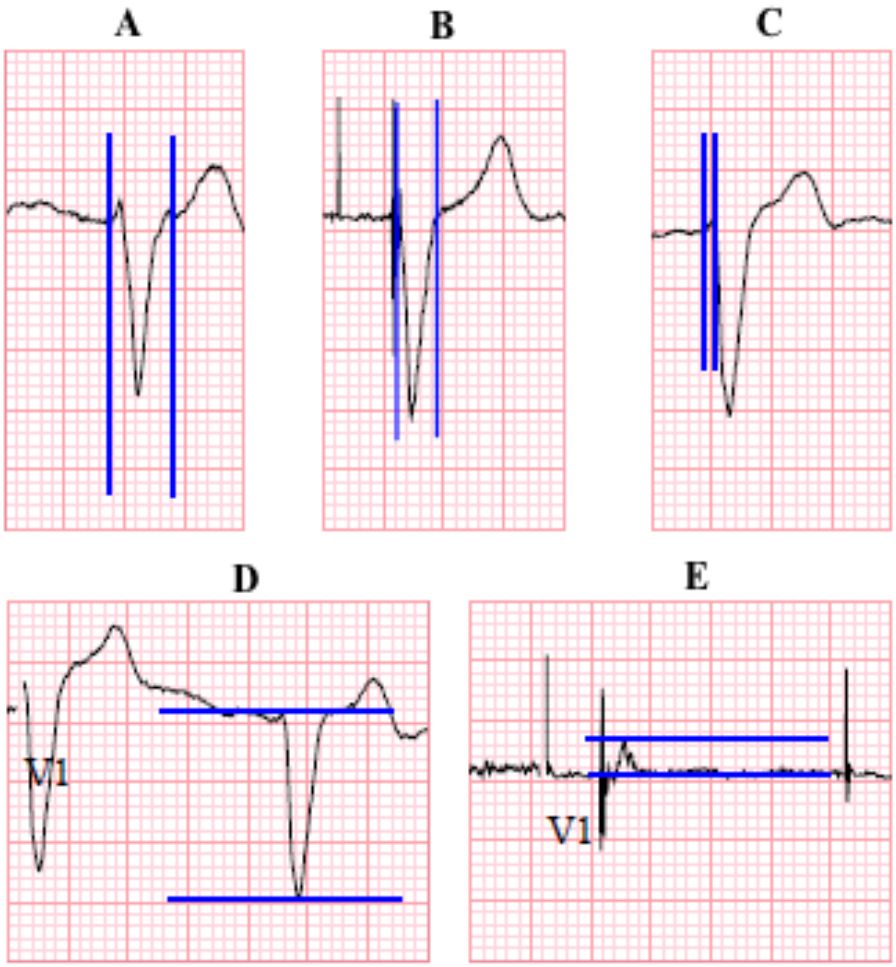


Figure 1. Measuring of the parameters of the score: (A) QRS duration before and (B) QRS duration after biventricular pacing, (C) time to ID in V1 lead, (D) Q+S amplitude before and (E) after CRT.

3.5.2.2. Construction of the score

The predetermined ECG score was based on the standard 12-lead ECG, and included three parameters:

- One point was assigned for a reduction of QRS width of at least 20ms compared from baseline ECG to post-implant ECG.
- One point was assigned for a reduction of at least 50% in the summed amplitude of R+S in lead V1 from baseline ECG to post-implant ECG.
- One point was assigned if the ID point was identified within the first 40ms from QRS onset at the follow-up ECG in the V1 lead.

Thus the total score ranged from 0 to 3 points, and this number was used in the statistical analyses for prediction of clinical endpoints and reverse remodeling. The exact cut-off values were chosen in order to be clinically relevant and easy to appreciate on a standard ECG 25mm/s or 50mm/s printout, without sophisticated extra measuring equipment other than a standard ECG recording facility. Intra- and inter-observer variability for the ECG measurements were very high: The intra-observer correlation coefficient was 0.966 for QRS duration, 0.963 for time to intrinsicoid deflection in V1, and 0.995 for amplitude in V1 (all $p<0.01$). The corresponding inter-observer coefficients were 0.981, 0.980 and 0.955 respectively (all $p<0.01$).

3.5.3. Vectorcardiography (VCG) based T-wave area

Patients with a pre-implantation ECG available in digital archives, either in sinus rhythm or atrial fibrillation (AF), were enrolled in this retrospective analysis. ECGs with <3 normal beats (e.g. due to premature ventricular complexes), remarkable interfering noise, or ventricular pacing were excluded from the analysis.

ECGs recorded up to one month before CRT implantation were included into the analysis. The vector graphics of these PDF files were obtained by converting the files to a .svg file using Inkscape version 2 (Boston, MA, USA). The calibration pulses, as indicated in Figure 2, were used to scale the signals to real time and amplitude.

DOI:10.14753/SE.2017.2002

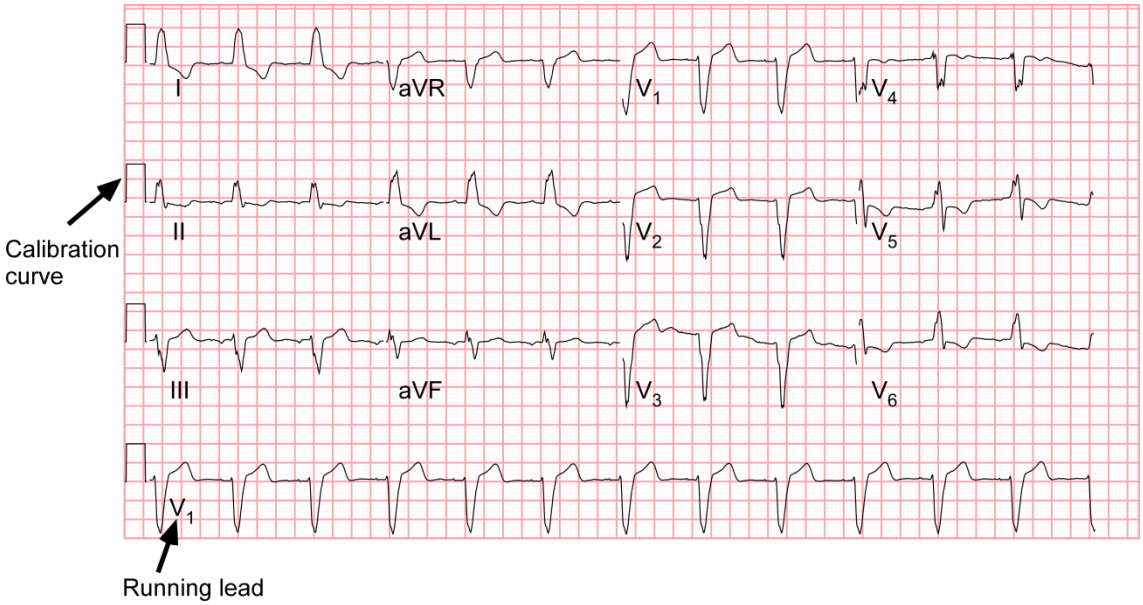


Figure 2: Typical example of the lay-out of a measured 12-lead ECG, showing calibration pulses and lead V_1 as running lead.

The digital ECG signals were semi-automatically analyzed using a custom-made computer program written in MATLAB R2010b (MathWorks, Natick, MA). After band-pass filtering between 0.5-40 Hz and baseline wander removal, the beginning and end of the QRS complex could be detected using the curve length transformation. (90) The beginning of the QRS complex corresponded to the last found minimum value and the end of the QRS complex was the first point with maximal cLT value. Additionally, the end of the T-wave was identified as the intersection between baseline and the tangent of the slope of the T-wave.

The QRS axis was calculated using lead I and II, where angles between -30º and -90º were defined as left axis deviation (LAD). Furthermore, patients were classified as LBBB or non-LBBB according to the MADIT-CRT criteria. (21)

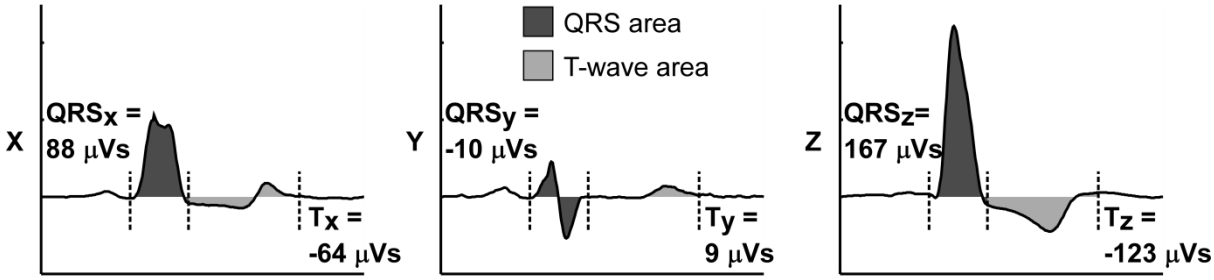
3.5.3.1. VCG analysis

From the digital 12-lead ECG signals, a VCG was synthesized using the Kors method. (91) The matrix proposed by Kors et al. (92), is based on a learning set from the Common Standards for Electrocardiography (CSE) multi-lead library and was generated by multiple linear regressions. The populations included both healthy subjects and patients. (91) The Kors method assumes all eight independent leads measured

simultaneously. However, in our case there were four groups of three leads (1: I, II, III; 2: aVR, aVL, aVF; 3: V_1, V_2, V_3; 4: V_4, V_5, V_6) and one running lead simultaneously measured, as shown in Figure 2. This running lead was needed to select the same beginning and end of an R-R interval in each lead. After selecting one beat for each lead, the VCG was synthesized.

For each patient, the QRS loop and T loop were identified using the same method as described for the ECG analysis. (90) The QRS duration and QT interval were defined as the time between the beginning of the QRS complex and the end of the QRS complex or the T wave, respectively. The QT interval was corrected for heart rate changes using Bazett's method (QTc interval). Subsequently, the maximum QRS- and T-vector were defined (maximal distance from the origin to a point on the loop), and its amplitude and location in space were calculated. The vector angles were expressed as azimuth and elevation. Azimuth is the angle in the transverse plane (0° left, +90° front, -90° back, 180° right). The elevation angle is the angle in the frontal plane defined from 0° (downwards) to 180° (upwards). The angle between the maximal QRS- and T-vector was defined as the QRS/T angle.

The VCG gave us the opportunity to also analyse the area of the loops. The QRS area is the 'three-dimensional' area between the curve and the baseline from QRS beginning to end in leads X, Y, and Z: $QRS_{area} = \sqrt{QRS_{area,x}^2 + QRS_{area,y}^2 + QRS_{area,z}^2}$. The T-wave area was calculated similarly, using the part from the end of the QRS complex to the end of the T wave. The sum QRST area was the sum of the absolute values of the QRS and T-wave area (Figure 3). The ratio between QRS and T-areas was defined as the QRS/T area ratio.



$$QRS_{area} = \sqrt{QRS_{area,x}^2 + QRS_{area,y}^2 + QRS_{area,z}^2} = 190\mu Vs$$

$$T_{area} = \sqrt{T_{area,x}^2 + T_{area,y}^2 + T_{area,z}^2} = 139\mu Vs$$

$$sumQRST_{area} = |QRS_{area}| + |T_{area}| = 328\mu Vs$$

Figure 3. Calculation of the three dimensional QRS and T-wave area using the integral between the signal and the baseline from beginning to end of the QRS complex or from the end of the QRS complex to end of the T-wave, respectively. From the QRS and T-wave area, the sum QRST area was calculated.

3.5.4. T-wave area in prediction of outcome

3.5.4.1. Substudy population

In the present study patients with previous pacing (n=116), frequent premature ventricular contractions or unacceptable noise on the ECG (n=38), or missing baseline ECGs (n=80) were excluded, leading to a total of 335 patients included in the analysis. This population is equal to the patient group described above, extended with 91 CRT patients whom did not have echocardiographic follow-up but did have long-term clinical follow-up.

3.5.4.2. Statistical analysis of the substudy

For descriptive purposes, analysis of subsets was performed in patients with a baseline T-wave area < and ≥ the median with use of the Breslow-Day test for heterogeneity testing.

3.5.5. Pre- and postoperative hyponatremia

Laboratory values for basic metabolic panel inclusive of serum sodium, potassium, chloride, blood urea nitrogen, creatinine, glucose and bicarbonate were collected at

baseline which was defined as 72 hours prior to device implantation. Sodium level was obtained at follow-up during their at 3-6 month visit. Hyponatremia was defined as sodium level <135 mEq/litre based on the previous description in the OPTIME-CHF trial. (55) Parameters with $p<0.05$ were selected for multivariate analysis.

3.5.6. Hypothyroidism

Hypothyroidism was defined by clinical history obtained by reviewing electronic medical record, treatment with thyroid hormone repletion and serum TSH around the time of device implantation. Reference range for TSH was 0.40-5.00 μU/mL. TSH level≥5.00 μU/mL was defined as uncontrolled hypothyroidism (if previously diagnosed); 6 patients had TSH level ≥5 and ≤10 μU/mL and were defined as having subclinical hypothyroidism and included in the hypothyroid group. There were 3 patients with hyperthyroidism which was too small a number for relevant analysis; 1 of these 3 patients was on amiodarone. TSH levels within 2 weeks of CRT device implantation were analyzed and were measured in outpatient settings. Other laboratory values of interest that were recorded included serum sodium and creatinine.

3.5.7. Device measured physical activity

This study evaluated 164 consecutive patients, whose detailed device diagnostic data were available. Data points of physical activity that were collected included 6-MWT and physical activity data from the devices.

The 6MWT was conducted according to a standardized manner. (93) The test was carried out in a straight, unimpeded 20 meter long hallway, where chairs were positioned at both ends providing patients a place for rest if needed. The subjects were instructed to walk as much as possible, but they were permitted to slow down or stop as necessary. They were encouraged in a standardized manner without influencing their walking speed. Before and immediately after the test, finger pulse oximetry (SpO2) was measured. If resting SpO2 was < 88% the patient was considered not eligible to begin the test.

Device-based physical activity data was obtained through device interrogations during follow-up visits. Diagnostic data from devices of two different companies (Medtronic &

St. Jude Medical) were used for this analysis: 86 patients had Medtronic and 79 patients had St. Jude Medical device implanted. Implanted devices measure activity by an accelerometer, which consists of a piezoelectric crystal and a moving component that enables the sensing of the intensity and frequency of body motion, and then converts it into an electrical signal. The sensor thresholds of measurements and the processing algorithms are variable within the two companies. Importantly, device measures of physical activity were displayed differently between the device companies. Medtronic devices (Medtronic Inc, Minneapolis, MN) recorded the physical activity regardless of mode and rate response programming. The data were averaged for each seven-day period, and the average was plotted for the latest day of that period. The trend demonstrated a line connecting each weekly average value (Figure 4, panel A). The activity threshold was nominally set so that a continuous 60-70 step per minute walk was registered as active for that minute. Most activities of daily living (such as doing dishes, vacuuming, removing the garbage) were considered as "active". St. Jude Medical device (SJM, St Jude Medical Inc., Sylmar, CA) report displayed bar graphs that indicated the number of hours the patients are active each day (Figure 4, panel B). Activity was defined as input to the sensor that exceeded the resting heart rate. That threshold rate was recorded in the first 48 hours after implant. Notably, there were no duration criteria for the activity level. Importantly, both of the manufacturers reported the daily activity in unit of hour/day.

DOI:10.14753/SE.2017.2002

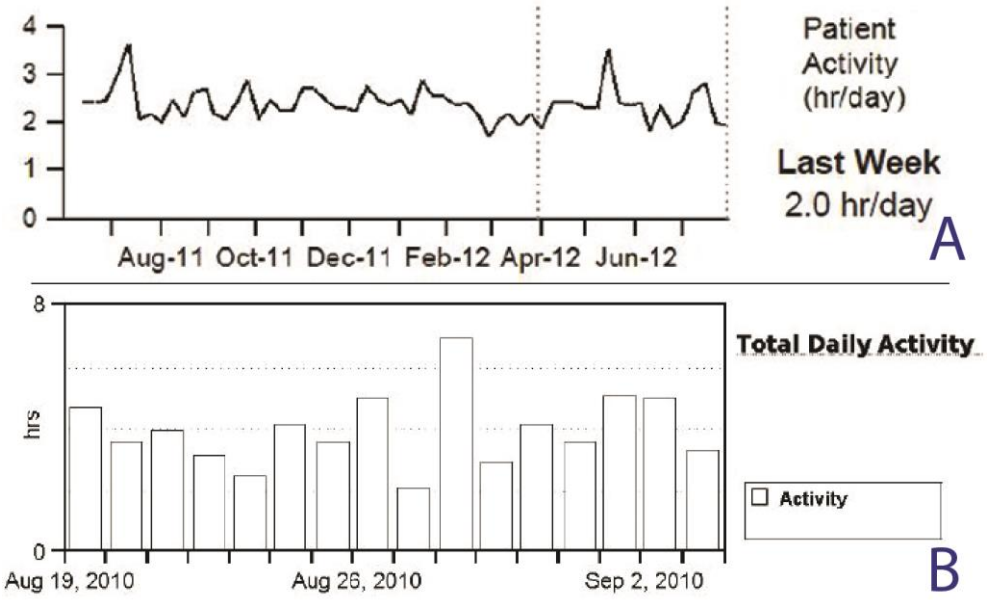


Figure 4. Device manufacturers present the measurements of physical activity in variant visualization. Examples from CRT device printouts: Panel A = Medtronic; B = St. Jude Medical.

Echocardiographic response was defined as a >10 % improvement in LVEF, after CRT. (94)

Since there are no defined categories for daily activity and 6MWT, patients were divided into tertiles based on the activity results and 6MWT distances. Cox proportional hazard models were adjusted for covariates significantly associated with 1 month daily activity tertiles (age, CABG, hypertension, ischaemic cardiomyopathy, diuretics) and traditional risk factors (gender, CAD, diabetes, usage of cardiovascular medications, baseline LVEF and creatinine level). During the multivariate modeling the significant univariates (for HF hospitalization end-point gender, CAD, usage of diuretics and digoxin, baseline creatinine; for composite endpoint gender, diuretics, creatinine) were included.

3.5.8. The study population of the coronary sinus side branch stenting study

Coronary sinus stenting has been performed since 2004 in Heart and Vascular Center, Semmelweis University, in selected patients after receiving informed consent. The consent form and the protocol were approved by the Hungarian Scientific and Research

Ethics Committee of the Medical Research Council. Data were collected in consecutive patients who underwent this procedure, between 2004 and 2010.

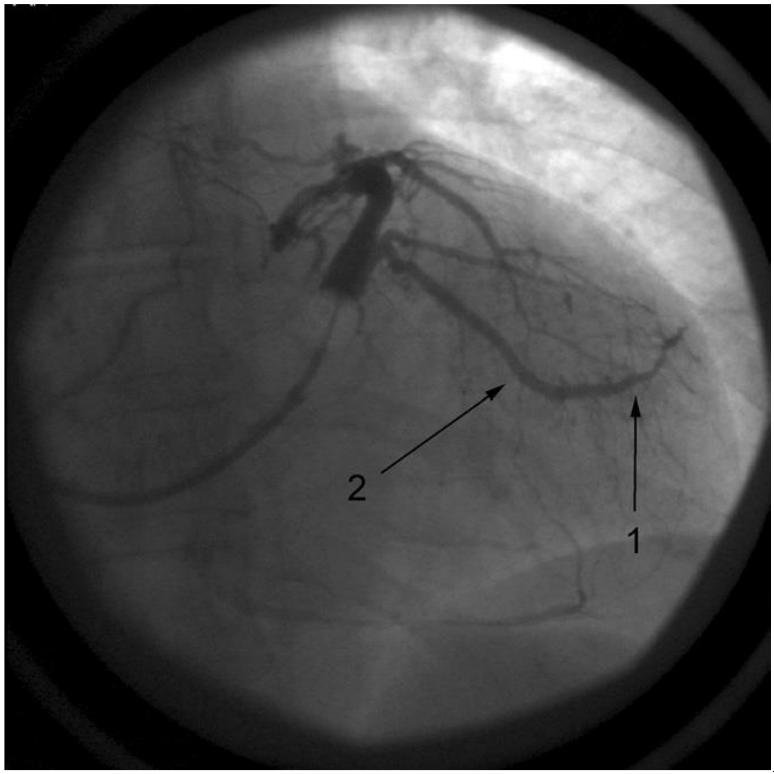
Table 2. Baseline Characteristics

Mean age	65.4
Male sex	236
Female	76
NYHA class at implantation:	
II	12
III	247
IV	53
Left ventricular ejection fraction (%, median)	28 (23–34)
Medication (% of patients):	
Aspirin	36
Clopidogrel or ticlopidine	24
Coumarin	48
Aspirin + coumarin	14
Clopidogrel+coumarin	7
Aspirin + clopidogrel	12
Spironolactone	54
Other diuretics	71
Beta-blocker	87
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	84

CS side branch stenting was performed in 312 patients with wide QRS (>120 ms). NYHA functional stage was mainly III-IV despite drug therapy, while 12 patients were in NYHA II stage at implantation, but their preceding clinical status made this treatment reasonable (Table 2). During this period 784 CRT systems were implanted in our institute, so stenting was applied in 39.7 % of CRT patients. Stent fixation of the CS lead was indicated in cases of postoperative dislocation (n=16). Stenting during the first

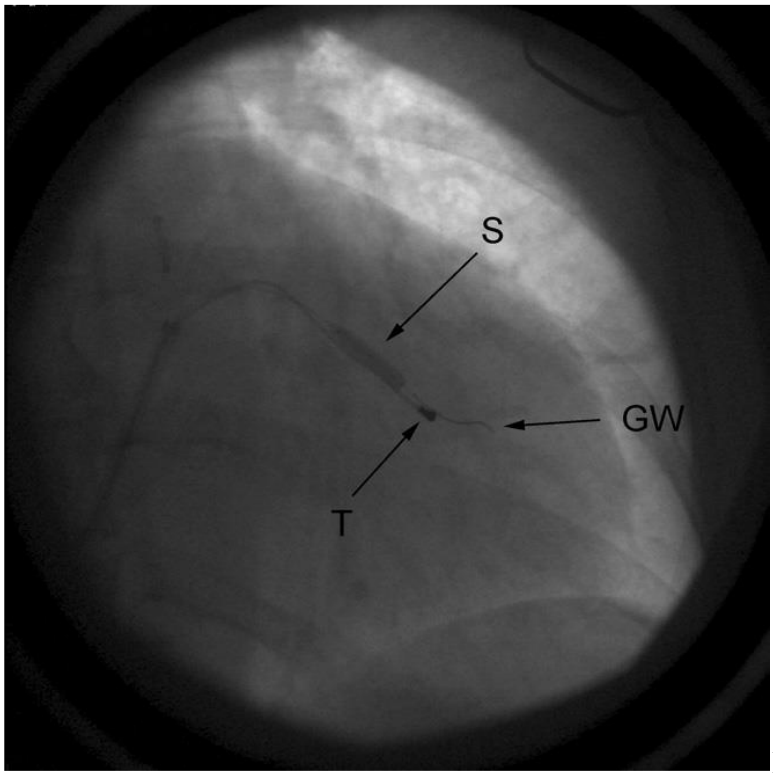
DOI:10.14753/SE.2017.2002

implantation (n=296) was applied when intraoperative macroscopic or microscopic dislocation occurred and there was no other suitable vein accessible or there was when phrenic nerve stimulation (PNS) was observed in a stable anatomical position in the distal part of the side-branch necessitating the lead to be fixed in a more proximal part of the target vein, where instability was present. (Figure 5A.)



A

DOI:10.14753/SE.2017.2002



B

Figure 5. A. Coronary venogram. Arrow 1: stable, distal wedge position, where PNS was observed. Arrow 2: proximal position with ideal pacing parameters. Intraoperative dislocation was experienced. B. Coronary stent implantation. S: inflation of the stent; GW: guide wire of the stent; T: tip of the lead in the final position.

CS side branch stenting was executed according to the previously described manner (83): after cannulation of the CS ostium with Scout Pro 8F (Biotronik GmbH&Co, Berlin, Germany; inner diameter: 8F) or Attain LDS 6216A MB2 (Medtronic Inc., Minneapolis, MN, USA; inner diameter: 7F) CS sheaths, coronary sinus venography was performed using an occlusion balloon. Generally “over the wire” left ventricular unipolar passive fixation electrodes were applied: Attain OTW 4193-78 (Medtronic; n=186), Corox OTW 75 UP/Steroid (Biotronik; n=118) and Quicksite 1056K-86 (St. Jude, Sylmar, CA, USA; n=1). Seven patients received bipolar passive fixation leads (Corox OTW 75 BP/Steroid, Biotronik). After positioning of the lead, signal amplitude, pacing threshold and pacing impedance were measured. Phrenic nerve stimulation was investigated in all cases. Repositioning of the LV lead was performed if phrenic nerve stimulation was apparent during 10 V @ 0.5 ms pacing. In case the physician performing the implantation decided to use stent implantation, another guide wire was

also introduced into the target vein through the same CS sheath. On this second guide wire a short (mainly 8-15 mm) bare metal coronary stent was positioned into the CS side branch. The distance between the pacing tip (or ring) of the lead and the distal end of the stent was 5 to 35 mm. The diameter of the stents (2.25-4 mm, mainly 3 or 3.5 mm) was chosen according to the diameter of the target CS side branch which was measured on the CS venogram. The applied bare metal stents were as follows: Trimaxx (Abbott Vascular, Redwood City, CA, USA, n=142) Driver (Medtronic, n=57), MicroDriver (Medtronic, n=21), S670 (n=6, Medtronic) Lekton Motion (Biotronik, n=35), ProKinetic (Biotronik, n=29), Liberte (Boston Scientific, Maple Grove, MN, USA, n=19), Tsunami Gold (Terumo, Tokyo, Japan, n=3). After measuring the control pacing threshold and testing phrenic nerve stimulation, the stent was deployed with a pressure of 6 to 14 atmospheres (Figure 5 B). The duration of balloon inflation was 4-6 seconds.

A biventricular pacemaker was implanted in 207 patients, while a biventricular defibrillator was indicated in 105 cases. Decision made between CRT-P and CRT-D was the discretion of the operator, according to the guidelines. In patients with permanent atrial fibrillation (n=99) only right ventricular and CS leads were implanted.

Additional antiplatelet or anticoagulant therapy was not used after CS side branch stenting; only the previous anticoagulant and/or antiplatelet treatment was continued (Table2). Treatment was chosen according to current guidelines. The mean daily dosages were the following: aspirin: 100 mg, clopidogrel: 75 mg, ticlopidine 2x250 mg. The INR target value was 2-3 for patients with anticoagulation.

Perioperative events were evaluated in all patients. After implantation, patients were seen in the office every six months. Median follow-up time was 28.4 (15-38, max. 70) months. 293 patients completed 6 months, 186 patients 1 year, 153 patients 2 years, 47 patients 3 years, and 13 patients 4 years follow-up. Left ventricular pacing threshold and pacing impedance values measured after the implantation were compared with the values recorded during 6, 24 and 36 months visits. If the patient felt phrenic nerve stimulation, PNS (phrenic nerve stimulation) threshold was also identified using different pulse width values. To minimize phrenic nerve stimulation, changing the pacing amplitude, pulse duration or pacing configuration was attempted. If these maneuvers failed to terminate ~~the~~ intolerable PNS, minimal invasive lead repositioning

was performed (95). A steerable ablation catheter (Celsius^{TM} , B curve, 36H-37R Biosense Webster, Diamond Bar, CA, USA) was introduced into the right atrium via the right femoral vein. The ablation catheter was looped around the atrial part of the CS lead and was retracted together with the CS electrode.

If stented CS leads were extracted for any reason, macroscopic analysis was fulfilled in all cases looking for injuries on the insulation. When it was possible, microscopic measurements were also executed.

3.5.8.1. Statistical analysis of the coronary sinus side branch stenting study

Statistical analysis was prepared with Prism for Windows 5.00 (GraphPad Software, San Diego, CA, www.graphpad.com). As all of the variables had non-Gaussian distributions, we used nonparametric tests throughout the analysis. We used the Wilcoxon signed rank test for comparisons between two repeated measures. All statistical analyses were two-tailed and $p<0.05$ was considered significant. Values presented in the text are medians (interquartile ranges), unless otherwise stated.

DOI:10.14753/SE.2017.2002

4. Results

4.1. PR interval

4.1.1. Baseline characteristics

From the total patient population, eighty patients were excluded because of missing ECG within one year prior to implantation, 116 patients who had ventricular pacing at baseline and 90 patients with chronic atrial fibrillation preoperatively. 283 patients were included in the final analysis.

Receiver operating curves analysis was performed to assess the best cut-off value for PR interval. A baseline PR interval value of 209 ms for prediction primary endpoint was identified by receiver operating characteristic curve analysis (area under the curve 0.581). PR interval 209 ms showed 42.1% sensitivity, 72.2% specificity and a positive predictive value of 42.1% for a negative outcome. The cutoff value was then rounded to 200 ms in order to make it clinically applicable and relevant, and the patients were divided into two groups based on normal (<200 ms) or prolonged (≥200 ms) PR interval.

Baseline characteristics of all patients are presented in Table 3, divided into two groups based on the PR-interval. 158 patients (55.8%) had a PR interval <200 ms and 125 patients (44.2%) had a PR interval ≥200 ms. Mean PR interval in whole study cohort was 198±43 ms (169±20 vs 235±36 ms in the respective groups, p<0.001). Patients in the normal PR interval group were less likely to have ischaemic cardiomyopathy (48.1% vs. 61.6%, p=0.024), paroxysmal AF (22.8% vs. 36.8%, p=0.010), right bundle-branch block (3.9% vs. 11.6%, p=0.016) and to be male (66.5%% vs. 86.4%, p<0.001) compared with prolonged PR interval group. Notably, there was no difference in mean QRS duration (154±23 ms vs. 155±25 ms, p=0.705), but there was a trend for more patients with left bundle branch block (LBBB) ECG morphology (66.7% vs. 57.9%, p=0.134). Patients with normal PR interval were more likely to experience an improvement in symptoms (improvement of ≥1 NYHA class) at the 6-month follow-up visit, compared to patients with PR interval ≥200 ms (104 [70.2%] vs. 86 [51.2%], respectively, p=0.007).

DOI:10.14753/SE.2017.2002

Table 3. Baseline characteristics of the entire population categorized by the PR interval

Characteristic	All (n=283)	PR interval <200 ms (n=158)	PR interval ≥200 ms (n=125)	p
PR interval, ms	198 ± 43	169 ± 20	235 ± 36	<0.001*
Age, y	66.0 ± 12.7	65.0 ± 13.4	67.3 ± 11.8	0.131
Sex: Female	70 (24.7%)	53 (33.5%)	17 (13.6%)	<0.001*
NYHA				
II	12 (5.0%)	5 (3.6%)	7 (6.9%)	0.247
III	198 (82.8%)	115 (83.3%)	83 (82.2%)	0.815
IV	29 (12.1%)	18 (13.0%)	11 (10.9%)	0.615
QRS duration, ms	154 ± 24	154 ± 23	155 ± 25	0.705
LBBB	172 (62.8%)	102 (66.7%)	70 (57.9%)	0.134
RBBB	20 (7.3%)	6 (3.9%)	14 (11.6%)	0.016*
Medical comorbidies				
CABG	100 (35.3%)	50 (31.6%)	50 (40.0%)	0.144
CAD	177 (62.5%)	94 (59.5%)	83 (66.4%)	0.233
Creatinine, mg/dl	1.50 ± 1.0	1.44 ± 0.85	1.57 ± 1.17	0.302
Diabetes	113 (39.9%)	64 (40.5%)	49 (39.2%)	0.824
Hypertension	213 (75.3%)	118 (74.7%)	95 (76.0%)	0.799
Ischaemic CM	153 (54.1%)	76 (48.1%)	77 (61.6%)	0.024*
Paroxysmal AF	82 (29.0%)	36 (22.8%)	46 (36.8%)	0.010*
PCI	73 (25.8%)	41 (25.9%)	32 (25.6%)	0.947
Valve surgery	36 (12.7%)	18 (11.4%)	18 (14.4%)	0.451
Echocardiographic characteristics				
LVEF, %	24 ± 7	24 ± 7	23 ± 8	0.487
LVIDd, mm	63 ± 9	62 ± 9	63 ± 9	0.380
LVIDs, mm	55 ± 10	55 ± 10	55 ± 10	0.526
Medications				
ACEi	180 (63.6%)	111 (70.3%)	69 (55.2%)	0.009*
ARB	55 (19.4%)	30 (19.0%)	25 (20.0%)	0.831

Aldosterone antagonist	102 (36.0%)	53 (33.5%)	49 (39.2%)	0.325
Beta-blocker	250 (88.3%)	144 (91.1%)	106 (84.8%)	0.099
Digoxin	86 (30.4%)	45 (28.5%)	41 (32.8%)	0.433
Diuretics	230 (81.3%)	125 (79.1%)	105 (84.0%)	0.295

ACE – angiotensin-converting enzyme; ARB – angiotensin receptor blocker; CABG – coronary artery bypass grafting; CAD – coronary artery disease; CM – cardiomyopathy; LBBB – left bundle branch block; LVIDd – left ventricular internal dimension diastole; LVIDs – left ventricular internal dimension systole; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association; PCI – percutaneous coronary intervention; VF – ventricular fibrillation; VT – ventricular tachycardia

4.1.2. Cardiac dimensions and reverse remodeling

There were no significant differences in cardiac dimensions and LVEF between the groups prior to CRT implant (Table 4). However, patients with prolonged PR interval had a smaller average improvement in LVEF, and were less likely to be echo-responders of LVEF (64% vs. 77%, OR 0.6 CI 0.3-1.0, p=0.06). When stratified for the presence of LBBB, it was evident that this difference was primarily driven by the results for the patients with non-LBBB, where a prolonged PR interval was strongly associated with lower odds ratio for echo-response (OR 0.3 CI 0.1-0.8, p=0.02, whereas for the group with LBBB there was no significant difference (OR 0.8 CI 0.3-1.9, p=0.61).

Table 4. Cardiac dimensions and ejection fraction before and after CRT treatment

	Normal PR group			Prolonged PR group			
	Baseline	Follow-up	Paired P-value	Baseline dimensions	Mean (SD) change in value	Paired P-value	P-value for difference in Δ between the groups
LVIDd mm	62±9	58±11	<0.001	63±9	61±10	<0.001	0.26
LVIDs mm	55±10	50±12	<0.001	55±10	53±11	<0.001	0.35
LVEF %	24±7	34±12	<0.001	23±8	30±10	<0.001	0.02

4.1.3. Clinical outcomes and survival

Patients were followed for 30.1±22.0 months after CRT implantation. In the study period, 10 patients underwent heart transplantation, 4 had LVAD implantation, 98 were hospitalized because of HF and 76 died. The primary endpoint of death from any cause, HF hospitalization, implantation of left ventricular assist device or heart transplantation was observed in 51 patients from the normal PR interval group (32.3%) and 56 patients from the prolonged PR interval group (44.8%). Kaplan-Meier analysis showed worse clinical outcomes in the group with prolonged PR interval (Figure 6 and 7, log rank test p=0.040).

DOI:10.14753/SE.2017.2002

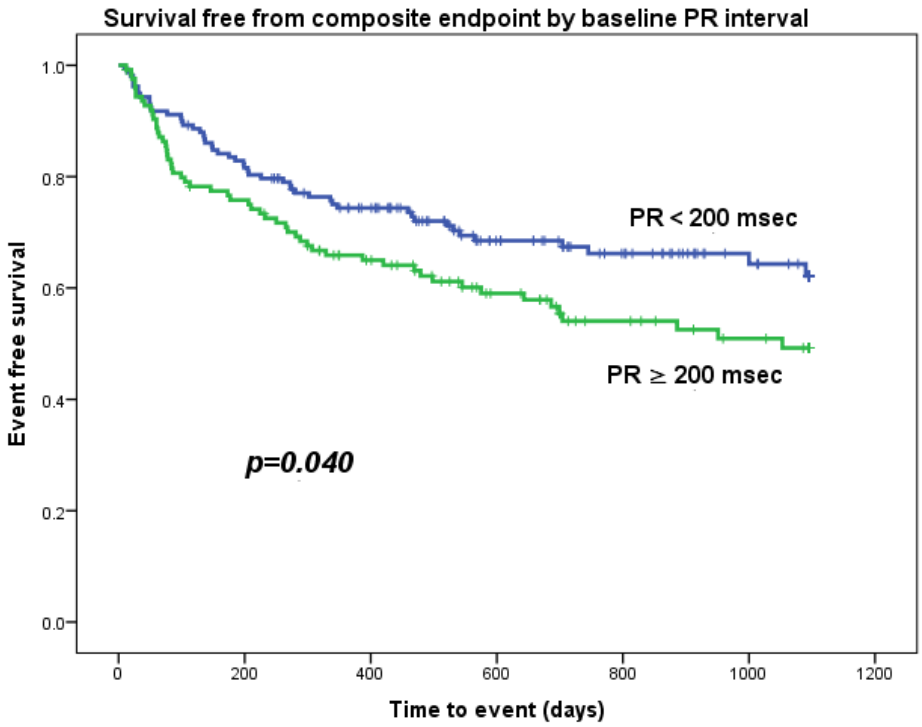


Figure 6. Survival free from composite endpoint by baseline PR interval

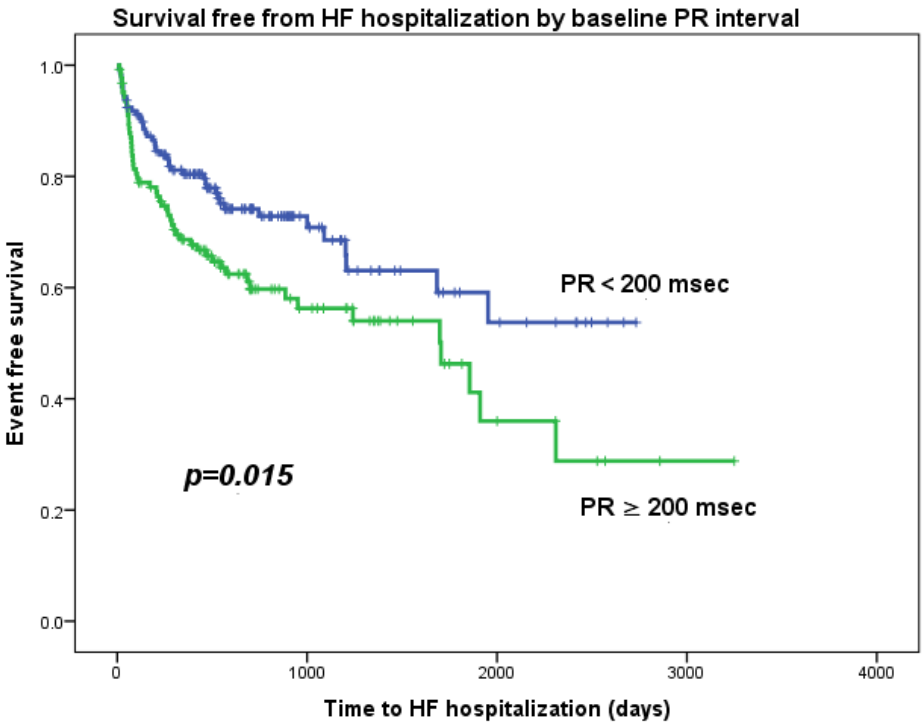
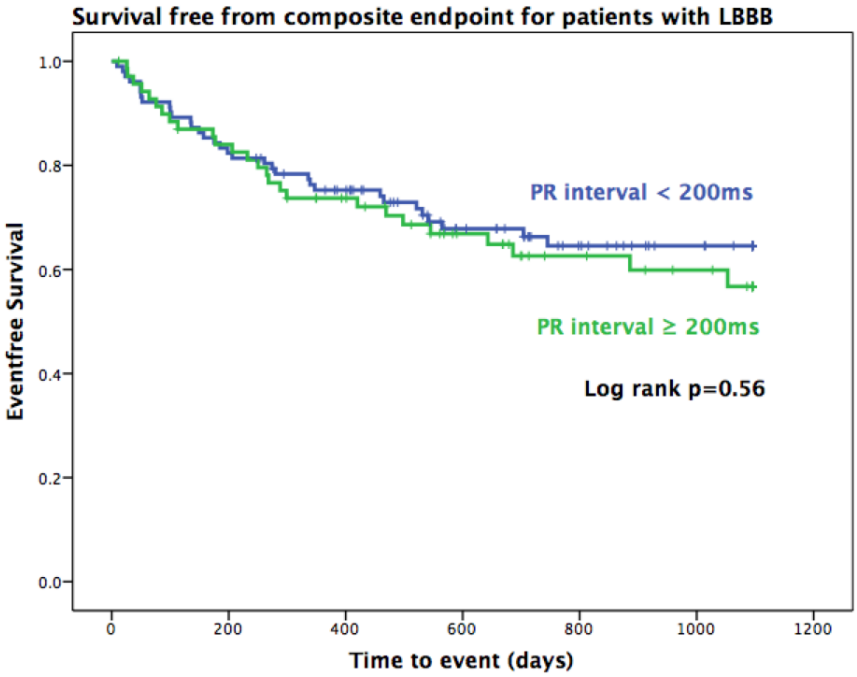


Figure 7. Survival free from HF hospitalization by baseline PR interval

DOI:10.14753/SE.2017.2002

When stratifying for presence of LBBB, it was again evident that the difference between the groups was primarily in the patients with non-LBBB, whereas in patients with LBBB a prolonged PR interval did not have a significant impact on prognosis (Figure 8A and 8B).

A



B

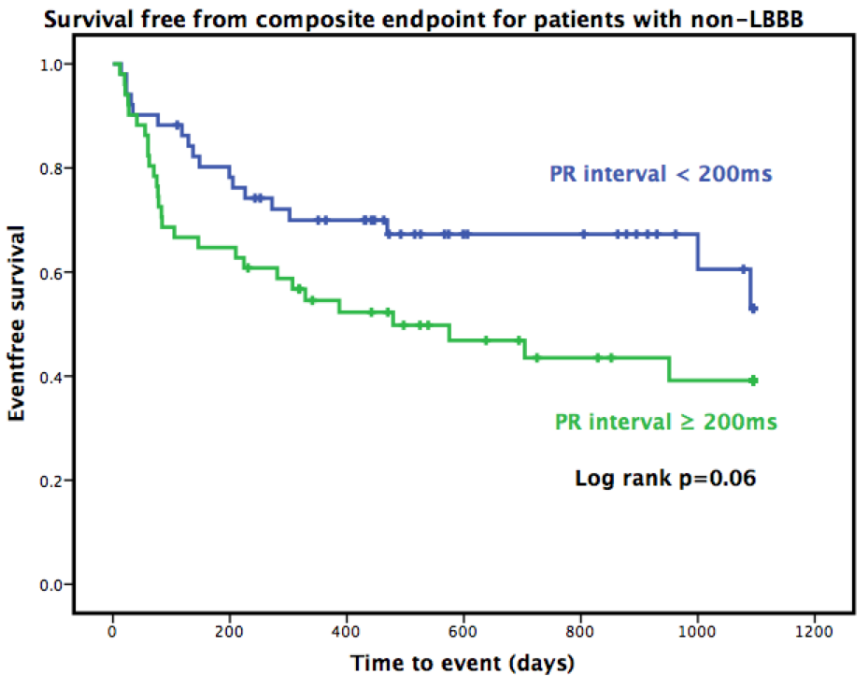


Figure 8A and 8B. Survival free from composite endpoint by baseline PR interval, for patients with LBBB (A) and non-LBBB (B).

Table 5. presents the results of uni- and multivariate Cox regression analysis of the primary endpoint. In univariate analysis, baseline PR interval, prolonged PR interval (dichotomized) (hazard ratio, HR 1.49; 95% confidence interval, CI 1.02-2.17; p=0.041), female gender (HR 0.69; 95% CI 0.49-0.96; p=0.041), ischaemic cardiomyopathy, and RBBB on ECG were associated with the primary endpoint. However, in multivariate analysis only ischaemic cardiomyopathy remained as a statistically significant predictor of poor prognosis (HR 1.64; 95% CI 1,07-2,53; p=0.024).

We further assessed the relationship between PR interval and hospitalization for heart failure (Table 5). This occurred in 44 patients from the group with normal PR interval (27.8%) and 54 patients from the group with PR interval (43.2%; p=0.015; Figure 7), and PR interval was the only independent predictor of HF hospitalization (HR 1.56; 95% CI 1.04-2.34; p=0.033).

Table 5. Results of uni- and multivariate analysis of primary endpoint and HF hospitalization

	HF hospitalization		Primary composite endpoint	
	Univariate analysis HR (95% CI)	Multivariate analysis HR (95% CI)	Univariate analysis HR (95% CI)	Multivariate analysis HR (95% CI)[b]
Baseline PR interval	1.6 (1.1-2.4, p=0.016)	1.6 (1.0-2.3, p=0.033)	1.5 (1.0-2.2, p=0.041)	1.2 (0.8-1.9, p=.281)
Female	0.7 (0.5-1.0, p=0.67)		0.69 (0.5-0.99, p=0.041)	0.97 (0.6-1.6, p=0.917)
Ischaemic cardiomyopathy	1.3 (0.9-1.7, p=0.112)		1.4 (1.1-1.8, p=0.007)	1.6 (1.1-2.5, p=0.024)
Paroxysmal AFib	1.1 (0.8-1.5, p=0.622)		1.1 (0.9-1.5, p=0.400)	
RBBB	1.9 (1.2-2.9, p=0.006)	1.4 (0.7-2.9, p=0.309)	1.9 (1.3-2.8, p=0.002)	1.5 (0.6-1.6, p=.255)
ACE	0.8 (0.6-1.1, p=0.152)		0.8 (0.6-1.2, p=0.274)	

DOI:10.14753/SE.2017.2002

DOI:10.14753/SE.2017.2002

4.2. ECG-based risk stratification score

4.2.1. Baseline characteristics

Out of the total of 569 consecutive patients that received CRT within the study period, 78 patients were excluded because of missing ECG either prior to or after implantation, or ventricular pacing at the baseline ECG.The final study population of 491 patients consisted of 101 women and 390 men with a median age of 71 (IQR 16) years.The full baseline characteristics are presented in Table 6. During the follow-up period 180 patients reached the heart failure hospitalization endpoint, 14 patients underwent cardiac transplantation, 5 patients had an LVAD implanted and 148 patients died.

DOI:10.14753/SE.2017.2002

Table 6. Baseline characteristics.

Baseline characteristics	**Total population**	**Score**				**p**
		0 (n=90)	1 (n=176)	2 (n=102)	3 (n=22)	
Age (years)	71 (IQR 16)	71 (16)	70 (16)	71 (16)	64 (19)	0.763
Female, n (%)	93 (21)	10 (10)	40 (21)	36 (30)	7 (29)	**0.004**
Hypertension, n (%)	331 (76)	70 (71)	153 (79)	90 (75)	18 (75)	0.505
Diabetes, n (%)	179 (41)	44 (45)	78 (40)	49 (41)	8 (33)	0.748
Ischaemic cardiomyopathy, n (%)	288 (59)	60 (61)	118 (62)	58 (48)	15 (63)	0.104
Chronic or persistent AF, n (%)	123 (28)	35 (36)	58 (30)	28 (23)	2 (8)	**0.028**
Paroxysmal AF, n (%)	126 (29)	24 (25)	63 (33)	35 (30)	4 (17)	0.263
Prior CABG surgery, n (%)	169 (39)	46 (47)	81 (42)	32 (27)	10 (42)	**0.011**
Valve surgery, n (%)	70 (16)	19 (19)	36 (19)	13 (11)	2 (8)	0.154
Prior PCI, n (%)	114 (26)	31 (32)	47 (24)	28 (23)	8 (33)	0.395
LBBB, n (%)	235 (49)					
Baseline creatinine	1.54 (IQR 1)	1.5 (1)	1.33 (1)	1.26 (1)	1.18 (1)	**<0.001**
Diuretics, n (%)	377 (87)	90 (92)	168 (87)	101 (84)	18 (75)	0.124
Aldosterone antagonist, n (%)	141 (32)	28 (29)	67 (35)	41 (34)	5 (21)	0.429
Digoxin, n (%)	156 (36%)	38 (39)	72 (37)	39 (33)	7 (29)	0.661
Beta-blocker, n (%)	383 (88%)	79 (81)	171 (89)	110 (92)	23 (96)	0.044
ACEi, n (%)	260 (60%)	58 (59)	115 (60)	75 (63)	12 (50)	0.719
ARB, n (%)	90 (21%)	18 (18)	37 (19)	27 (23)	8 (33)	0.366
LVEF	24% (IQR 11%)	24 (9)	24 (11)	25 (10)	22 (12)	0.239
Baseline QRS (msec)	166 (IQR 45)	150 (32)	160 (46)	171 (37)	173 (36)	**<0.001**
Lateral lead position, n (%)	381 (88%)	84 (86)	165 (86)	113 (94)	19 (79)	0.059
QRS narrowing (n, %)	161 (37%)	0 (0)	53 (28)	84 (70)	24 (100)	**<0.001**
V1 amplitude decrease > 50% (n, %)	194 (45%)	0 (0)	92 (48)	78 (65)	24 (100)	**<0.001**
Onset of intrinsicoid deflection <40 ms (n, %)	150 (35%)	0 (0)	48 (25)	78 (65)	24 (100)	**<0.001**

AF – atrial fibrillation, NYHA – New York Heart Association, CABG – coronary artery bypass grafting, PCI – percutaneous coronary intervention, LBBB – left bundle branch block, ACEi – angiotensin-converting-enzyme inhibitor, ARB – angiotensin receptor blocker, LVEF – left ventricular ejection fraction

Several of the well-known baseline clinical parameters were correlated to an increased risk for the primary composite endpoint; male gender, diabetes, ischaemic cardiomyopathy, chronic atrial fibrillation, previous CABG, non-LBBB on ECG, higher serum creatinine, loop diuretic therapy and digoxin therapy. Table 7 shows individual hazard ratios and the final multivariate model including correlations for the proposed ECG score.

Table 7. Univariate and multivariate Cox regression analysis for predictors of the combined primary endpoint death, left ventricular assist device, heart transplantation or hospitalization for heart failure.

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	p			
Age (years)	1.008	.997-1.019	.143			
Female	.696	.490-.989	.043	0.9	0.6-1.4	0.66
Hypertension	1.207	.893-1.633	.222			
Diabetes	1.390	1.077-1.796	.011	1.5	1.1-2.0	0.02
Ischemic cardiomyopathy	1.368	1.045-1.790	.023	1.2	0.8-1.7	
Chronic AF	1.309	1.001-1.712	.049	0.95	0.7-1.3	0.76
Paroxysmal AF	1.131	.857-1.494	.384			
CABG	1.368	1.059-1.766	.016	1.01	0.7-1.4	0.97
Valve surgery	.934	.655-1.333	.708			
PCI	1.139	.860-1.507	.364			
LBBB	.675	.517-.811	.004			
Baseline creatinine	1.30	1.198-1.422	<0.001	1.3	1.2-1.4	<0.001
Diuretics	2.47	1.486-4.101	<0.001	2.7	1.4-5.3	0.002

Aldosterone antagonist	.945	.726-1.252	.733			
Digoxin	1.409	1.091-1.820	.009	1.3	0.95-1.7	0.11
Beta-blocker	.715	.503-1.016	.061			
ACEi	.796	.615-1.029	.082			
ARB	.823	.594-1.165	.283			
LVEF	.989	.970-1.007	.235			
Baseline QRS (msec)	1.000	.995—1.005	.989			
Lateral lead position	.723	.513-1.019	.064			
QRS narrowing	.655	.477-.900	.009			
V1 amplitude decrease	.668	.494-.904	.009			
ID V1 <40 ms	.625	.455-.858	.004			
ECG score	.645	.536-.777	<0.001	0.7	0.5-0.8	<0.001

AF – atrial fibrillation, NYHA – New York Heart Association, CABG – coronary artery bypass grafting, PCI – percutaneous coronary intervention, LBBB – left bundle branch block, ACEi – angiotensin-converting-enzyme inhibitor, ARB – angiotensin receptor blocker, LVEF – left ventricular ejection fraction

4.2.2. QRS duration

The median QRS duration was 166 msec (range 102-273, IQR 45) before CRT and median 155 msec (range 93-279, IQR 29) at the one-month follow-up. At least 20 msec narrowing was observed in 163 (37%) cases. Those patients were more likely to be women (28 vs. 17%, p=0.010), had broader baseline QRS (median 186 vs. 151 msec, p<0.001), less dilated left ventricle (end-systolic left ventricular internal diameter median 50 vs. 55 mm, p<0.001), less frequently a history of CABG (30% vs. 28%, p=0.004) and valve surgery (12 vs. 19%, p=0.044). The patients with at least 20msec reduction in QRS amplitude had a lower risk of experiencing the composite endpoint; HR 0.66 ([0.48-0.90] p=0.009), and they were more likely to have significant reverse remodeling on echo; OR 2.90 [1.8-4.7], p<0.001).

4.2.3. Summed V1 amplitude

The median summed QRS amplitude in V1 lead was 1.05 mV (range 0.12-4.07, IQR 0.89) at baseline and 0.74 mV (range 0.12-3.43, IQR 0.57) at the one-month follow-up ECG. The summed amplitude in V1 lead decreased in 309 cases (71%) and the magnitude was less than 50% of the baseline value in 194 cases (45%). The patients in this group were more likely to have LBBB morphology (56% vs. 43%, p=0.007), but no other significant differences were noted between the two groups. Decrease in summed amplitude in V1 was associated with a HR of 0.67 ([0.49-0.90], p=0.09) for reaching the primary endpoint, and an OR of 1.3 ([0.85-2.1], p=0.21) for LV remodeling on echocardiography.

4.2.4. Intrinsicoid deflection onset duration

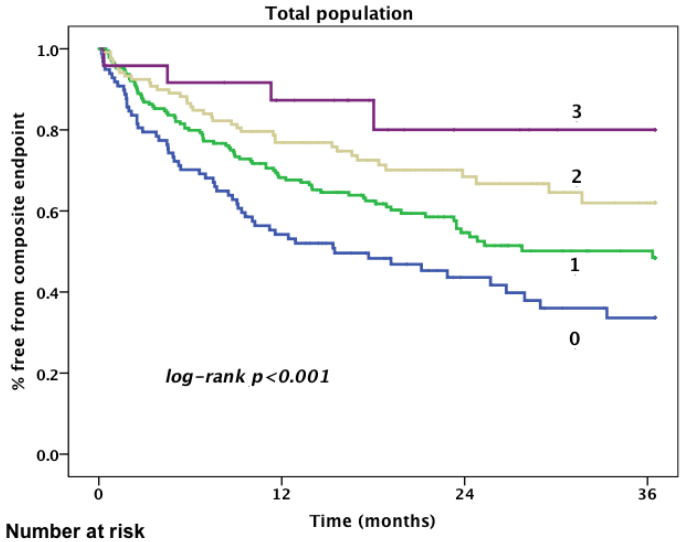
At follow-up, the median time from QRS start to the ID onset was 66 msec (range 0-233, IQR 75). In 167 (34%) patients the time to onset was ≤40 msec, and this was associated with a HR of 0.62 ([0.46-0.86] p=0.004) for reaching the primary endpoint. The corresponding odds ratio for significant LV remodeling was 1.6 ([1.03-2.5] p=0.04). The patients with time to ID onset >40ms were slightly older, more men, were more likely to have ischaemic cardiomyopathy, previous CABG and have chronic atrial fibrillation. They were less likely to have LBBB morphology on ECG prior to implant, and less likely to be on beta-blocker-medication.

4.2.5. ECG score

We assigned one point for each predictor investigated above, as the HR and Wald values for the independent predictors were comparable. Overall median score was 1 (IQR 1). In survival analysis increasing total score was associated with a reduced risk for the combined primary endpoint, as well as a reduced risk for heart failure hospitalization (Figure 9). The trends seen in Figure 9 were the same for prediction of all-cause mortality (Figure 10), although numbers of events in this category were more limited (overall 99 events, 33, 45, 18, 3 by the score (0-3), respectively) and the curves less separated.In regression analysis each additional point in the risk score translated to a 42% risk-reduction for reaching the composite endpoint (HR 0.58 [0.44-0.77]

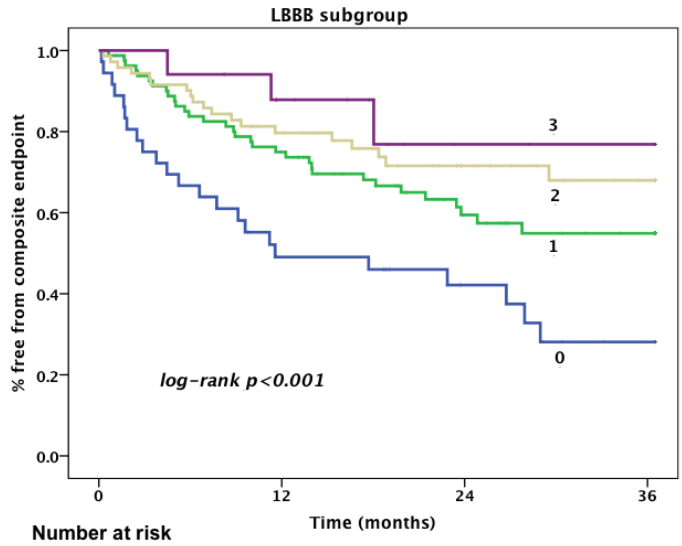
p<0.001). When correcting for other significant predictors in the multivariate model, the independent HR was 0.68 [0.55-0.83] p<0.001). The unadjusted hazard ratio for the score in predicting echo-response (≥10% improvement in LVEF) was 1.8 ([1.4-2.4] p<0.001) for each increasing point, and the corresponding adjusted HR was 1.7 ([1.3-2.3] p<0.001).

DOI:10.14753/SE.2017.2002



Number at risk

0	98	50	23	14
1	192	116	54	30
2	120	84	41	21
3	24	18	7	4



Number at risk

0	36	16	9	3
1	80	58	29	19
2	72	49	25	13
3	17	12	4	3

Figure 9. Kaplan-Meier curves of survival free of composite endpoint according to ECG score, for all patients (above) and for patients with LBBB (below).

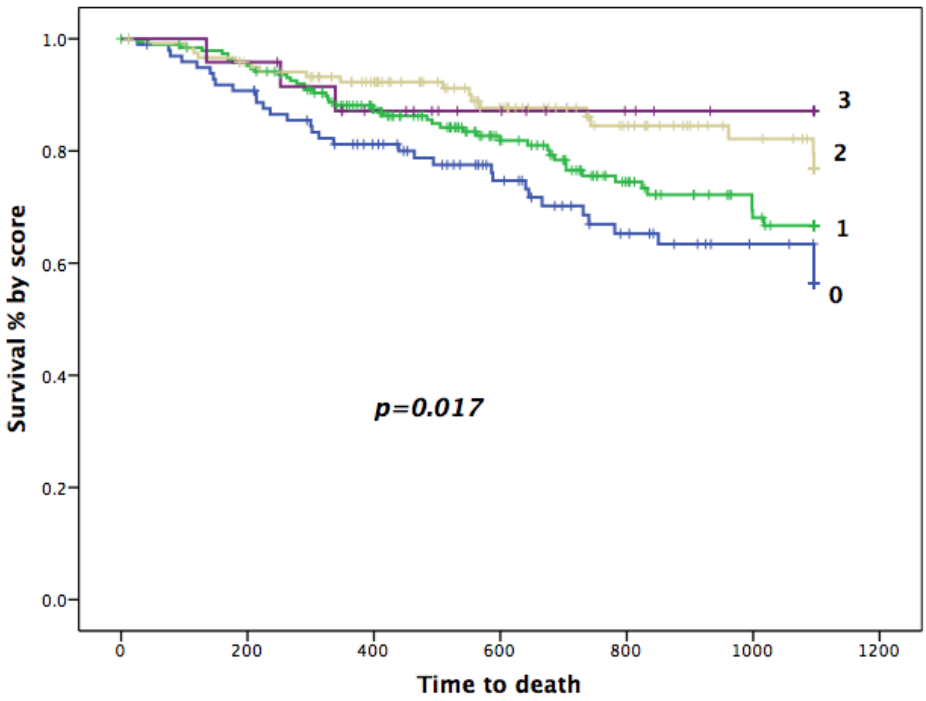


Figure 10. Kaplan-Meier curves of survival (all cause mortality). Time to death (days)

4.2.6. ECG score performance in patients with specific conduction blocks

The three individual components were to varying degrees associated with LBBB-morphology on ECG, and as a post hoc test the score was therefore applied to this ECG-homogenous, specific group of patients, as well as the remaining group of patient with non-LBBB. The adjusted hazard ratio for the combined score for prediction of the primary endpoint in the LBBB group was 0.62 ([0.46-0.84] p=0.002). The univariate OR for reverse remodeling was 1.8 ([1.2-2.6] p=0.004), and the adjusted OR was 1.4 (0.92-2.1] p=0.12). In the non-LBBB group the unadjusted predictive value was of similar magnitude; univariate HR for primary endpoint was 0.77 ([0.59-0.99] p=0.044), but the adjusted HR was not a significant predictor; HR 0.83 ([0.63-1.10] p=0.19). The association with reverse remodeling was non-significant. If patients with baseline ECG<120ms were excluded, the unadjusted HR for the combined score for prediction of the primary endpoint in the LBBB group was 0.57 ([0.43-.76] p<0.001) and the adjusted HR was 0.55 ([0.40-0.75] p<0.001). In the non-LBBB group a sub-analysis was also done for only patients with QRS>150ms at baseline; the trends were similar,

but due to lower absolute numbers, the correlations were not as strong; the unadjusted HR for the primary composite endpoint was 0.77 ([0.56-1.05] p=0.096) and the adjusted HR was 0.84 ([.60-1.18] p=0.312).

4.3. T-wave area in prediction therapy response

4.3.1. Patient characteristics

A total of 244 patients were included into the analysis. Table 8. presents the baseline characteristics, indicating that the included patient group was similar to the entire cohort. The 244 patients represent a typical CRT population with a mean age of 67 years and a baseline LVEF of 24%. Most patients were male, about half of the patients had ischaemic cardiomyopathy, and most had NYHA class III or IV symptoms (Table 8).

Table 8. Baseline patient characteristics, ECG, and VCG analysis results of the entire cohort (n=244).

Variable	Included N=244	Entire cohort N = 569
Baseline characteristics		
Age (y)	66.9±12.8	68.6±12.4
Female (n,%)	51(20.9)	116(20.4)
Baseline LVEF (%)	24.3±7.0	24.2±7.2
NYHA class		
II (n,%)	8(3.3)	
III (n,%)	190(77.9)	
IV (n,%)	22(9.0)	
Unknown (n,%)	24(9.8)	
Ischemic HF aetiology (n,%)	136(55.7)	337(59.3)
LBBB (n,%)	154(63.1)	258(48.5)
Chronic AF (n,%)	53(21.7)	168(29.5)
ECG measurements		
Heart rate (BPM)	75±15	

QRS axis (°)	-15±61
VCG measurements	
QRS duration (ms)	175±33
QT interval (ms)	472±88
QTc interval (ms)	520±77
QRS area (μVs)	90±47
QRS-vector azimuth (°)	-65±53
QRS-vector elevation (°)	90±24
T-vector amplitude (mV)	0.5±0.2
T-wave area (μVs)	84±45
T-vector azimuth (°)	78±63
T-vector elevation (°)	87±26
QRS/T angle (°)	156±29
Sum QRST area (μVs)	174±83

Variables are shown as counts (percentage) or mean±standard deviation when appropriate. LVEF: left ventricular ejection fraction,

4.3.2. ECG & VCG analysis

The patients had a prolonged QRS duration. The average QRS axis was in the normal axis range (-30°–90°) but the SD was large, indicating a large variation between patients. The QRS-vector amplitude was three times larger than the T-vector amplitude, but the areas of the QRS and T loop were similar, because the T-wave lasted longer. In general, the QRS-vector pointed to the left and the back while the T-vector was pointing to the left and the front, indicating a large angle between the two vectors (Table 8). Typical examples of 12-lead ECGs and corresponding three-dimensional vector loops for two patients, diagnosed with LBBB with a large or small T-wave area, are shown in Figure 11A and Figure 11B, respectively.

DOI:10.14753/SE.2017.2002

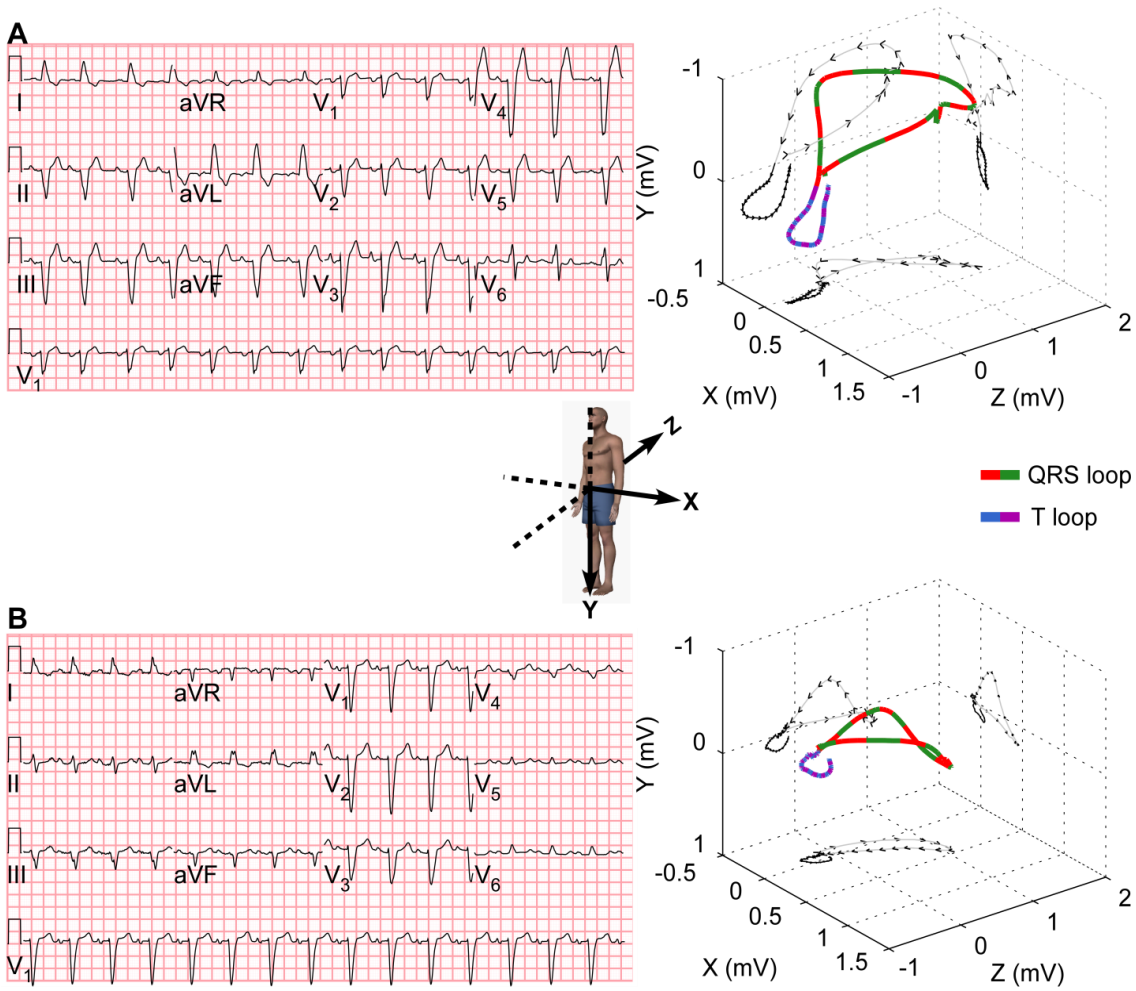


Figure 11. Typical examples of 12-lead ECGs and corresponding 3D vector loops for a patient with a large (A) and a small (B) T-wave area, despite being both classified as having LBBB.

4.3.3. Echocardiographic response predicted by ECG and VCG variables

Logistic regression models indicated VCG-derived repolarization variables as good predictors of CRT response (Table 9). An increase in T-vector amplitude or T-wave area was associated with a greater probability of ≥5% or ≥10% points increase in LVEF. Prediction of LVEF increase by the T-vector amplitude and T-wave area was even stronger than by the QRS-vector amplitude or QRS area (Table 9). Adding QRS area to a model including only the T-wave area, did not improve the goodness-of-fit significantly ($p=0.4$), while adding T-wave area to a model consisting of QRS area alone, the goodness-of-fit improved significantly ($p<0.01$). The sum QRST area had a

predictive power comparable to that of the T-wave area alone. A larger angle between the QRS and T vector (QRS/T angle) was associated with a non-significantly (p=0.06) higher probability of echo-response. Patients without LAD of the QRS-vector did not show a better CRT response (OR = 1.15 (0.69-1.91), p=0.59).

Table 9. Logistic regression model for prediction of ≥5% or ≥10% absolute increase in LVEF. Presented are median values and 95% confidence intervals (CI). The increase column indicates the step size of the variables used to calculate the odds ratios (OR).

Variable	OR (95% CI) for ΔLVEF≥5%	p-value	OR (95% CI) for ΔLVEF≥10%	p-value	Increase
QRS duration (ms)	0.994 (0.919-1.077)	0.890	0.983 (0.907-1.066)	0.679	10 ms
QRS-vector amplitude (mV)	1.071 (1.017-1.129)	0.009	1.068 (1.015-1.124)	0.011	0.1 mV
T-vector amplitude (mV)	1.256 (1.115-1.413)	<0.001	1.231 (1.101-1.377)	<0.001	0.1 mV
QRS/T angle (°)	1.094 (0.990-1.195)	0.067	1.105 (0.990-1.231)	0.063	10 °
QRS area (μVs)	1.116 (1.051-1.195)	0.001	1.094 (1.030-1.149)	0.003	10 μVs
T-wave area (μVs)	1.172 (1.083-1.255)	<0.001	1.127 (1.062-1.207)	<0.001	10 μVs
Sum QRST area (μVs)	1.175 (1.090-1.266)	<0.001	1.131 (1.057-1.210)	<0.001	20 μVs

Corresponding p-values were calculated using the Wald-test. LVEF: left ventricular ejection fraction, OR: odds ratio

DOI:10.14753/SE.2017.2002

4.3.4. T-wave area as an additional predictor of echocardiographic response

In order to better understand the good prediction of CRT response by the T-wave area, this variable was further evaluated in its relation to QRS duration, QRS area, as well as presence of LBBB and ischaemic aetiology. T-wave area was poorly related to both the QRS duration (R=0.34) and LBBB (R=0.36). Nevertheless, patients diagnosed with LBBB had a significantly larger T-wave area than patients without LBBB (97.8±45.4 vs. 60.6±33.6, $p<0.001$). Similarly, T-wave area was smaller in patients with ischaemic aetiology compared to non-ischaemic aetiology (88.6±44.9 vs. 105.5±47.3, $p=0.014$). T-wave area correlated better with QRS area, although the correlation coefficient of 0.63 indicated that more factors than QRS area alone determine T-wave area (Table 10 and Figure 12). The OR of the QRS/T area ratio for predicting CRT response was 0.753 ($p=0.13$), indicating that a large T-wave area relative to the QRS area tends to increase the odds of becoming a CRT responder.

DOI:10.14753/SE.2017.2002

Table 10. Baseline and outcome patient characteristics after dividing patients according to their QRS morphology and T-wave area.

	LBBB		Non-LBBB	
	T-area<median (n=51)	T-area≥median (n=103)	T-area<median (n=61)	T-area≥median (n=29)
Age (y)	66.1±10.6	68.1±12.0	66.9±13.5	64.3±16.8
Female (n,%)	8(15.7)	32(31.1)*	8(13.1)	3(10.3)
Ischemic HF aetiology (n,%)	33(64.7)	50(48.5)	37(60.7)	16(55.2)
Hypertension (n,%)	36(70.6)	83(80.6)	45(73.8)	17(58.6)
CABG (n,%)	22(43.1)	34(33.0)	24(39.3)	12(41.4)
QRS duration (ms)	173±30	183±31	162±32	174±39
QTc interval (ms)	524±92	533±75	495±61	518±78
QRS area (μVs)	78.0±32.7	122.1±44.0+	50.1±22.5	83.4±36.3+
T-wave area (μVs)	53.0±14.1	120.0±38.6+	41.7±13.7	100.5±27.5+
NYHA class baseline (-)	3.0±0.4	3.1±0.4	3.0±0.3	3.2±0.4
NYHA class follow-up (-)	2.3±0.8	2.0±0.8	2.4±0.9	2.3±0.4
ΔNYHA class (-)	0.8±0.8	1.0±0.8	0.7±0.8	0.9±0.7
LVEF baseline (%)	25.1±7.1	24.5±6.6	24.3±7.5	22.4±7.2*
LVEF follow-up (%)	31.2±11.1	35.8±10.9*	28.6±10.8	28.9±13.4
ΔLVEF (%)	6.1±9.7	11.3±9.1*	4.3±10.0	6.5±14.3
ΔLVEF≥5% (n,%)	27(52.9)	78(75.7)+	24(39.3)	12(41.4)
ΔLVEF≥10% (n,%)	19(37.3)	58(56.3)*	14(23.0)	10(34.5)

Continuous variables are presented as mean±standard deviation (SD), discrete variables as counts (percentages). HF: heart failure, CABG: Coronary artery bypass graft, LVEF: left ventricular ejection fraction.

*p-value<0.05 compared to the T-area < median group with the same LBBB conditions

+p-value<0.01 compared to the T-area < median group with the same LBBB conditions

DOI:10.14753/SE.2017.2002

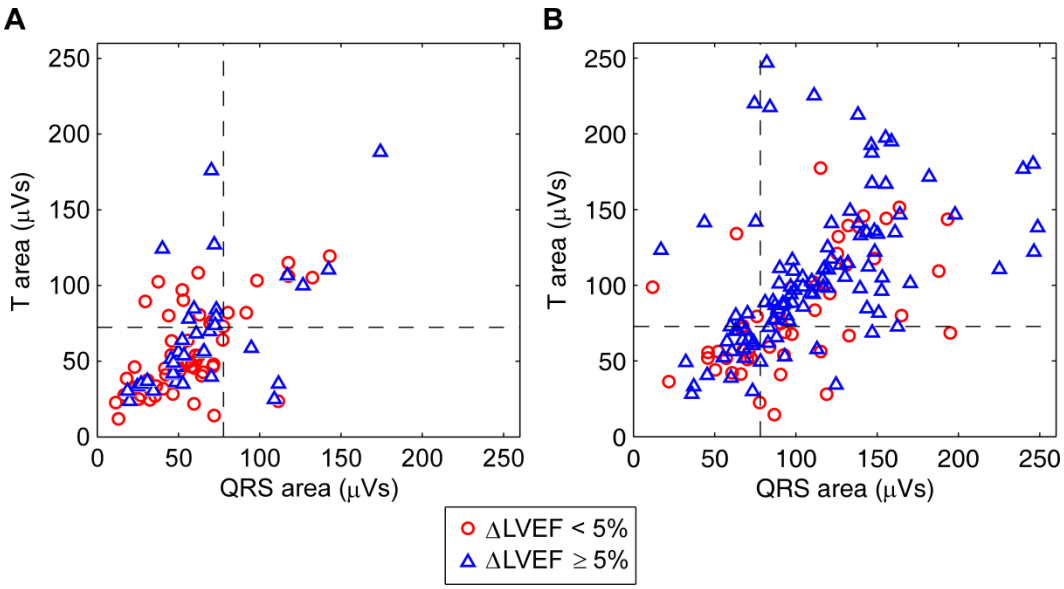


Figure 12. Scatter plot of the relation between QRS-area and T-wave area within non-LBBB (A) and LBBB patients (B). The responders are indicated by blue triangles, non-responders by red circles.

As expected, non-LBBB patients were more commonly non-responders than responders. Non-LBBB patients also had fairly small T-wave area and QRS area (Figure 12).In the LBBB group most patients were responders and T-wave area and QRS area were larger than in the non-LBBB group (Figure 12).

In order to investigate whether T-wave area had a predictive value complementary to LBBB, the LBBB and non-LBBB patient groups were subdivided in subgroups with a baseline T-wave area < or ≥ the median. Between these four subgroups, the only patient characteristic showing differences were a higher percentage of females (p=0.04) and a lower percentage of patients with ischaemic HF aetiology (p=0.06) in the LBBB-high T-wave subgroup (Table 10). In this subgroup also the decrease in NYHA class (1.0 vs. 0.7-0.9) was slightly larger and the increase in LVEF was significantly larger than in the other three subgroups (11.3% vs. 4.3-6.5%, p<0.01). This larger increase in LVEF also translated into a significantly higher percentage of echocardiographic-responders (75 vs. 39-53%, Figure 13). Table 10 and Figure 13 also indicate that T-wave area had no predictive value in the non-LBBB sub-group. While Figure 13 shows the ORs before

adjustments to covariates, values of ORs remained similar after adjustment of multiple covariates, such as gender, ischemia, age, hypertension, coronary artery bypass graft and the usage of diuretics and beta blockers (adjusted OR within LBBB patients was 2.50 (1.16-5.39), p=0.02).

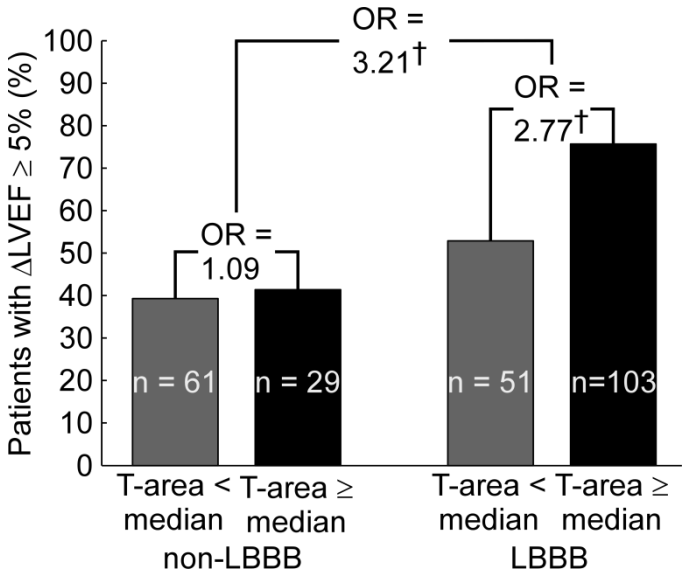


Figure 13. The percentage of echocardiographic responders in LBBB and non-LBBB QRS morphology, subdivided into cohorts with T-wave area < or ≥ the median value. The number of patients within one group is indicated in the bars. The ORs between the two QRS morphologies and between small and large T-wave areas are indicated.†indicates p<0.01.

The use of QRS area or sum QRST area instead of T-wave area did not provide a higher distinctive power in both the LBBB (OR=1.76 (N.S.) and OR=2.40 (p=0.02), respectively) and non-LBBB patient groups (OR=1.39 (N.S.) and OR=1.50 (N.S.), respectively).

4.4 T-wave area in prediction of outcome

4.4.1. Patient characteristics

The baseline characteristics of the 335 patients are listed in Table 11. The patients had a low LVEF and a prolonged QRS duration, consistent with the established indications for CRT. Most patients were male and in sinus rhythm. In addition, two-thirds of the patients had ischaemic HF aetiology and the same amount of patients had LBBB.

DOI:10.14753/SE.2017.2002

Table 11. Baseline ECG and VCG analysis results of the entire cohort (n=335) as well as the entire cohort divided by primary endpoint (HTLD) or survival status at the end of a 3-year follow-up. Variables are shown as mean ± standard deviation or N (%) when appropriate.

Variable	Entire cohort (n = 335)	- HTLD (n = 203)	+ HTLD (n = 132)	Survivors (n = 262)	Non-survivors (n = 73)
Baseline characteristics					
Age (y)	67±13	66±13	69±12	66±13	71±11§
Female (n,%)	70(21)	50(25)	20(15)*	59(23)	11(15)
Baseline LVEF (%)	24±7	24±7	23±7	24±7	23±7
Ischemic HF aetiology	192(57)	105(52)	87(66)*	143(55)	49(67)
LBBB (n,%)	199(59)	132(65)	67(51)†	164(63)	35(48)‡
Chronic AF (n,%)	85(25)	47(23)	38(29)	66(25)	19(26)
ECG measurements					
Heart rate (BPM)	75±15	75±15	76±14	75±15	75±14
QRS axis (º)	-20±58	-17±57	-24±59	-22±56	-11±64
VCG measurements					
QRS duration (ms)	172±33	172±32	172±35	173±34	170±31
QT interval (ms)	467±86	467±83	466±90	466±86	469±85
QTc interval (ms)	516±77	515±74	517±82	515±78	518±75
QRS-vector amplitude (mV)	1.5±0.5	1.5±0.5	1.4±0.5	1.5±0.5	1.4±0.5
QRS area (μVs)	88±46	92±47	82±45	91±47	78±40‡
QRS-vector azimuth (º)	-62±57	-69±47	-49±70†	-66±52	-44±73‡
QRS-vector elevation (º)	90±24	89±24	92±24	90±23	90±24
T-vector amplitude (mV)	0.5±0.2	0.5±0.3	0.4±0.2†	0.5±0.3	0.4±0.2§
T-wave area (μVs)	82±47	88±47	74±45†	87±49	66±35§
T-vector azimuth (º)	77±65	77±62	76±71	77±64	76±72
T-vector elevation (º)	85±26	87±26	83±26	85±26	85±27
QRS/T angle (º)	155±30	156±30	154±27*	155±31	156±21
Sum QRST area (μVs)	170±85	179±84	156±82*	177±87	144±68§

Variables are shown as counts(percentage) or mean±standard deviation when appropriate.

*p<0.05; †p<0.01 compared to the patient-group whom did not reach HTLD.

‡p<0.05; §p<0.01 compared to the survivor-group.

4.4.2. The predictive ability of areas derived from the VCG

The predictive power of LBBB and QRS duration is shown in Figure 14A using Kaplan Meier curves for the HTLD endpoint. There is no significant difference in the chance of reaching HTLD for patients with a QRS duration≥150 ms compared to patients with a QRS duration<150 ms (p=0.41). However, patients with a LBBB morphology performed significantly better than patients without LBBB (p<0.01). This distinction by LBBB was larger than that for QRS-area but similar to that for T-wave area and sum QRST area (Figure 14B). Patients with QRS-, T-, and sum QRST areas ≥ than their median values all reached the primary endpoint significantly less than patients with areas < the median values. Moreover, patients reaching the primary endpoint had a significantly smaller T-wave area compared to patients not reaching the primary endpoint, while QRS area was not significantly different between the two groups (Table 11).

DOI:10.14753/SE.2017.2002

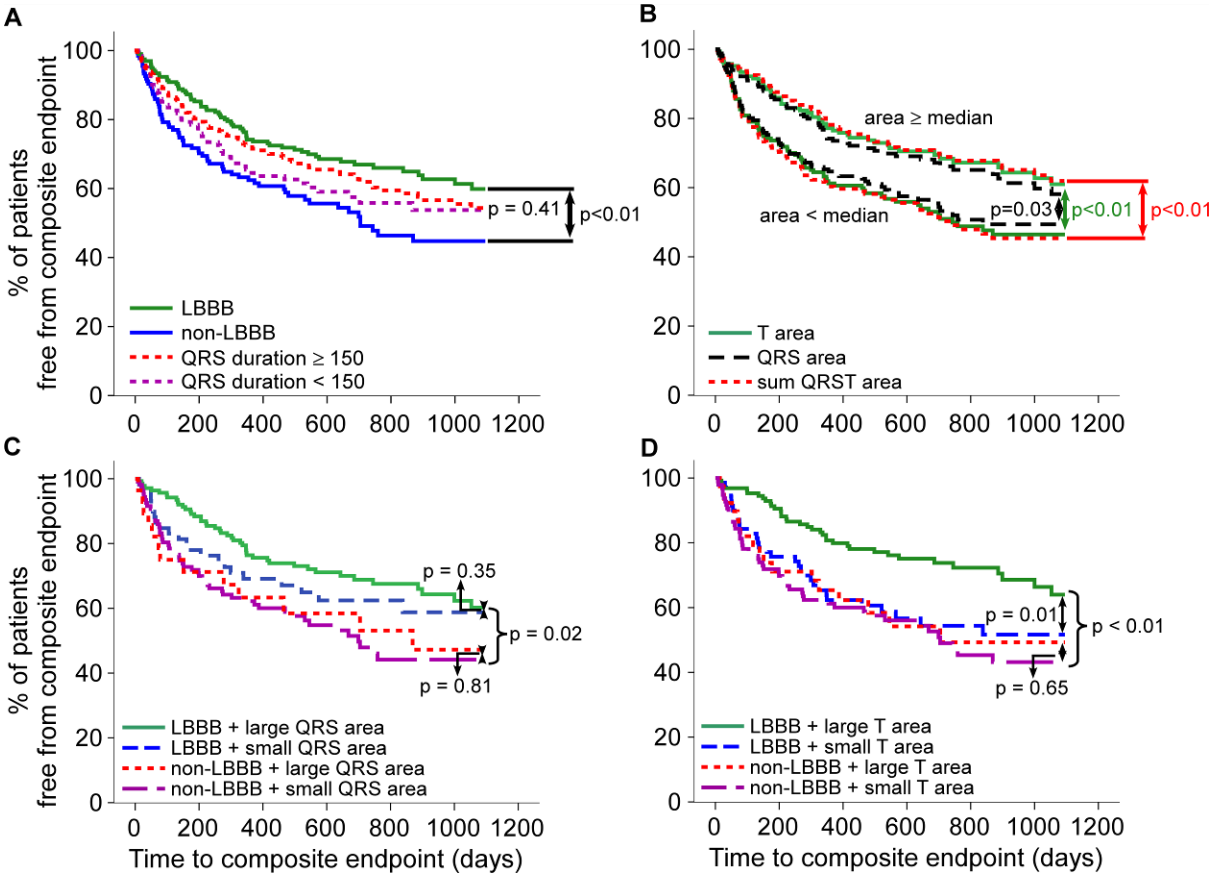


Figure 14. Kaplan-Meier estimates of the probability free of composite end-point HTLD after 3 years. The results of current guideline variables LBBB and QRS duration are shown in panel A and the results of the new VCG variables T-wave area, QRS area and sum QRST area are shown in panel B. The patients were then subdivided into four groups according to their QRS morphology and QRS area (C) or T-wave area (D). Large QRS or T area are values ≥ median value and small QRS or T area are values < median value.

Since LBBB morphology of the QRS complex is a well-known predictor for CRT response and because the percentage of patients with LBBB morphology was significantly higher in the patient group not reaching the primary endpoint (Table 11), the patient population was divided according to QRS morphology and subsequently subdivided into cohorts with < or ≥ median QRS- or T-wave areas. Within non-LBBB and LBBB subgroups, QRS area did not significantly influence the chance of reaching the HTLD endpoint (p=0.81 and p=0.35, respectively; Figure 14C). In contrast, the

subgroup of patients with LBBB and a large T-wave area had a significantly lower incidence of reaching the HTLD endpoint (36%) compared to the LBBB patients with a small T-wave area (48%, p=0.01) as well as the non-LBBB patient groups(p<0.01) (Figure 14D). T-wave area did not significantly affect HTLD in the non-LBBB patients (57% for a small T-wave area vs. 51% for a larger T-wave area, p=0.65).

The cohort with LBBB and a large T-wave area trended to contain more females (p=0.09) and contained significantly less patients with ischaemic HF aetiology compared to the other subgroups (Table 12). In addition, 129 out of 168 patients (77%) with a large T-wave area had a LBBB QRS morphology while LBBB was only present in 70 out of 167 patients (42%) with a small T-wave area (p<0.01, Figure 15). The QRS duration increases when the T-wave area increases, but the association between these two variables is not as high as the association between T-wave area and number of LBBB patients.

DOI:10.14753/SE.2017.2002

Table 12. Baseline patient characteristics after dividing patients according to their QRS morphology and T-wave area. The median cut-off value for the T-wave area was based on the entire cohort.

	LBBB		Non-LBBB	
	T-area < median (n = 70)	T-area ≥ median (n = 129)	T-area < median (n = 97)	T-area ≥ median (n = 39)
Age	67.3±10.4	67.6±12.8	67.1±13.3	65.7±15.9
Female	13(18.6)	38(29.5)	14(14.4)	5(12.8)
Ischemic HF aetiology	45(64.3)	63(48.8)*	61(62.9)	23(59.0)
Hypertension	53(75.7)	104(80.6)	75(77.3)	25(64.1)
CABG	33(47.1)	46(35.7)	44(45.4)	18(46.2)
Heart rate (BPM)	74±14	75±15	77±14	74±15
QRS duration (ms)	170±29	184±30†	158±32	173±39
QTc interval (ms)	514±87	532±74	492±64	526±87
QRS area (μVs)	77±34	121±44†	50±22	88±36†
T-wave area (μVs)	52±15	121±40†	42±15	108±42†

*p-value<0.05 compared to the T-area<median group with the same LBBB conditions

†p-value<0.01 compared to the T-area<median group with the same LBBB conditions

HF: heart failure

DOI:10.14753/SE.2017.2002

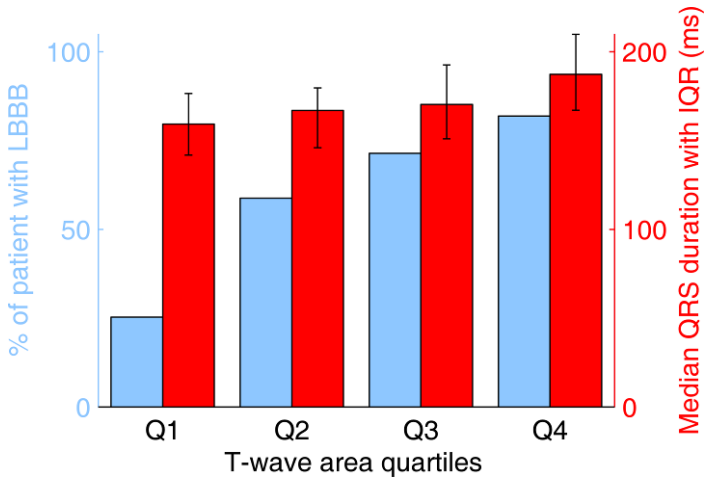


Figure 15. Histogram showing the associations between LBBB (light blue, left y-axis) or QRS duration (red, right y-axis) with T-wave area. The percentage of ischaemic patients was indicated by shading in the LBBB bars. T-wave area was divided into quartiles, indicated by Q1, Q2, Q3, and Q4 on the x-axis.

In a univariate analysis of the total population ischaemic HF aetiology, LBBB, QRS area, T amplitude, and T-wave area were some of the significant predictors for reaching HTLD (Table 13). Since QRS amplitude and T-wave area as well as T amplitude and T-wave area are mutually dependent (R=0.77 and R=0.87), only the area variables were included in the multivariate model. Multivariate analysis indicated that besides baseline creatinine levels, diuretics, and β-blocker usage only T-wave area remained in the model. The multivariate model indicated that patients with a large T-wave area had a 44% lower risk of reaching HTLD compared to those with a small T-wave area. Additionally, within LBBB patients the hazard ratio for HTLD between a T-wave area ≥ or < the median value was 0.54, a ratio that remained significant after adjustment for significant covariates (HR=0.48, p=0.01) (Table 13).

Table 13. Univariate and multivariate analysis of different parameters in the entire cohort (left) and the LBBB patient group (right) taking HTLD as the outcome parameter. Shown are the adjusted and unadjusted hazard ratios (HR) with their corresponding 95% confidence intervals and p-values.

Variable	Total population univariate			Total population multivariate			LBBB population univariate			LBBB population multivariate		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age (years)	1.01	0.99-1.03	0.10				1.03	1.01-1.05	0.02	1.04	1.00-1.06	0.02
Female	0.64	0.40-1.04	0.07				0.41	0.20-0.83	0.01	0.44	0.20-0.99	0.05
Hypertension	1.79	1.12-2.85	0.02				1.83	0.91-3.69	0.09			
Diabetes	1.42	1.01-1.99	0.05				1.26	0.78-2.04	0.34			
Ischaemic HF aetiology	1.52	1.06-2.18	0.02				2.06	1.23-3.46	0.01			
Chronic AF	1.16	0.79-1.65	0.45				1.37	0.80-2.35	0.26			
Paroxysmal AF	1.10	0.75-1.60	0.64				1.24	0.75-2.05	0.41			
CABG	1.28	0.91-1.81	0.15				1.41	0.87-2.27	0.16			
Valve surgery	0.66	0.38-1.14	0.13				0.75	0.35-1.54	0.41			
PCI	1.36	0.94-1.96	0.11				1.44	0.86-2.39	0.16			
LBBB	0.59	0.42-0.83	<0.01									
Baseline creatinine	1.25	1.13-1.39	<0.01	1.38	1.21-1.56	<0.01	1.23	1.08-1.40	<0.01	1.23	1.06-1.43	0.01
Diuretics	2.23	1.20-4.13	0.01	2.31	1.15-4.63	<0.01	2.37	1.02-5.48	0.04			

DOI:10.14753/SE.2017.2002

Aldosterone antagonist	0.94	0.66-1.35	0.74				1.10	0.67-1.80	0.71			
Digoxin	1.35	0.96-1.93	0.08				1.27	0.70-2.11	0.35			
β-blocker	0.65	0.40-1.04	0.07	0.56	0.34-0.92	.02	0.71	0.32-1.54	0.38			
ACEi	0.87	0.62-1.23	0.44				0.85	0.53-1.38	0.52			
ARB	0.92	0.60-1.42	0.71				1.06	0.60-1.89	0.83			
LVEF (%)	0.99	0.96-1.01	0.26				0.97	0.93-1.00	0.09	0.96	0.92-1.00	0.04
QRS duration ≥150 ms	0.86	0.61-1.22	0.41				1.08	0.62-1.89	0.79			
QT interval (ms)	1.00	0.99-1.00	0.95				1.00	0.99-1.01	0.34			
QRS/T angle (°)	1.00	0.99-1.00	0.34				0.99	0.99-1.00	0.16			
QRS amplitude (mV)	0.75	0.53-1.05	0.09				0.77	0.47-1.25	0.29			
T amplitude (mV)	0.31	0.14-0.68	<0.01				0.33	0.11-1.00	0.05			
QRS area ≥ median	0.68	0.48-0.95	0.03				0.79	0.47-1.31	0.35			
T-wave area ≥ median	0.58	0.41-0.82	<0.01	0.56	0.38-0.82	<0.01	0.54	0.34 - 0.88	0.01	0.48	0.28-0.82	0.01

ACE: angiotensin-converting-enzyme, AF: atrial fibrillation, ARB: angiotensin II type 1 receptor blocker, CABG: coronary artery bypass graft, LBBB: left bundle branch block, LVEF: left ventricular ejection fraction, PCI: percutaneous coronary intervention

DOI:10.14753/SE.2017.2002

4.4.3. Echocardiographic versus clinical outcome

The relation of reaching any adverse clinical outcome and echocardiography based on echocardiographic reverse remodelling was also examined. The mean increase in LVEF in patients reaching none of the combined endpoint HTLD was 10.4%±10.6% while this improvement in LVEF was only 3.4%±8.9% in patients who did reach the combined endpoint ($p<0.01$). Similarly, echo-responders (ΔLVEF ≥5% after 6 months follow-up) reached HTLD less often than the echo-nonresponders did (24% vs. 51%, $p<0.01$).

4.4.4. T-wave area as additional predictor of mortality and HF hospitalization

Cox-regression hazard model revealed the T-wave area also as a strong predictor of HF hospitalization and mortality, even after adjusting for significant covariates such as age, gender, and medication. The chance of HF hospitalization was almost twice as high for patients with a small T-wave area (HR = 0.53, 95% confidence interval (CI): 0.35-0.82, $p<0.01$). Indeed, the amount of HF hospitalizations after 3 years of CRT was highest in the non-LBBB group and LBBB subgroups with a small T-wave area, whereas HF hospitalization was significantly lower in LBBB patients with a large T-wave area (Figure 16A).

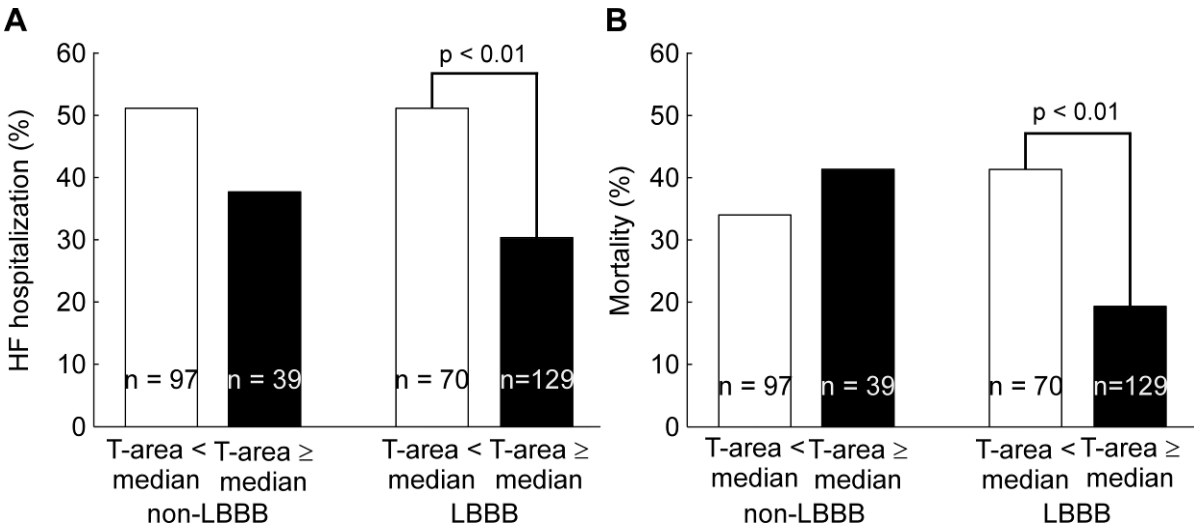


Figure 16. The percentage of patients reaching either HF hospitalization (A) or death (B) after dividing patients into those with LBBB or non-LBBB QRS morphology, and subdividing those with T-wave area < or ≥ the median value. The number of patients within one group is indicated in the bars.

With regard to mortality, survivors had a higher prevalence of LBBB and large T-wave area. Similarly, the chance of survival was approximately twice as large in the patient group with a large T-wave area compared to patients with a small T-wave area (HR = 0.57, 95% CI: 0.35-0.96, p=0.03). This difference was even larger when only LBBB patients were analyzed, i.e. LBBB patients with a large T-wave area had on average a ~3 times lower chance of death compared to LBBB patients with a small T-wave area (HR = 0.34, 95% CI: 0.17-0.67, p<0.01). Although descriptive subset analysis showed that the effect of T-wave area on mortality was constant throughout different subgroups, it was not present for patients without LBBB (Figure 17). Analyzing all subgroups, the mortality risk was highest in patients with non-LBBB and a large T-wave area (33%). For patients with LBBB, mortality was significantly and considerably lower in patients with a large T-wave area (19%) than in those with a small T-wave area (42%) (Figure 16B).

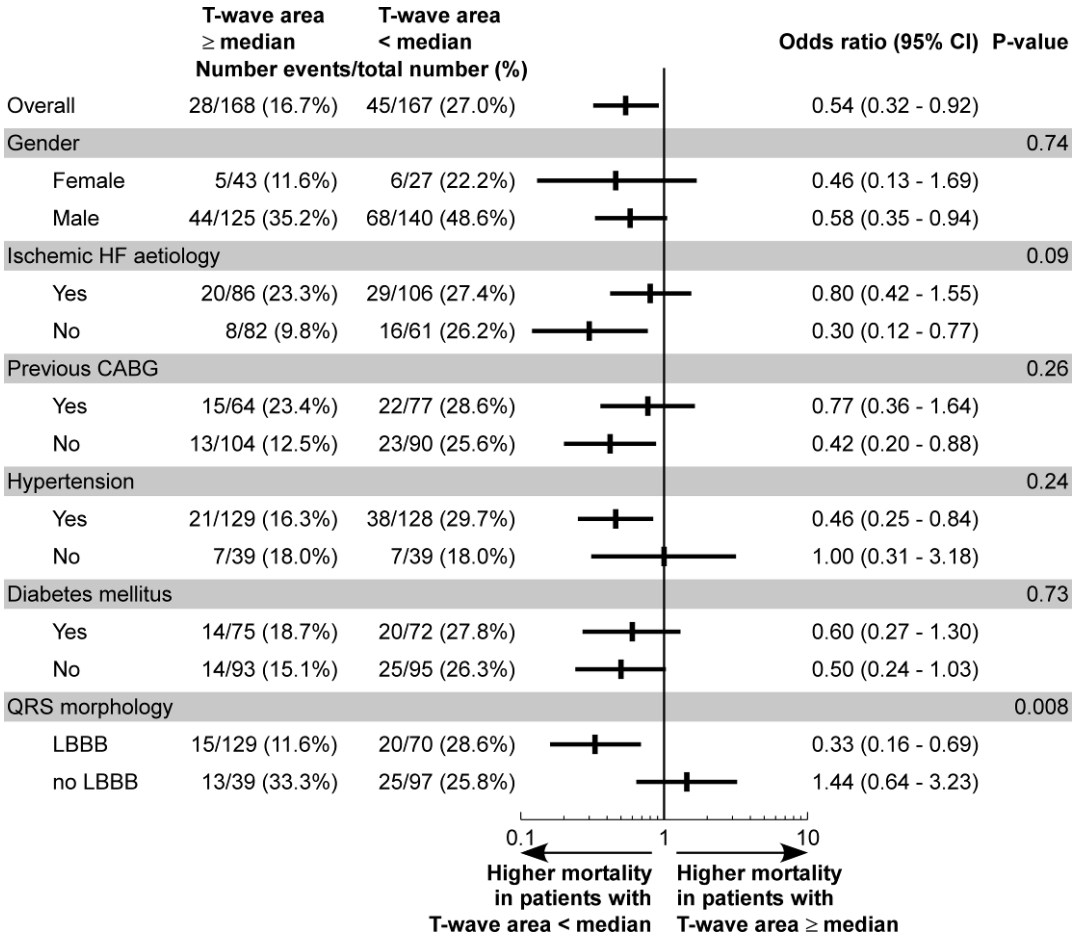


Figure 17. Subset analysis of all-cause mortality. Odds ratio and 95% confidence interval (CI) are plotted for the secondary end point of all-cause mortality at 3-years follow-up, comparing patients with a large and small T-wave area. CABG: coronary artery bypass graft, HF: heart failure.

4.5. Hyponatremia

4.5.1. Baseline characteristics

Of 569 patients, a total of 402 patients with available serum sodium levels within the defined time period were included. Mean baseline characteristics cohort were as follows:- age 68.7±12.3 years, 84 (20.9%) were females, 164 had history of diabetes mellitus (40.8%), creatinine 1.51±0.8 mg/dl, LVEF prior to device implantation 24.2±7.1% and QRS duration 160.2±27.4 milliseconds (msec). In total, 300 patients (74.6%) had NYHA class III or IV and there was no significant difference between hyponatremic and normonatremic patients.

DOI:10.14753/SE.2017.2002

Table 14. shows baseline characteristics in detail for the entire cohort. Hyponatremic patients were significantly younger as compared to normonatremic patients. They also were more likely to have history of diabetes mellitus and had significant difference in baseline serum creatinine (1.62±1.2 mg/dl and 1.47±0.64 mg/dl, p<0.001). The baseline LVEF was significantly less in them; and they had significantly larger LV internal diameters, both diastolic and systolic. These patients were also on a higher dose of furosemide and aldosterone antagonist usage was significantly higher in them. There was no significant difference in any other co-morbidites and medication usage. Post-implant evaluation at 6-months did not shown any significant difference in change in New York Heart Association classification, absolute and percent change in LVEF in both the groups (in regards to baseline serum sodium levels).

Table 14. Baseline characteristics for the whole cohort, hyponatremic and normonatremic patients

Characteristic / Frequency or mean	Whole cohort (N=402)	Hyponatremia YES (N=88)	NO (N=314)	p value
Age (year)	68.7 ±12.3	65.4 ±13.6	69.7 ±11.6	<0.003
Female	84 (22%)	14 (17%)	70 (22%)	0.193
Creatinine (mg/dL)	1.51 ±0.80	1.69 ±1.20	1.47 ±0.64	0.012
NYHA class: III/IV	300 (75%)	67 (76%)	233 (74%)	0.713
LVEF (%)	24.2 ±7.1	22.7 ±6.8	24.6 ±7.2	0.026
LVIDd (mm)	62.09 ±9.07	64.55 ±10.05	61.38 ±8.69	0.006
LVIDs (mm)	54.22 ±9.74	56.72 ±11.13	53.5 ±9.22	0.022
QRS duration (msec)	160.24 ±27.46	160.71 ±32.87	160.88 ±25.5	0.837
Coronary bypass	168 (42%)	42(48%)	126 (40%)	0.201
Chronic atrial fibrillation	113 (28%)	20 (23%)	93 (30%)	0.204
Paroxysmal atrial fibrillation	124 (31%)	33 (38%)	91 (29%)	0.126

Diabetes Mellitus	164(41%)	48 (55%)	116 (37%)	0.003
Hypertension	302(75%)	66 (75%)	236 (75%)	0.976
Coronary Artery Disease	272 (68%)	55 (63%)	217 (69%)	0.241
Cardiomyopathy	239 (60%)	49 (56%)	190 (61%)	0.396
PCI	107(27%)	23 (26%)	84 (27%)	0.908
Valve surgery	66 (16%)	15 (17%)	51 (16%)	0.857
Medications				
Angiotensin Converting Enzyme Inhibitor	242 (60%)	56 (64%)	186 (59%)	0.456
ARB	79 (20%)	13 (15%)	66 (21%)	0.192
Aldosterone antagonist	131(33%)	42 (48%)	89 (28%)	0.001
Beta-blockers	353 (88%)	77 (88%)	276 (88%)	0.921
Digoxin	161 (40%)	41 (47%)	120 (38%)	0.157
Diuretics	355 (88%)	83 (94%)	272 (87%)	0.047
Total daily dose of furosemide (mg)	68.8 ±58.3	84.8 ±75.3	63.9 ±51.3	0.007

In univariate Cox proportional hazard model for predictors of primary end-point, hyponatremia, creatinine and diuretics were associated with clinical outcome (Table 15). In a multivariate model, creatinine [HR 1.40 95% CI (1.238-1.595), p<0.001] and diuretics [HR 3.916 95%CI (1.791-8.694, p= 0.001) continued to remain significantly associated with composite endpoint (Table 15).

Table 15. Univariate and multivariate Cox regression models to identify predictors for composite endpoint

Characteristic	Univariate		Multivariate	
	HR (95%CI)	p value	HR (95%CI)	p value
Age	1.011 (0.998-1.025)	0.087	-	-
Creatinine	1.267 (1.156-1.389)	<0.001	1.405 (1.238-1.595)	<0.001
Hyponatremia	1.54 (1.113-2.131)	0.009	1.254 (0.879-1.789)	0.212
LVEF	0.995 (0.974-1.016)	0.612	-	-
LVIDd	1.007 (0.992-1.023)	0.33	-	-
LVIDs	1.008 (0.993-1.023)	0.33	-	-
Diabetes mellitus	1.336 (0.998-1.789)	0.052	-	-
Diuretics	2.652 (1.401-5.019)	0.003	3.916 (1.791-8.694)	0.001
Aldosterone antagonist	0.913 (0.668-1.248)	0.567	-	-

Kaplan-Meier curve for event free survival showed that patients with hyponatremia had significantly higher incidence of composite endpoint as compared to normonatremic patients (Figure 18). Chi-square comparison between the two groups for primary composite endpoint showed that 57.9% of hyponatremic patients had adverse events as compared to 40.7% of normonatremic patients (p=0.004). Notably, in comparison to patients with a normal serum sodium level, the hyponatremic patients

DOI:10.14753/SE.2017.2002

were more likely to be hospitalized with HF exacerbation (p=0.033) but there was not a significant difference between mortality (p=0.159).

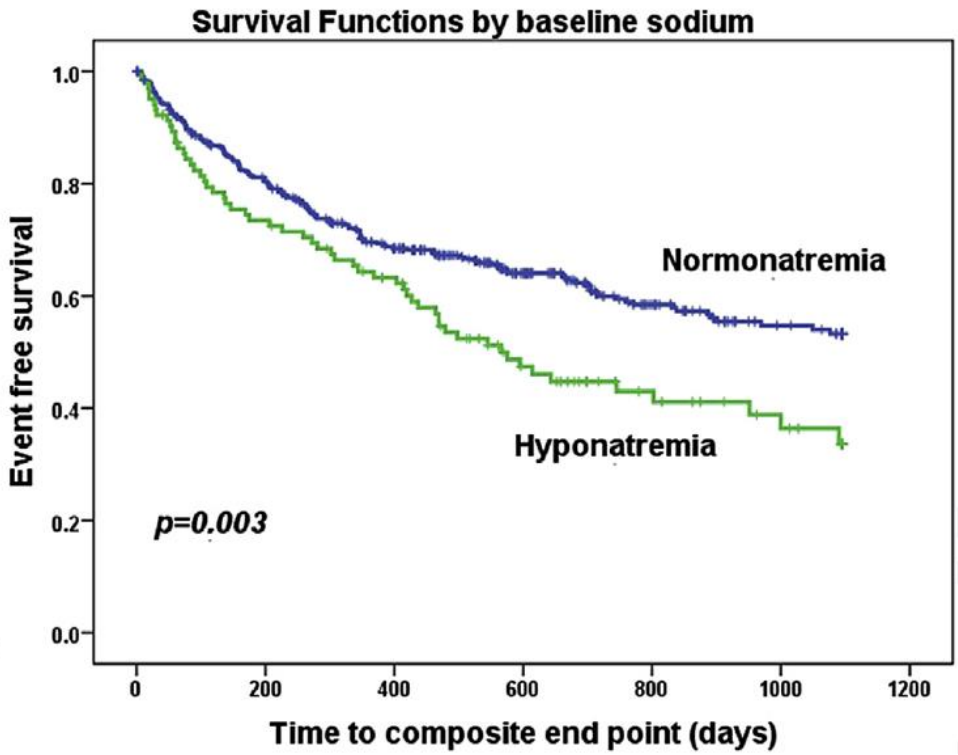


Figure 18. Kaplan-Meier curve depicting significantly higher composite endpoint in patients with hyponatremia as compared to normonatremic patients after CRT implantation

4.5.2. The predictive ability of follow-up hyponatremia

We also analyzed the data in regards to follow-up serum sodium levels after CRT implantation. Out of 88 patients with baseline hyponatremia, serum sodium level normalized in 37 cases. Kaplan-Meier curve (Figure 19) in regards to event free survival showed that patients who were initially hyponatremic but had normalized serum sodium levels post-device implantation also had better long-term outcome. Interestingly, patients who had normal serum sodium levels before device but developed low serum sodium levels later did as poorly as patients who consistently remained hyponatremic.

DOI:10.14753/SE.2017.2002

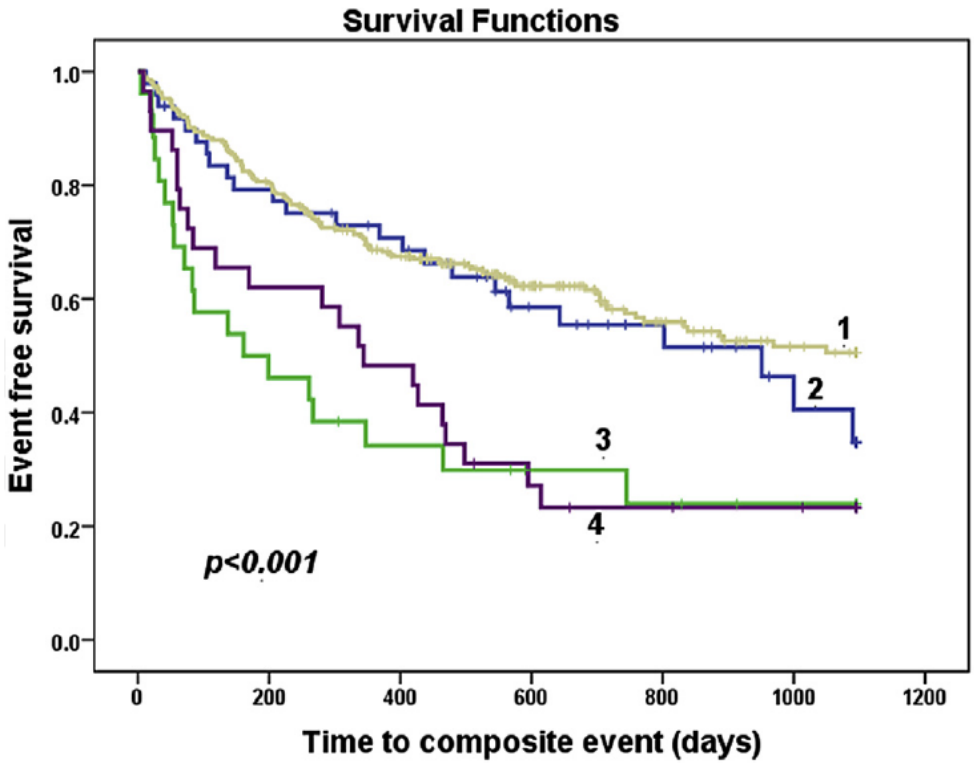


Figure 19. Kaplan-Meier curve showing occurrence of adverse events in different patient

groups

1. Normonatremic patients who stay normonatremic post CRT implantation.
2. Hyponatremic patients who become normonatremic post CRT implantation.
3. Hyponatremic patients who stay hyponatremic after device implantation.
4. Normonatremic patients who become hyponatremic after device implantation.

On follow-up laboratory values in regards to serum sodium levels, a difference was seen in echocardiographic response to CRT device implantation. LVEF after 6 months of device placement was noted to be significantly less in patients with follow-up hyponatremia (25.9%±10.9%) as compared to patients with normal sodium levels on follow-up (31.8%±11.7%, p=0.004). Similarly a change in LVEF was significantly less in the hyponatremic (follow-up) patients (3.1%±10.5% vs. 7.9%±10.1%, p=0.009). The proportion of the patients who subsequently developed low sodium levels (from normonatremia) or those who continued to remain hyponatremic (21.1% and 22.2% of the group respectively) had a change in LVEF ≥ 10. In contrast patients within whom the electrolyte abnormality resolved, 56.8% of the group had change in LVEF >10%

(p=0.021). Kaplan Meier curve showed that hyponatremia on follow-up was associated with poorer outcomes as compared to normonatremia on follow-up (p=0.001). (Figure 20)

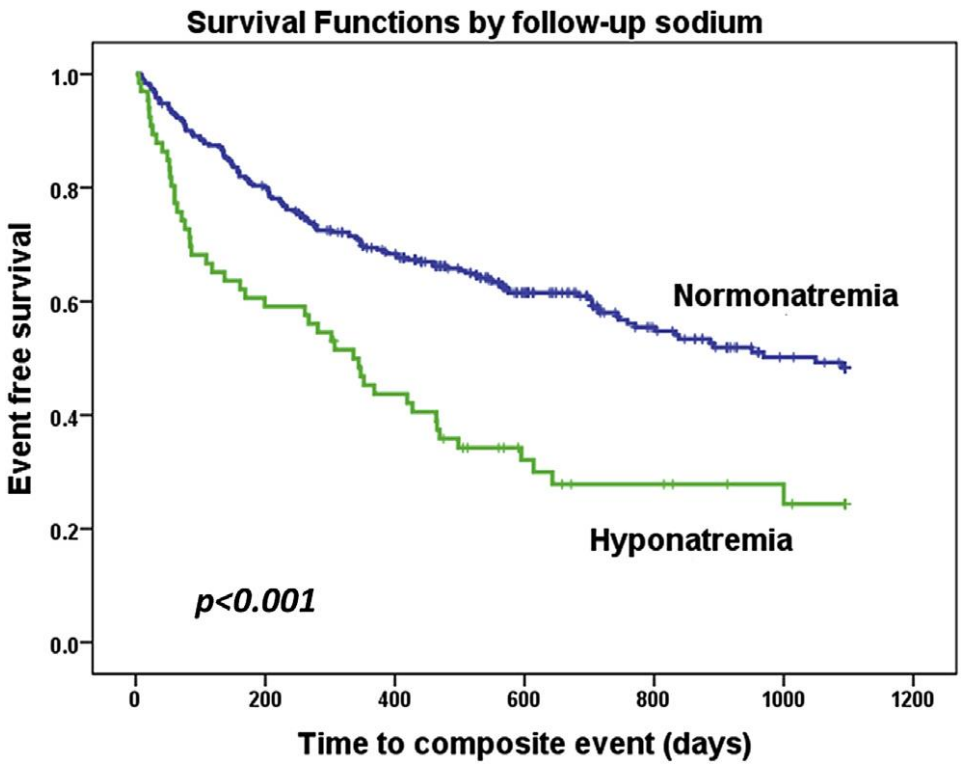


Figure 20. Kaplan Meier curve showing effect of follow-up sodium level after CRT implantation on composite outcome

4.6. Hypothyroidism

4.6.1. Baseline characteristics

Of 511 patients who met study criteria, 84 had a history of hypothyroidism prior to CRT placement. 60 of these 84 patients with a known history of hypothyroidism had TSH within 2 weeks of CRT implant. Baseline characteristics for the 511 patients in the study cohort are presented in Table 16.

DOI:10.14753/SE.2017.2002

Table 16 Baseline characteristics for the whole cohort, hypo- and euthyroid patients

Characteristic	Whole cohort (N=511)	Hypothyroid (N= 84)	Euthyroid N=427	p value
Age (years)	68.5 ±12.4	73.2 ±10.8	67.5 ±12.4	<0.001
Female	116 (23%)	32 (38%)	74 (17%)	<0.001
Creatinine (mg/dL)	1.5 ±0.8	1.7 ±0.7	1.47 ±0.80	0.018
NYHA: III/IV	387 (76%)	61 (73%)	326 (76%)	0.495
LVEF	24 ±7(%)	26 ±7	24 ±7	0.014
LVIDd (mm)	62.1 ±8.9	58.8 ±8.4	62.0 ±8.8	0.001
LVIDs (mm)	54.2 ±9.4	50.2 ±8.7	54.0 ±9.3	<0.001
QRS duration (msec)	161 ±28	162 ±23	161 ±28.5	0.795
Coronary artery bypass graft	209 (41%)	42(50%)	167 (39%)	0.063
Chronic atrial fibrillation	146 (29%)	29 (35%)	117 (27%)	0.186
Paroxysmal atrial fibrillation	152 (30%)	26 (31%)	126 (30%)	0.791
Diabetes mellitus	205(40%)	39 (46%)	166 (39%)	0.197
Hypertension	381(75%)	64 (76%)	317 (74%)	0.707
Coronary artery disease	379(74%)	61 (73%)	274 (64%)	0.093
Ischemic cardiomyopathy	294 (58%)	52 (62%)	242 (57%)	0.623
Baseline sodium (mEq/L)	137.6 ±3.51	137.4 ±3.1	137.6 ±3.6	0.655
Hyponatremia	102 (20%)	16 (19%)	86 (20%)	0.804
ACEi	310 (61%)	42 (50%)	268 (63%)	0.029
ARB	102 (20%)	20 (24%)	82 (19%)	0.334
Aldosterone antagonist	164(32%)	23 (27%)	141 (33%)	0.189
Beta-blockers	448 (88%)	69 (82%)	379 (89%)	0.92
Digoxin	194 (38%)	40 (48%)	154 (36%)	0.046
Diuretics	449 (88%)	74 (88%)	375 (88%)	0.55
Antiarrhythmics	95 (19%)	18 (21%)	77 (18%)	0.561
Amiodarone	74 (15%)	18(21%)	56 (13%)	0.01
TSH (μU/mL)	3.8 ±8.3	8.5 ±15.7	2.3 ±1.6	0.003

Hypothyroid patients were significantly older as compared to euthyroid patients (73.2±10.8 v/s 67.5±12.4 years, p<0.001) and were more likely to be female. They also had significant difference in baseline serum creatinine. The baseline left ventricular ejection fraction was significantly greater in the hypothyroid group with significantly smaller left ventricular internal diameters, both diastolic and systolic. Hypothyroid patients were significantly less frequently treated with angiotensin converting enzyme inhibitors and more frequently treated with digoxin. There were no other significant differences in other co-morbidites or medication usage. There was no significant difference between the included and excluded population regarding baseline characteristics.

Table 17. Univariate and multivariate Cox regression models to identify predictors for composite endpoint

Characteristic	Univariate		Multivariate	
	HR (95%CI)	p value	HR (95%CI)	p value
Age	1.01 (0.997-1.019)	0.137	-	-
Creatinine	1.29 (1.183-1.405)	<0.001	1.26 (1.142-1.381)	<0.001
Hypothyroidism	1.47 (1.064-2.052)	0.020	1.46 (1.027-2.085)	0.035
Left ventricular ejection fraction	0.98 (0.970-1.007)	0.237	-	-
Diabetes mellitus	1.34 (1.025-1.789)	0.052	1.29 (0.971-1.708)	0.080
Female gender	0.69 (0.48-0.998)	0.049	0.64 (0.428-0.963)	0.032
Angiotensin converting enzyme inhibitor	0.79 (0.604-1.037)	0.09	0.86 (0.642-1.150)	0.309
Digoxin	1.42 (1.100-1.847)	0.010	1.26 (0.946-1.675)	0.114
Amiodarone	1.30(0.651-2.605)	0.455	-	-

4.6.2. Hypothyroidism in prediction of long-term outcomes

Univariate predictors of the composite outcome with p<0.10 (i.e., female gender, hypothyroidism, creatinine, diabetes mellitus, digoxin and angiotensin converting enzyme inhibitors use) were considered for multivariate analysis which demonstrated that creatinine, female gender and hypothyroidism were significantly associated with the composite outcome (Table 17). Kaplan-Meier curve for event free survival showed that patients with history of hypothyroidism had a significantly higher incidence of the composite endpoint as compared to euthyroid patients (Figure 21).

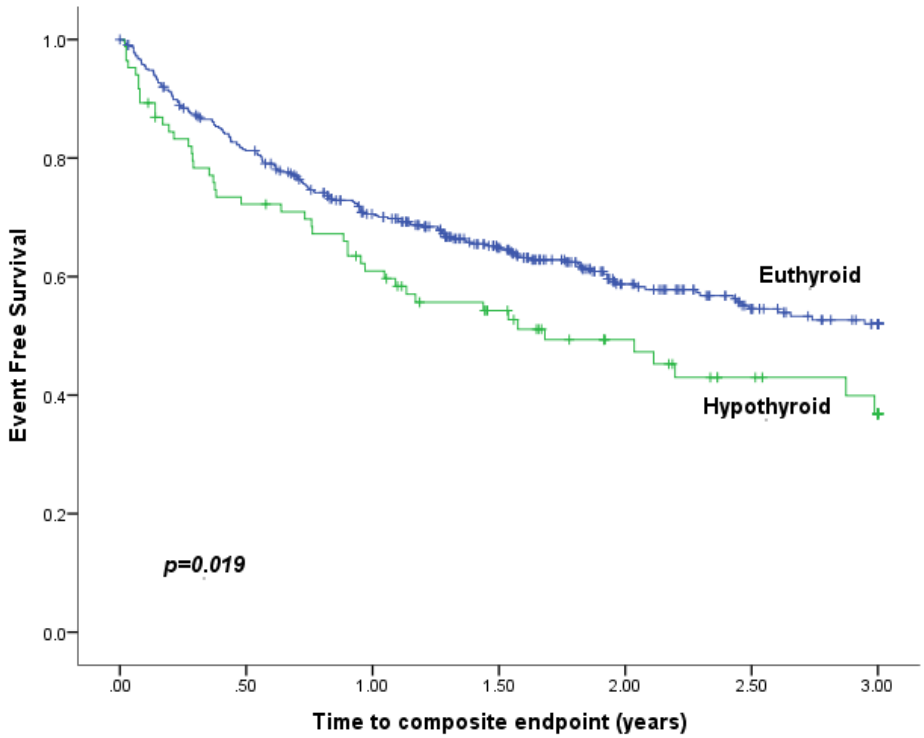


Figure 21. Kaplan-Meier curve showing a significantly higher composite end-point in hypothyroid patients as compared to euthyroid patients [HR 1.46, 95%CI (1.027-2.085), p=0.035]

Chi-square comparison between the two groups demonstrated that 53.6% of hypothyroid patients as compared to 39.8% of euthyroid patients (p=0.02) reached the composite end-point. 45 patients reached the composite endpoint at the end of 3 years [HR 1.48, 95%CI (1.06-2.05) p=0.02]; 33 patients had mortality during this time period [HR 1.48, 95%CI (1.01-2.18) p=0.046] and 38 patients had heart failure hospitalizations [HR 1.51, 95%CI (1.06-2.17) p=0.022]. There was no significant difference between

echocardiographic response to CRT implantation in hypothyroid as compared to euthyroid patients in regard to change in left ventricular ejection fraction after CRT placement (delta left ventricular ejection fraction- hypothyroid patients 10.1±10.5, euthyroid 7.3±10.5, p=0.09; %change in LVEF- hypothyroid 42.5±50.7, euthyroid 35.9±52.1, p=0.426). On a breakdown of the composite endpoint into individual components, hypothyroid patients were more likely to be hospitalized with HF exacerbation (p=0.021) and had a significantly higher mortality (p=0.044) as compared to euthyroid patients.

4.7. Device measured physical activity

4.7.1. Baseline characteristics

Regarding the baseline characteristics of the entire study cohort, it was a typical CRT population (Table 18). Significant differences in device measured activity levels were seen for the summarized data between visits. Specifically, there was increase in median activity at 3- (168 (96-237) min/day, p=0.001) & 6-months (162 (87-237) min/day (p=0.011)) when compared to 1 month (135 (72-210) min/day) in the entire cohort. The 6MWT also showed significant improvement from baseline during subsequent follow-up visits (1 month: 320 (380-350) meters, 3 months: 332 (256-402) meters, p=0.007, 6 months: 338 (274-421) meters, p<0.001). Significant correlation between 6MWT and device based physical activity data was observed at each visits. The correlation between summarized device diagnostic activity data and 6MWT was observed at 1 month (R=0.407, p<0.01), at 3 months (R=0.358, p<0.01), and at 6 months visit (R=0.392, p<0.01). The patients were followed-up for median 1.4 years (IQR 0.9 years).

DOI:10.14753/SE.2017.2002

Table 18. Baseline characteristics of the population by 1 month activity

	Activity (minutes/day)			
Characteristic	< 72(n=54)	72≤ and< 210(n=55)	≥ 210 (n=55)	p value
Age (year)	72.55 ± 9.69	69.6 ± 12.56	60.81 ± 12.94	<0.001
Women	10 (18.9 %)	12 (27.3 %)	14 (24.6 %)	0.578
NYHA class: III	38 (77.6 %)	41 (80.4 %)	42 (75.0 %)	0.923
NYHA class: IV	2 (4.1 %)	2 (3.9 %)	4 (7.1 %)	0.923
Biventricular upgrade of pacemaker device	30 (56.6 %)	24 (43.6 %)	24 (42.1 %)	0.252
LVEF (%)	25.04 ± 6.92	25.3 ± 5.93	24.82 ± 6.89	0.939
Coronary bypass	27 (50.9 %)	25 (45.5 %)	10 (17.5 %)	< 0.001
Chronic atrial fibrillation	14 (26.4 %)	13 (23.6 %)	9 (15.8 %)	0.372
Diabetes	25 (47.2 %)	21 (38.2 %)	18 (31.6 %)	0.244
Hypertension	44 (83.0 %)	41 (74.5 %)	33 (57.9 %)	0.012
Ischaemic cardiomyopathy	37 (69.8 %)	33 (60 %)	22 (38.6 %)	0.006
Percutaneous coronary intervention	15 (28.3 %)	14 (25.5 %)	11 (19.3 %)	0.528
Valve surgery	10 (18.9 %)	11 (20 %)	6 (10.5 %)	0.334
ACE/ARB	43 (81.1 %)	44 (80 %)	52 (91.2 %)	0.199
Aldosterone antagonist	14 (26.4 %)	18 (32.7 %)	17 (29.8 %)	0.773
Beta-blockers	48 (90.6 %)	49 (89.1 %)	52 (91.2 %)	0.927
Digoxin	15 (28.3 %)	17 (30.9 %)	10 (17.5 %)	0.227
Diuretics	48 (90.6 %)	46 (83.6 %)	40 (70.2 %)	0.020

NYHA - New York Heart Association Class; LVEF - left ventricular ejection fraction; ACE - angiotensin converting enzyme; ARB - angiotensin receptor blocker.

4.7.2. Prediction of HF hospitalization

To assess the predictive value of the device based physical activity and 6MWT data we substratified the patients into tertiles. Patients with higher levels of activity had a significantly improved clinical outcome comparing to patients with tertile of lower level of activity.

The time to first heart failure hospitalization was examined during a follow-up period of 3 years. In the entire cohort, 20.5 % (n=45) were hospitalized over 3 years: 30.9 % in the lowest tertile of device-based physical activity compared to 13.7% in the highest activity tertile (p=0.026). Patients with higher levels of device-based activity had a better event free survival with respect to time to first HF hospitalization compared to the lowest tertile (p=0.004) by log-rank test) (see Figure 22). Kaplan Meier survival method demonstrated superior event free survival with respect to time to first HF hospitalization in patients with a longer 6MWT (p=0.001).

4.7.3. Prediction of composite outcome

The composite outcome of all-cause mortality, HF hospitalization, LV assist device implantation, and cardiac transplantation occurred in 28.5% (n=61) of the entire cohort. A higher proportion (44.3%) in the group with the lowest level of physical activity had poorer event free survival and met the criteria for the composite endpoint compared to 19.7% in the most active group (p=0.009). Patients with higher levels of device-based activity had a better event free survival with respect to time to composite outcome compared to the lowest tertile (p<0.001) (Figure 22). Kaplan Meier survival method demonstrated superior event free survival with respect to time to the composite outcome in patients with a longer 6MWT (p<0.001 by log-rank test).

DOI:10.14753/SE.2017.2002

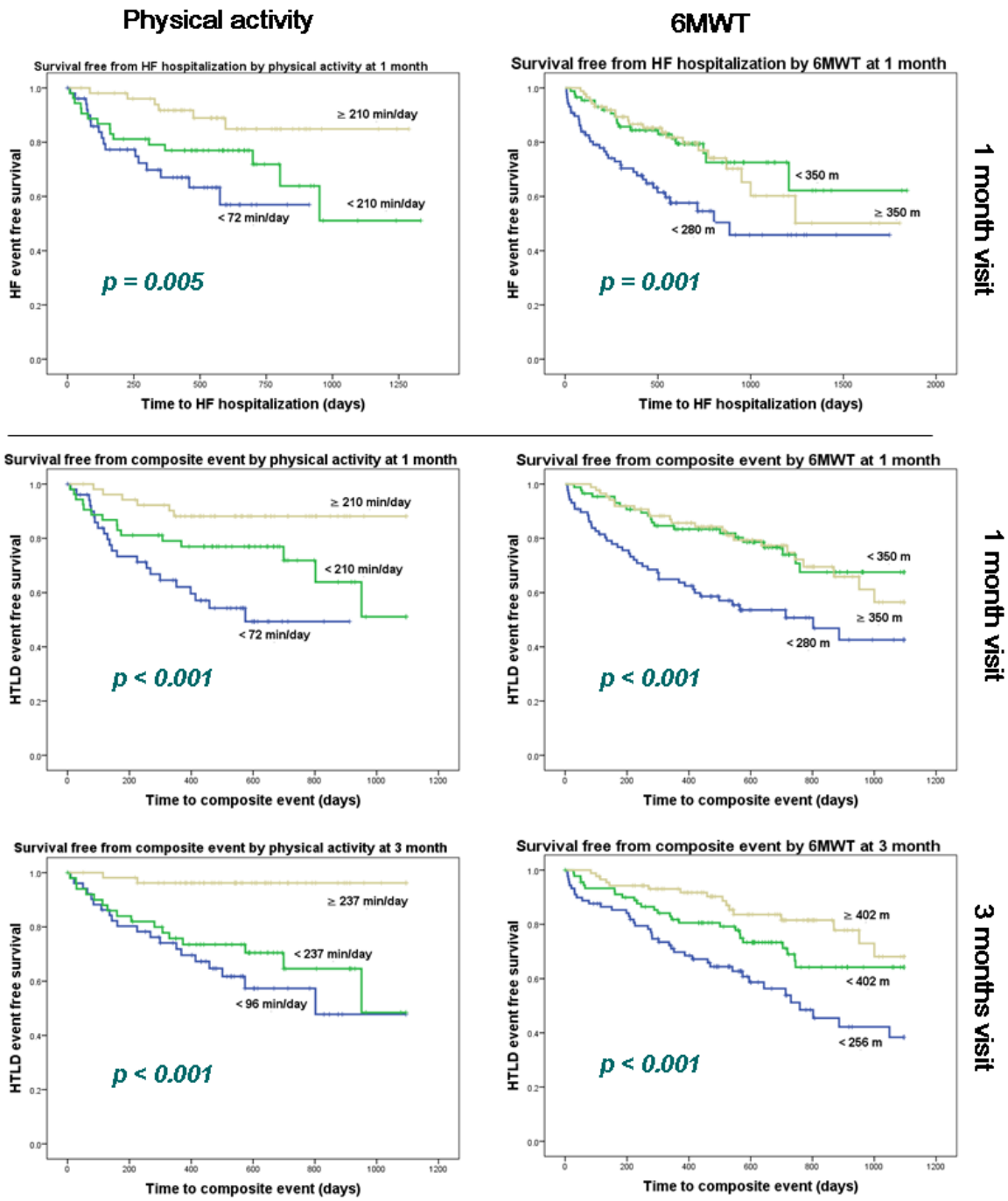


Figure 22. Freedom from the primary end-point of heart failure hospitalization (first line) and the secondary composite end-point of all-cause death, cardiac transplantation, LVAD implantation, or HF hospitalization at 3 years stratified by physical activity and 6MWT values at 1 and 3 months visit (second and third lines).

DOI:10.14753/SE.2017.2002

In univariate analysis, gender, coronary artery disease, baseline creatinine level, usage of diuretics and digoxin were significant predictors of HF hospitalization. In adjusted multivariate Cox-proportional hazard modeling, device-based physical activity at 1- and 3- months remained a significant predictor of HF hospitalization. (Table 19.) In a model predicting composite outcome, physical activity was a predictor, regardless of baseline creatinine level.

Table 19. Predictors of heart failure hospitalization and composite outcome

	HF hospitalization outcome		Composite outcome	
	Univariate analysis HR (95% CI)	Multivariate analysis HR (95% CI)[a]	Univariate analysis HR (95% CI)	Multivariate analysis HR (95% CI)[b]
Physical activity				
1 month	0.51 (0.34-0.78, p=0.002)	0.57 (0.38-0.91, p=0.017)	0.48 (0.32-0.71, p<0.001)	0.55 (0.36-0.82, p=0.004)
3 months	0.41 (0.26-0.64, p<0.001)	0.46 (0.29-0.73, p=0.001)	0.40 (0.26-0.61, p<0.001)	0.44 (0.28-0.69, p<0.001)
Creatinine	1.25 (1.13-1.38, p<0.001)	1.25 (1.00-1.58, p=0.054)	1.28 (1.18-1.39, p<0.001)	0.76 (0.37-1.53, p=0.048)
6MWT				
1 month	0.65 (0.48-0.86, p=0.003)	0.61 (0.44-0.85, p=0.003)	0.40 (0.24-0.68, p=0.001)	0.58 (0.43-0.80, p=0.001)
3 months	0.59 (0.44-0.79, p<0.001)	0.60 (0.44-0.82, p=0.001)	0.55 (0.32-0.86, p=0.010)	0.55 (0.43-0.75, p<0.001)

[a] adjusted for gender, CAD, diuretics, digoxin, creatinine

[b] adjusted for gender, diuretics, creatinine

DOI:10.14753/SE.2017.2002

Patients with higher levels of physical activity, had a 45% (p=0.004) and 56% (p<0.001) relative risk reduction in the composite outcome at 1 and 3 months respectively. Similarly, increased 6MWT was associated with 42% (p =0.001) and 45% (p<0.001) relative risk reduction in the composite clinical endpoint at 1 and 3 months, respectively. (Table 19.)

4.7.4. Activity level and CRT response

Echocardiographic response was defined as an improvement in LVEF by 10%. Echo response was lower in lowest tertile vs. the highest tertile of device based physical activity at 1 month (20 % vs. 45%, p=0.005), respectively. Similar differences were observed for device-based data at 3 months. An additional hour of higher activity at 1 month translated to 1.38 times (95% CI: 1.075-1.753, p=0.011) higher likelihood of improved echocardiographic response. Similarly, higher physical activity at 3-month control improved the likelihood of response 1.34 fold (95% CI: 1.066-1.686, p=0.012).

4.8. The coronary sinus side branch stenting

4.8.1. The results of long-term follow-up

Coronary sinus side branch stenting was successfully performed in 312 of 317 patients (98.4%). In five cases it was not possible to introduce the stent into the side branch due to tortuosity of the proximal part or the small diameter of the vessel. In four cases the electrode was left in the side branch without stenting add, in one patient we changed to transseptal endocardial implantation because of intraoperative dislocation. No implantation related death occurred in our patient group. Mechanical injury caused by CS stenting was not experienced. During implantation coronary sinus dissection with pericardial tamponade was detected in one patient. Since contrast dye extravasation was seen in the pericardial space of the first CS venogram prior to stent deployment, the effusion was presumably caused by CS dissection during positioning of the CS guide. Following percutaneous aspiration from a subxyphoideal puncture, pericardial effusion did not recur.

Early lead dislocation with loss of LV capture was detected in two patients (0.6%). Potential causes of the dislocation might be in both cases proximal lead position in a lateral side branch, underestimation of the diameter of the stent and the localization of

the stent in a curvature of the vessel. Re-operation was performed; in one patient left ventricular pacing was carried out via the anterolateral branch. Phrenic nerve stimulation was found in the in-hospital period in seven patients (2.2%). Changing of the pacing parameters finally or transiently solved the problem. During follow-up 54 patients died, an average 13.4 months after implantation (n=11 in the first 1-3 months, n=17 in the 3 month-1 year period, n=16 in the 1-2 year period, n=10 after 2 years).

Compared with the values measured after the implantation, the LV pacing threshold did not change significantly either after 6 months (1.0 [0.6-1.6] V vs. 0.8 [0.6-1.3] V, p=0.052; Figure 23, panel A) or after 24 months follow-up (0.8 [0.6-1.6] V vs. 0.8 [0.6-1.5] V, p=0.419; Figure 23, panel C). A clinically remarkable rise in pacing threshold was observed in two cases (0.6%). In one patient the threshold increased after two years (2.2 vs 5.6 V). In the other case the lowest threshold value was 5.8 V @ 0.5 ms during implantation which increased to 7.2 V @ 0.5 ms. In two other cases the threshold increased more than 2 V, but did not exceed 4 V @ 0.5 ms. Macroscopic dislocation was not detected on X-ray in these four patients. Although a slight decrease of the LV pacing impedance was found both at 6 months (600 [522-720] Ω vs. 550 [475-639] Ω, p=0.0007; Figure 23, panel B) and 24 months visits (608 [535-780] Ω vs. 575 [508-656] Ω, p=0.0181; Figure 23, panel D), results of impedance measurements did not suggest insulation failure or fracture of the left ventricular electrode in any cases during follow-up. In patients with three (n=47, Figure 23, panel E-F) or four years' (n=13) follow-up, pacing threshold remained stable (median 0.9 [0.6-1.65] V vs. 0.9 [0.6-1.3] V and 0.9 [0.7-2] V vs. 1.25 [0.85-2.1] V @0.5 respectively), no signs of lead injury were detected (608 [522-810] Ω vs. 563 [511-676] Ω and 600 [529-688] Ω vs. 636 [553-709] Ω).

DOI:10.14753/SE.2017.2002

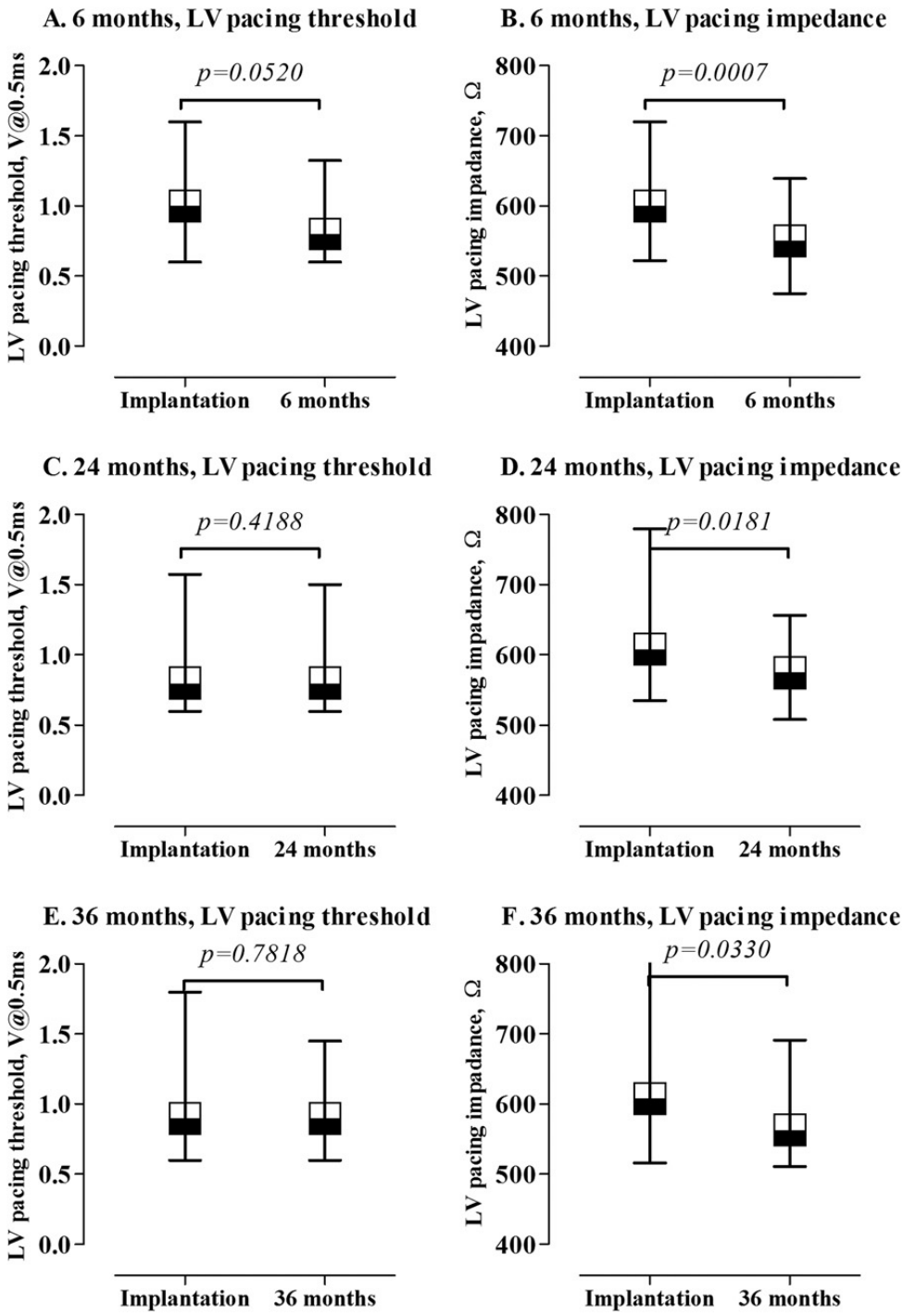


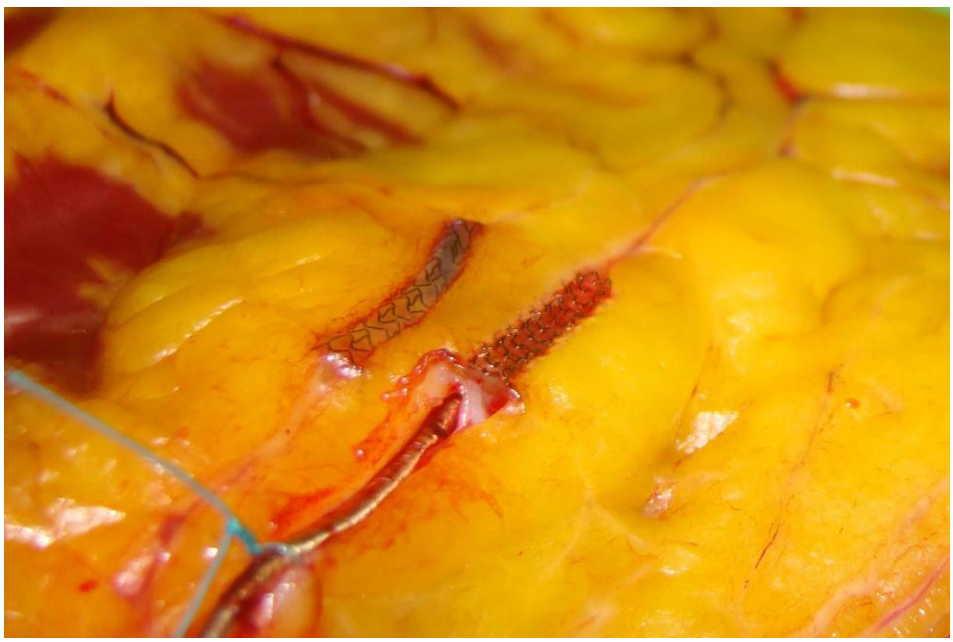
Figure 23. Changes in LV pacing and impedance values at 6, 24, and 36 months after implantation. LV pacing threshold did not change at 6, 24, and 36 months of follow-up, while a slight decrease in the LV pacing impedance values was found without any signs of injury of the lead insulation. (n = 293 at 6 months, n = 153 at 24 months, n = 47 at 36 months). Medians and interquartile ranges are presented. P-values were calculated with the Wilcoxon signed rank test.

DOI:10.14753/SE.2017.2002

Phrenic nerve stimulation was observed in 18 patients (5.7%). In 11 cases reprogramming of pacing parameters was successful to terminate PNS. In 7 cases (2.2%) repositioning of the lead was necessary. The stented LV leads were retracted with an ablation catheter introduced via the femoral vein in all patients 1-28 months after implantation. In 5 cases suitable pacing threshold was reached, while in one patient the threshold increased to 5.0 V@1 ms. In another patient the CS lead dislocated into the right atrium, it was explanted and a new lead was implanted. PNS was not detected after repositioning.

4.8.2. The extraction of the stented lead

Explantation of the stented LV lead was needed in three patients because of pocket infection (n=2) and endocarditis (n=1) after 3, 49 and 18 months. Leads were extracted without any complication while the stent remained in the CS side branch. Neither signs of insulation failure nor other macroscopic damage was seen on the extracted electrodes. Four patients underwent heart transplantation (7-27 months after implantation). During the operation, leads were cut in the superior vena cava and after explantation of the heart (Figure 24.) the surgeon was able to extract easily the stented leads from the CS side branch. Between the stent and the lead, macroscopically identifiable layer of tissue was observed. Macroscopic injuries could not be seen.



DOI:10.14753/SE.2017.2002

Figure 24. Epicardial view of the explanted heart: Arterial (left) and venous (right) coronary stents in an explantated heart. An endothelial sheath separates the stent from the lead. The left arterial stent was implantated percutaneously when a nSTEMI was experienced and PCI performed during follow-up.

Microscopic evaluation was performed on five CS electrodes. (Figure 25.) The examination of the stented area revealed surface damages as a result of the continuous friction between the stent and the electrode with a depth of 3-7 μm. This depth involved 1.7 – 4 % of the total insulation wall thickness, therefore the integrity and safety of insulation was not threatened. In one lead a deeper injury (27% of the insulation thickness) was also found, but the sharp edges and long, narrow shape of the deepest injury suggest, that it was produced during the extraction of the lead.

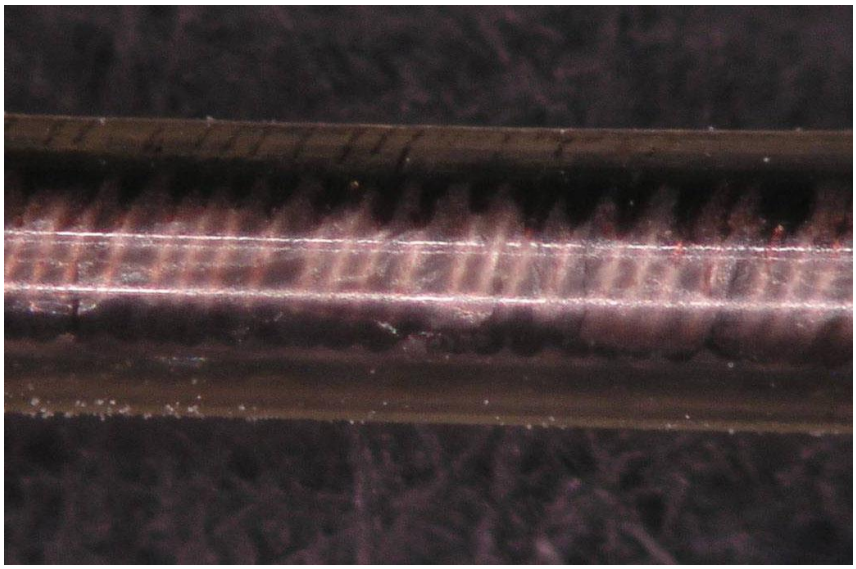


Figure 25. CS lead extracted during heart transplantation. Metal-microscopic imaging about the surface covered by the stent: no remarkable injury was observed.

DOI:10.14753/SE.2017.2002

5. Discussion

5.1. PR interval

This study shows that in patients undergoing CRT implantation (with individual echo-guided AV optimization postoperatively), PR prolongation is independently associated with an increased risk of heart failure hospitalization. Prolonged PR interval also predicts the combined endpoint of all-cause mortality and heart failure hospitalization in univariate analysis, but this association can partly be attributed to a higher number of a priori comorbidities in this patient group. Furthermore, the patients with prolonged PR interval are less likely to improve their ejection fraction, and particularly in patients with non-LBBB there seems to be a higher risk of non-response in patients with a prolonged PR interval.

5.1.1. General prognostic impact of prolonged PR interval

PR prolongation may be a sign of an underlying structural heart disease, or it can represent the early stage of progressive degenerative cardiac conduction pathology. Indeed, PR prolongation has in several studies been shown to have negative prognostic implications in the general population (96-99). Specifically, in the Framingham cohort there was a 44% increase in risk of all-cause mortality during long-term follow-up for individuals with a PR interval >200ms, and these individuals were also more likely to develop atrial fibrillation and heart failure, or require pacemaker therapy. Similar findings have been presented in two other large studies (100, 101).

5.1.2. Prognostic effect of prolonged PR interval in patients receiving CRT

The PR interval is especially interesting in the setting of CRT treatment, since AV optimized biventricular pacing may “cure” the detrimental hemodynamic effects of the PR prolongation. First degree AV block can reduce left ventricular filling, because of prolonged time of filling ventricles. This can induce delayed and ineffective mitral valve closure and, hence, diastolic mitral regurgitation which is associated with an unfavorable outcome in patients with systolic or diastolic left ventricular dysfunction (47-49).

The net effect of the prolonged AV interval in combination with prolonged isovolumic contraction and relaxation can be observed by echocardiography and quantified as the "ratio of overlap between the E and A wave in the mitral inflow". It has been shown that patients with more E- and A-wave overlap (ratio of overlap ≥ 33%) at baseline are more likely to be positive responders to CRT (102), suggesting that patients with longer AV delays (i.e. more likely to have AV dyssynchrony) would also be more likely to respond positively to CRT. This was supported by a post hoc analysis of the COMPANION study (51). The authors showed that patients with a prolonged PR interval were more likely to experience the primary endpoint (death or HF hospitalization), but at the same time these were the patients that derived the most relative benefit from active treatment (HR 0.54, p<0.01vs. HR 0.71, p=0.02 for patients with normal PR interval). Indeed, in the intervention group with CRT, there was no significant difference in outcome for patients with prolonged PR interval as compared to those with normal PR interval.

However, other studies have found that a prolonged PR interval is associated with more severe heart failure disease, and that the a priori poorer prognosis is not offset by a better effect of the CRT. For instance, in the CARE-HF trial it was demonstrated that prolonged PR interval was an independent predictor of worse outcome, regardless of treatment arm (CRT or optimal medical therapy) (53). In the PROSPECT-ECG study, the pre-implantation PR interval measured as a continuous variable had no influence on the clinical composite score endpoint at 6 months. (103)

Prolonged PR interval is a marker of atrial electric and structural modeling itself and it might be regarded as a marker of more advanced underlying heart disease and older "physiologic" age (100, 101, 104). Moreover, PR interval prolongation increases the risk of AF (105), and AF is one of the factors which increases the risk of death and HF hospitalization (106). In our study, the patients with PR prolongation were more likely to be men, have ischaemic cardiomyopathy, atrial fibrillation, non-LBBB ECG morphology, and less likely to be on ACE-inhibitors – all factors associated with non-response to CRT or to a worse prognosis. The PR interval did have an independent association with heart failure hospitalization risk, and in these patients were less likely

to be echo-responders and showed less improvement in LVEF after six months. Thus, our results confirm that patients with PR interval prolongation seem to be “sicker” than patients with normal PR interval, and even though we employed an individual AV optimization strategy, effectively curing the patients from their AV dyssynchrony, the net effect was still negative on the clinical outcome post-CRT. However, there seem to be a major difference between patients with or without typical LBBB on the native ECG. Patients with native LBBB are more likely to be echo-responders and clinical responders than patients with non-LBBB, and in our cohort a prolonged PR interval did not affect outcome in this group.

5.2. ECG-based risk stratification score

In this large cohort of 491 patients we show that a simple score based on the pre and post-BiV pacing 12-lead surface ECG, has an independent value for prediction of future clinical endpoints. The ECG score includes: QRS duration shortening, intrinsicoid deflection time and post-pacing change of R+S amplitude. The score is applicable regardless of the intrinsic conduction block pattern on ECG at baseline, but seems to be more robust for patients with an a priori LBBB.

5.2.1. Electrical resynchronization by QRS evaluation

Cardiac resynchronization therapy is based on the assumption that a wide QRS complex represents electrical dyssynchrony, which then transforms into mechanical dyssynchrony and ensuing reduced cardiac output, progressive left ventricular dilatation, increased mitral regurgitation and progressivesymptoms of heart failure. A common end-point in CRT studies is echocardiographic remodeling measured at six months post-implant, and it has been shown that a reduction of LVESV≥15% correlates to a better survival. (107) Theoretically, the more dyssynchrony at baseline, the higher the likelihood that the dyssynchrony is a significant part of the patient’s cause of heart failure, and the higher the likelihood that CRT is gives a favorable outcome. (108, 109) Indeed, sub-analyses from the large prospective randomized trials have shown that those patients with wider QRS complex and left bundle branch block are more likely to be “responders” to CRT than other patients (7, 8, 75), but meta-analyses have pointed to

limitations in using the preoperative QRS-width as a predictor of response (110, 111). The perfect prediction model has yet to be found, and even within the group of patients with true LBBB and very wide QRS complexes, there is no preoperative guarantee for a positive response to CRT. Therefore, any additional available information that can help optimizing the LV lead placement for the individual patient may be of value.

5.2.2. Usefulness of the different components of the proposed ECG score

The proposed score is based solely on a 12-lead ECG in order to make it simple, clinically applicable and relevant. Lead V1 for the analysis of ID duration and amplitude was chosen because the changes in QRS morphology in this lead - with an appropriately placed LV electrode during biventricular pacing- are predictable. During native LBBB the QRS complex is usually uniformly negative with a deep Q or S wave due to the activation of the left ventricle in a vector away from the V1 electrode. On the contrary, during successful biventricular pacing, there is early activation of the LV free wall from the LV electrode, resulting in an early positive deflection on ECG. We hypothesized that the earlier the rapid negative deflection starts after the R-wave in lead V1, the more likely it is that the resynchronization is successful. The presence of an R wave in V1 is widely thought of as a sign of optimal resynchronization, indicating successful early activation of the posterolateral part of the LV (112). However, there is also simultaneous activation of the apical and septal region from the RV electrode, and in theory if the timing is appropriate then the depolarization wave will spread rapidly to the entire ventricular myocardium, and the width of the QRS complex will narrow down accordingly. During this faster, more synchronized depolarization process, the two opposing vectors from the left lateral and septal wall respectively, will (to a larger extent than during the prolonged native conduction) “cancel out” from the direction of projection used in lead V1. This will then result in lower net summed R+S amplitude in lead V1, as compared to the preoperative amplitude. The reduction of amplitude in lead V1 may also be a reflection of the left -> right axis-shift in the QRS main electrical axis after resynchronization. In accordance with our findings, baseline QRS and narrowing of QRS after biventricular pacing have proved to have an impact on CRT response and outcome in randomized clinical trials and observational studies (113),(114).

The ID onset measures the electrical activation time recorded when a unipolar lead is placed in direct contact with the myocardium. When the myocardial depolarization moves towards the electrode, the tracing is positive. As the activation wave passes the point of the electrode, and starts to move away in the opposite direction, the tracing changes polarity, and this represents the ID time. Similar results can be obtained from the surface ECG (in this case from lead V1) and the ID onset is defined as the point of time where the rapid downward deflection starts, at or after the peak of the R-wave (115).

In the recent study by Del-Carpio Munoz both the ID onset in lead I, and the difference in time of ID onset between lead I and lead V1 were evaluated, and an independent correlation was found between lateral delay of ID onset on the pre-implant ECG and CRT response (89). Furthermore, the authors found that the ID time was significantly different depending on the type of the present conduction abnormality (LBBB, RBBB or intraventricular conduction delay), and, therefore, stratified their results accordingly. However, they did not use the post-implant ECG during pacing, which was used in our study. During successful biventricular pacing there are two wave-fronts moving simultaneously from the respective RV and LV electrodes, and this occurs in a similar fashion regardless of the underlying (more proximal) conduction pathology. Therefore, we did not a priori subdivide the patients into different the groups depending on their pre-CRT ECG morphology. In a post-hoc analysis, similar results were found for both patients with LBBB and non-LBBB morphology (albeit a little stronger for the LBBB group, and due to fewer patients some of the significant results were only trends in the same direction in the non-LBBB group), implying that the method is robust for both groups.

5.2.3. Clinical perspective

Several other studies have used ECG-based prediction models for response to CRT, including evaluation of prolonged LV activation (116), LV lead electrical delay (40, 117), change in QRS-width (118) and time to intrinsicoid deflection (89). The previous reports have mostly focused on QRS-width at baseline and then reduction in QRS-width during biventricular pacing, and generally the hazard ratios or odds ratios have therefore been of lower magnitude than those of our study. The requirement of only a standard

ECG and the simplicity of our score makes it appealing to use as a source of additional information for optimization of the left ventricular lead position already in the operating room, in addition to optimization at follow-up outpatient visits. With the now widely available quadripolar LV leads, it is easy to evaluate different pacing vectors during the implant, and pacing vectors can be changed both preoperatively, but also during structured follow-up outpatients visits. Applying the proposed ECG score could then be used in the setting of non-response and different pacing vectors can be tried an evaluated subsequently. The additive value of our proposed score should therefore ideally be tested in a prospective clinical trial using quadripolar LV electrodes and serial evaluation of the ECG parameters.

In summary, by adding the three aforementioned ECG criteria together in a simple 0-3 point score, we were able to show a gradual improvement in long-term survival free of heart failure hospitalization or transplantation for each additional point in the score. The score also correlated significantly to reverse remodeling of the LV, thus providing a solid pathophysiologic background for the increased long-term survival. The combined predictive value in this cohort is greater than that of each of the included parameters by itself.

5.2.4. Limitations

In this project a minority of patients had to be excluded due to lack of paired ECG recordings, and this should be acknowledged when interpreting the results. However, in separate analyses we found that the baseline demographics did not differ significantly for the patients included in the study as compared to the group of excluded patients based on missing ECG. Our ECG data was based on measurements from the one-month follow-up visit, before any echocardiography- or vendor-based optimization algorithms of biventricular pacing were applied. The ECG tracing in V1, and thereby the results, could have been influenced by differences in localization of the lead electrode on the chest. All patients should have had a standard ECG lead position, but this could not retrospectively be validated. However, our data reflect the real-life situation where different operators record the ECGs, and if anything a spread in the positions of the relevant ECG electrodes would be likely to attenuate the correlations in the analyses. We therefore believe that the results are robust, but they should be interpreted with

caution in light of the retrospective study design. RV lead position was not taken into account for the algorithm, which may have affected the ECG pattern for patients with RV leads in the outflow tract, but the vast majority of the patients had RV leads placed in the apical region, which would result in only minimal differences on the surface ECG.

5.3. T-wave area as an additional predictor of therapy response

The present study demonstrates that the T-wave contains information that improves the prediction for echocardiographic CRT response at 6 months. VCG-derived T-wave area predicts CRT response even better than any QRS-complex related parameter. This better outcome prediction especially applies to patients diagnosed with LBBB.

This report clearly illustrates the added value of the VCG-derived T-wave in predicting CRT response in LBBB patients. The data indicate that the chance of echocardiographic CRT response in patients with LBBB and a large T-wave area is 75%, as opposed to 53% in LBBB patients with small T-wave area and 40% in non-LBBB patients. Considering the fact that large studies show an average echocardiographic response rate of ~50% (119), the combination of LBBB and T-wave criteria strongly improves patient selection for CRT. The sum QRST area showed similar prognostic value within LBBB patients (unadjusted OR = 2.40 vs. 2.77 for T-wave area alone) but this parameter was probably mainly determined by the T-wave area itself. The lack of additional predictive value of T-wave area in the non-LBBB group might be due to the fact that the LBBB-sequence of electrical activation is the dominant electrical substrate for CRT. (21)

There may be several reasons why T-wave area improves predicted CRT response. First of all, there is, to some extent, a positive relation between T-wave area and QRS duration. It is well known that QRS duration is an independent predictor of CRT response, especially when differentiating between QRS duration values below and over 150 ms. (19, 20) Moreover, the T-wave amplitude is known to be smaller in patients with large BMI (120), possibly simply related to the larger distance of the surface to the heart. Large BMI is known, for not well-understood reasons, to reduce CRT response. (121) Notably, in this study the ORs were not adjusted for BMI.

In contrast to Brenyo et al. (122)we did not find a significant effect of the QRS axis deviation on the benefit of CRT in the present study. A possible explanation for these discrepant findings might be that the patients in the current study had severe HF (mostly NYHA class III to IV) while the MADIT-CRT study consisted of patients with NYHA class I to II. Another explanation may be that the MADIT-CRT study consisted of a larger number of patients.

Even though different heart conditions might also reduce QRS area, in the present study the QRS/T area ratio showed a tendency to predict CRT response, pointing towards specific repolarization related factors. One possible explanation might be hypertrophy. In patients with narrow QRS complex hypertrophy is known to lead to smaller T-waves: T-wave-flattening, also referred to as “strain-pattern” of the T-wave. (123) It is incompletely understood whether similar conditions also reduce the T-wave in patients with wide QRS complex. Finally, it is known that HF in general and dyssynchronous HF in particular, leads to extensive changes in expression of many ion channels, such as K^+- and Ca^{2+}-channels. (124) In short, the predictive power of the T-wave reflective of electrical recovery suggests that this component of the action potential may give additional information of the responsiveness of the myocardial substrate.

Regardless of the exact mechanism, the present study shows that several categories of patients, which are known to respond well to CRT, are overrepresented in the higher T-wave area category, namely patients who are females and/or have non-ischaemic aetiology of HF. Several studies indicate that women respond better to CRT. (125, 126) Although they tend to have less ischaemic aetiology of HF and more LBBB, the reason for this sex-related beneficial effect is unclear. Additionally, the MIRACLE study (127) showed that ischaemic cardiomyopathy patients show a smaller volumetric response than patients with non-ischaemic cardiomyopathy. During ischemia, degeneration or cellular coupling can occur (128) resulting in non-conducting fibrotic tissue leading to a smaller amount of tissue that can be resynchronised by CRT. Indeed, as shown by a computer modelling study (129), uncoupling leads to a reduction in T-wave amplitude, which would also reduce the T-wave area.

5.3.1. Potential clinical implications

The VCG, as analysed in this study, can be constructed from a regular 12-lead ECG. Subsequently, the T-wave area can be automatically calculated. Consequently, combined analysis of QRS morphology and T-wave area provides an easy and widely applicable approach to improve selection of CRT candidates. The advantage of this T-wave area is that it is both a three-dimensional measure and a continuous variable that provides additional objective evidence as a predictor of reverse remodeling. Therefore, the addition of T-wave area in patient selection for CRT is an easily available objective measure for better selection of patients with LBBB for CRT. Other studies showed the value of echocardiography (130, 131) and MRI in patient selection (132, 133). It will be worthwhile to investigate whether our T-wave analysis can replace or add information to these approaches.

5.3.2. Limitations

This was a retrospective, single center study with missing data as detailed in the methods section. Only 73% of patients had echocardiograms, suitable for vectorcardopgraphy, available before and after CRT implantation. A multicenter prospective study is required to confirm our results. Moreover, using an adapted version of the Kors method to calculate the VCG from the ECG is an estimation of the gold-standard Frank VCG. However, previous studies have demonstrated that the Kors method shows the best resemblances to the Frank VCG. (92, 134, 135)

5.4. T-wave area in prediction of outcome

This study shows that in CRT patients with LBBB, a large baseline T-wave area is a strong predictor of a good clinical outcome (HF hospitalization, transplantation, LVAD, death) during 3-year follow-up. In combination with the data from the previous project, the present study implies that T-wave area may be useful as an additional biomarker to stratify CRT candidates and improve selection of those most likely to benefit from CRT.

5.4.1. T-wave area, an additional predictor of long-term clinical response to CRT

The present study corroborates findings from large randomized trials that LBBB is an important predictor of CRT response. However, interestingly, T-wave analysis appears to contribute to the prediction of CRT response on top of LBBB morphology. While LBBB patients with a large QRS area tended to respond better to CRT than those with small QRS areas, this difference was more obvious in the T-wave area. Patients with a large T-wave area and LBBB morphology had a lower chance of reaching one of the composite endpoints (HTLD) when receiving CRT compared with non-LBBB patients with small or large T-wave area and LBBB patients with a small T-wave area (36% as opposed to 57%, 51%, and 48% respectively). Similar differences were seen for the secondary outcomes HF hospitalization (31% vs. 51%, 38%, and 51%) and death (19% vs. 34%, 42%, and 42%) alone.

Because the present study was based on retrospective analysis and did not contain a control (non-paced) group, the better outcome in the LBBB-large-T-wave area patients may be explained by either a better baseline condition of these patients or a larger benefit of CRT. The latter idea is supported by the observation in our previous study. It seems plausible that this larger increase in cardiac function further translates into a better clinical outcome, as observed in the present study. Using the T-wave area in the LBBB patient could help predict whether CRT may be useful, especially in a subset of LBBB patients who have additional co-morbidities in whom the risk-benefit ratio may not be as clear as in other LBBB patients.

A large T-wave area (as well as QRS area) may also imply a better baseline condition, because it is known that electrical uncoupling (129) or RV dilatation leads to lower ECG amplitudes. RV dilatation could lead to loss of myocardial tissue due to the replacement by fibrofatty tissue or could lead to a rotation of the heart affecting both QRS and T-wave amplitudes. However, in the previous study we showed that a large QRS area is commonly accompanied by a large T-wave area, but that there is also considerable variability. A possible explanation for this variability was given by Feldman et al. (136) who showed that in acute measurements in patients the T-wave area and the ratio of T:R wave amplitude increased with increasing cavity diameter while the QRS area did not change. This, however, cannot be an explanation why patients with a relatively large T-wave area respond better to CRT since it is well

known that too dilated ventricles respond less to CRT. (137-139) This suggests that other factors, such as ionic channel properties present during the plateau and repolarization phases of a myocardial action potential, play a role in the variability between QRS- and T-wave area. These ion channel properties may change due to heart failure and dyssynchrony. (124) Additionally, the small T-wave areas might be related to hypertrophy. For patients with severe LV hypertrophy and narrow QRS complexes this phenomenon is also known as T-wave flattening. (123) It is, however, not known whether T-wave flattening also applies to patients with a wide QRS complex. An important difference in this respect is that while narrow QRS complexes are commonly accompanied by concordant T-waves, this is rare in patients with wide QRS complex, and even rarer in case of LBBB.

Finally, females and patients without a history of ischaemic cardiomyopathy were overrepresented in the patient group with a large T-wave area and LBBB morphology. Both patient characteristics are known to have a positive influence on the response to CRT (125-127), for reasons incompletely understood.

Therefore, the T-wave area appears to be an objectively determined biomarker, expressed as a continuous variable, revealing various subgroups with known better outcome to CRT. Beside the possible practical use of this finding, these data also indicate that for better understanding of the mode of action of CRT, not only information on the sequence of ventricular depolarization is needed, but also that of processes determining later phases in the action potential.

5.4.2. Potential clinical implications

The present study demonstrates for the first time that, besides a LBBB morphology, the T-wave area may be a valuable biomarker for the prediction of long-term clinical outcome after CRT. In order to determine the T-wave area, a VCG needs to be synthesized from the 12-lead ECG. If the VCG is not constructed by the ECG equipment, it can be easily calculated from every 12-lead ECG that is saved digitally or in pdf-format. (134) After this conversion the analysis only requires a semi-automatic detection of the beginning and end of the T-wave. Therefore, assessment of the T-wave area in candidates for CRT device implantation is easy, non-invasive and can be implemented without significant investments.

5.4.3. Limitations

Above the aforementioned limitations, to confirm predictive ability, a prospective multicentre study is required, that should also include systematic coverage of the cause of death, which was not included in the present study.

5.5. Hyponatremia

Our study shows that a low serum sodium level may also be a predictor of poor response to CRT. Besides this our study also shows for the first time that post-CRT implant, changes in serum sodium may further predict clinical outcomes. Hyponatremia resolves in a proportion of patients after CRT device placement and this in turn is associated with an improved survival in this subset of patients. Our results also show for the first time that serum sodium changes post-CRT device implant may have predictive value in identifying non-responders.

The prevalence of hyponatremia is variable and determined by cut-offs and clinical settings, ranging from 5% in chronic (140) to 19.7% in acute settings as in OPTIMIZE-HF registry(54). In our database 21.9% patients had baseline hyponatremia. This could be related to a different patient population with more advanced HF having an indication for CRT.

Progressive HF is associated with neurohormonal activation which involves activation of RAAS (renin angiotensin aldosterone system), arginine vasopressin release and up-regulation of sympathetic nervous system. (141) This leads to impairment of free water excretion via different mechanisms contributing to the development of a hyponatremic state. (141, 142) Additionally, heart failure patients receive diuretics which may cause loss of sodium in urine and further decrease serum sodium. (143) Daily diuretic dose has been identified as a powerful predictor of mortality in patients with HF. (144) Of note, our analysis showed similar findings that patients with hyponatremia were on significantly higher daily dose of furosemide.

Mechanistically, hyponatremia may not only be a reflection of worsening HF; but may further depress a declining LVEF. Prior experimental work in cardiac myocytes of failing hearts demonstrate a decreased calcium conductance with a decreased external sodium that may in turn partly explain the depressed cardiac contractility and poor

outcomes encountered by patients suffering from persistent low serum sodium and HF. (145) This can explain, why the patients in whom the electrolyte abnormality resolved after CRT device implantation, had better clinical outcomes in comparison to those who turned or continued to have hyponatremia. Our results are supported by recent report from Arao et al in a small cohort of patients showing that baseline low serum sodium levels are associated with poor outcomes after CRT device implantation. (146) This study, besides being limited by its sample size (n=77), also did not examine the impact of CRT on serum sodium and the consequent interaction on clinical outcomes.

Of note, six months after CRT device implantation there was no significant difference in echocardiographic findings between hyponatremic and normonatremic patients. Absolute and percent change in LVEF was comparable. Interestingly, however patients who had hyponatremia on follow-up had lesser improvement in echocardiographic parameters. We could hypothesize that this improvement in LVEF during follow-up in patients with normonatremia is reflective of better mechano-energetics (secondary to coordinated ventricular contraction) and improved glomerular perfusion. This in turn, can cause a decrease in level of activation of RAAS, decreased up-regulation of sympathetic nervous system, decreased arginine vasopressin secretion and decreased dose requirement for diuretics. Post-CRT reversal of these factors to different extent i.e neurohormonal changes, improvement in renal perfusion and decrease in daily dose of furosemide, could be contributing factors to the improvement in serum sodium levels. However, it is important to note we did not record the changes in the diuretic doses over the follow-up period which could confound our findings.

5.6. Hypothyroidism

Even though CRT has proven benefit in reducing mortality in HF patients, mortality rates still remain high in part due to frequent co-morbidities. (147) Hypothyroidism is known to be associated with poor outcomes in patients with heart failure. Our study shows that a history of hypothyroidism is associated with a poor clinical outcome, even after CRT device implantation. In our patient group, 16.4% had a history of hypothyroidism which is relatively high compared to other studies evaluating the impact of thyroid function on HF. (58, 63) This may relate to the overall severity of HF in typical patients undergoing CRT placement.

Thyroid hormone influences cardiac performance by genomic and non-genomic effects and increases cardiac output by affecting stroke volume and heart rate. (148, 149) Genomic nuclear physiological effects result from binding of T3 to specific nuclear thyroid hormone receptors which further bind to thyroid hormone response elements in the promoter regions of some genes modifying the rate of transcription of specific target genes. (148-151) Non-genomic effects involve the transport of ions (calcium, sodium and potassium) across the plasma membrane, glucose and amino acid transport, mitochondrial function and a variety of intracellular signaling pathways. (149) Thyroid hormones also have pro-angiogenic effects via both genomic and non-genomic mechanisms and stimulate arteriolar growth. (152, 153) As a result, hypothyroid hearts show poor substrate use (glucose, lactate and free fatty acids) by mitochondria (154) and lack of thyroid hormones lead to effects on chronotropy (rate), inotropy (contractility) and lusitropy (relaxation). (148, 155) On the basis of the evidence obtained from cell and animal models it is possible that treatments targeting the thyroid hormone signaling may promote endogenous regeneration of the damaged myocardium. (156) In adult rats, chronic hypothyroidism led to loss of coronary arterioles and impaired blood flow inducing maladaptive changes in the shape of myocytes and the development of HF. (157) These changes in cardiac structure and function have been reported in patients with hypothyroidism, both overt and subclinical hypothyroidism, with a severity depending on degree and duration. (148, 149, 158, 159)

Cross-sectional studies demonstrate that about 30% of patients with HF have low T3 levels and the decrease in serum T3 is proportional to the severity of the heart disease as assessed by the New York Heart Association classification. (160) Impaired peripheral conversion of T4 to the biologically active T3 hormone by 5’-monodeiodination leads to a low T3 syndrome (low serum T3 with normal T4 and TSH level). (161) Cardiac myocytes are particularly vulnerable as they have a negligible deiodinase activity hence depend on plasma T3. (162) Consequently, when circulating T3 is low, the myocardium may become relatively hypothyroid. T3 controls the inotropic and lusitropic properties of myocardium, cardiac growth, myocardial contractility and vascular function. (148, 149) Hypothyroidism is characterized by reduced diastolic and systolic functions at rest and during exercise. (163) Of note, a case of complete lack of ventricular lead capture

was recently described associated with new development of subclinical hypothyroidism which was reversible after treatment with thyroid hormone supplementation. (164)
Hypothyroid patients in our study were older, had higher baseline creatinine, lower usage of angiotensin converting enzyme inhibitors and higher usage of digoxin and amiodarone. Apart from baseline creatinine, the other three factors were not significant in univariate analysis. Interestingly, hypothyroid patients had a higher baseline left ventricular ejection fraction than euthyroid patients but this did not reach statistical significance. Studies which have investigated the effects of hypothyroidism in heart failure have suggested that even mildly elevated TSH level can lead to heart failure progression and increased mortality and that timely treatment should be initiated. (165, 166) It is important to follow HF patients on amiodarone closely for the development of hypothyroidism so that it can be identified and treated as rapidly as possible. To our knowledge there is no other study looking specifically at the impact of thyroid function on outcomes after CRT. It is not clear from these data how supplementation with T3 would impact the outcomes. A randomized, double blinded, placebo controlled study investigating the effects of T3 treatment in patients with myocardial infarction is underway (THiRST).

As a limitation of the study we have to recognize, that we did not have values for complete thyroid panel (free T3, T4 values). TSH values were not available on follow-up with consistency. Hypothyroid patients had important baseline differences from euthyroid patients including age, gender, renal function, and use of angiotensin converting enzyme inhibitors and digoxin.

5.7. Device measured physical activity

Physical activity has been recognized as a determinant of clinical outcome in patients with heart failure. Our study shows that device-derived measures of physical activity can help predict clinical outcome and ventricular remodeling in patients receiving cardiac resynchronization therapy. Our results show that device diagnostic measures of averaged physical activity correlate well with 6MWTs and could serve as a surrogate for functional response and long-term clinical outcome and survival.
Reduced exercise tolerance and physical activity in HF patients are reflective of disease progression, hence monitoring physical activity is important in the clinical management

of these patients. (167, 168) Recent work by investigators of HF-ACTION trials, showed that the prognostic value of 6MWT is comparable to the gold-standard cardiopulmonary exercise test in predicting HF-hospitalization and mortality in HF patient population. (65) However it is well recognized that performing the 6MWT at each clinical evaluation is logistically challenging, requiring additional time and resources. Also the test is often flawed by the subjective component and unintentional bias created by encouragement during the performance of a 6MWT. (70) Finally, the 6MWT is only representative of the patient's functionality at that particular point in time. In contrast, device derived data provides a real time assessment of the patients physical activity, which can be averaged over hours and weeks, to give a more representative picture of the patients true functional status. This does not require additional resources and can be acquired at any point in time using remote monitoring. Furthermore, device measured physical activity is not biased by the patients' motivation and familiarity with the clinical tests.

Earlier work has used device measured physical activity as one of the several variables to predict acute heart failure decompensation and mortality. (71, 72) However, our study for the first time demonstrates the ability of sequential measurements of physical activity to predict HF hospitalizations, mortality and echocardiographic reverse remodeling. Unlike the previous study examining the ability to predict long-term outcomes, this study was able to perform multivariate analyses and show the value of device measured physical activity as an independent predictor of adverse clinical outcomes.

These novel devices have embedded sensors (accelerometers) that record physical activity. Previous work validating the efficacy of these sensors examined external accelerometers in heart failure cohort and a significant correlation was found between the changes of activity log index and changes of 6MWT. (169) Notwithstanding this, a recent study by Pressler et al., failed to validate the measurements of implanted devices using external accelerometers. They observed that daily physical activity assessed by CRT/ICD devices showed strong intra-individual correlations, but differ substantially regarding the absolute amount of physical activity, when compared to external sensors. (170) It appears that within the same individual, however that device based measures provide a good comparison to track changes in the level of physical activity. (167)

DOI:10.14753/SE.2017.2002

5.8. The coronary sinus side branch stenting

Stable left ventricular lead position in the area of latest activation is important in CRT (40, 171, 172). Left ventricular lead implantation into the recommended lateral or posterolateral side branch of the CS is not feasible due to anatomical and/or technical limitations in up to one-third of patients (173). An important cause of suboptimal lead positioning, lead dislodgement or extracardiac stimulation is the unstable electrode position in the target vein (174). The original idea was that CS stenting may decrease the dislocation rate and improve success rate of lead implantation into the recommended side branches by anchoring the LV lead in an anatomically unstable position (83). CS stent implantation was first used in cases of postoperative lead dislocation. Since complications have not been observed, stenting has also been performed in cases of intraoperative dislocation, unstable lead position or when phrenic nerve stimulation was found adjacent to the tip of the CS lead. In these cases the aim was to prevent potential electrode dislocation.

Stents successfully anchored the CS leads in this patient group. The consistency of pacing thresholds support the stability of the stented leads. Macrodislocation was detected in only two patients. In seven other cases, the cause of lead repositioning was phrenic nerve stimulation. PNS is found in 13-18 % of CRT implantations, and it is one of the main reasons for intraoperative lead repositioning from an anatomically acceptable location (175, 176). Pacing with high energy during implantation may help to avoid subsequent PNS, but despite high energy stimulation, intraoperative testing in a supine position can not rule out later PNS in other body positions (177), even if the electrode remains in the same place. In seven cases a new, minimally invasive method was performed using ablation catheter for repositioning using an EP catheter to loop the RA componment of the lead via a femoral approach. The pacemaker pocket had to be opened for lead repositioning in only 3 of our 312 patients (0.9%). This ratio is much lower than the rate of re-operation reported in the literature in large multicenter studies (75, 178, 179).

Potential complications due to CS stent implantation may be the injury of the target vein and mechanical damage of the electrode. Our observations agree with prior case reports of stent implantation into the venous system of the heart (180-182) or to fix the attained

electrode position (83-85) in that no injuries were noted. Mechanical damage of the lead insulation caused by the stent may also be a potential problem especially over a longer period of time. In our patients, impedance measurements did not suggest insulation failure or fracture of the left ventricular electrode during follow-up. Optical and mechanical microscopic analysis of the explanted CS electrodes revealed only rugged and lumpy surface damages in the area of contact with the stent. The depth involved only less than 4% of the total insulation wall thickness. This result suggests, that the stent does not jeopardize the integrity of the lead insulation. (183) On explanted hearts a fibrotic sheath was observed around the stent enveloping the electrode, which may decrease direct friction between the stent and the lead.

There may be significant concern regarding extraction of a CS lead fixed with a stent should it become necessary. Although one might believe that it is only possible by a surgical exposure of the heart (184), stented CS leads were explanted with simple traction in three patients (in one case after four years), and during heart transplantation four more electrodes were also easily extracted by traction. Moreover stented CS leads were retracted from a distal position with an ablation catheter in cases of phrenic nerve stimulation.

Our study is a non-randomized, uncontrolled single center clinical experience. In this study mainly unipolar passive fixation CS leads were implanted. Although our results seem to be favourable, longer-term performance of the stented LV leads is unknown. Mechanical damage of lead insulation may occur because of motions between the stent and the implanted lead, but according to our microscopy measurements, the probability of clinically important injury is low. CS stent implantation may limit the ability of lead removal, but data regarding safe extraction of other actively fixed CS leads (like StarFix Attain 4195 (Medtronic) (185-187) or screw-in pacemaker electrodes in the CS (188)) are inconsistent or missing. On the other hand it was possible to extract stented LV leads without heart surgery in all of our patients when necessary (n=3; 1%). Moreover minimally invasive lead repositioning with an ablation catheter was also successful 7 patients (2.2%). Although our implantation success rate was very high, and the dislocation rate of the stented CS leads was low, a direct comparative multicenter study would be beneficial to clarify the real advantages of CS lead stenting.

DOI:10.14753/SE.2017.2002

6. Conclusion

Cadiac resynchronization therapy is a highly effective treatment of heart failure patients with conduction abnormalities. In the last two decades of application and extensive research has contributed to improved patient selection and implantation techniques. In the quest for improvement of CRT, I have been devoted to observe and analyze the complex process of pre- and postoperative care of this patient group.

Our results has shown, that in patients with LBBB morphology of the QRS complex, a larger baseline T-wave area is an important independent predictor of LVEF increase following CRT.

A vectorcardiographically derived T-wave area assessed before the start of CRT was able to strengthen the prediction of long-term clinical outcome in a CRT patient cohort, especially in patients with LBBB morphology on the ECG. The combined analysis of QRS morphology and T-wave provides an easy and widely applicable approach to improve selection of CRT candidates.

Prolongation of the pre-implant PR interval in CRT recipients is associated with a higher risk of heart failure hospitalization or death, even in the presence of individual echo-guided AV optimization post-implant. The a priori increased risk for patients with prolonged PR interval, is not compensated by the positive effect of CRT on restoring AV synchrony, and the clinical prognosis remains worse than for patients with normal PR interval. These findings should be taken into account when addressing risk stratification in patients with heart failure scheduled for CRT, especially for those with non-LBBB morphology on ECG.

Ready-at-hand data from a simple 12-lead ECG can predict the remodeling effect and long-term clinical prognosis after CRT-treatment. The proposed ECG score may be a valuable added tool in the early evaluation and risk assessment during and after CRT implant, but will need further validation in prospective trials. It also can contribute to personalized lead positioning.

Coronary sinus side branch stenting to stabilize CS lead position seems to be an effective and safe procedure. Using this technique, the electrode can be fixed in an anatomically unstable but electrically appropriate position, such that the frequency of lead dislocations, PNS, and reoperations may be decreased. In our practice stented CS

leads were transvenously explantable in all patients when necessary. We endorse CS stent implantation in cases of postoperative or intraoperative lead dislocation or if the electrode position is not stable enough and an alternative side branch is not available at the chosen location.

In an era where there is an explosion of novel biomarkers to aid in diagnosis, guide therapy and HF management, simple conventional chemistry including serum sodium level could hold added value. Serum sodium level is a dynamic marker and its changes are seen soon after CRT device implantation. Post- CRT device implantation, hyponatremia holds negative prognostic influence and may aid further risk stratification and lead to consideration of alternative interventional strategies (i.e. LV assist device implantation and heart transplant evaluation) of this patient cohort.

Our study shows that a history of hypothyroidism is associated with a poor clinical outcome, even after CRT device implantation. Those results draw attention to multidisciplinary postoperative patient care, where heart failure specialist can adjust medical therapy according to comorbidities and status of the patient, beside the electrophysiologist.

Device-derived measures of physical activity can help predict clinical outcome and ventricular remodeling in patients receiving cardiac resynchronization therapy. This study shows that device diagnostic measures of averaged physical activity correlates with the 6-minute walk tests and further, can serve as a surrogate in the prediction of functional response and long-term clinical outcome and survival after CRT. It can serve as an easy to approach "status report", during follow-up.

I hope the these minor observations of retrospective analyses can contribute to the improved care of this special patient group.

DOI:10.14753/SE.2017.2002

7. Summary

Nowadays, cardiac resynchronization therapy (CRT) is a well-established therapeutic strategy for patients with advanced congestive heart failure and prolonged QRS complex, but despite its proven clinical value, a significant minority of patients do not derive benefit from CRT. Our goal was to find novel predictors of therapy response and long-term outcome.

Retrospective analysis of a single-center patient population (n= 569) was performed, who underwent CRT between 2004-2010 and were prospectively followed in a multidisciplinary clinic. Therapy response was defined as improvement of left ventricular ejection fraction, measured by echocardiography. Clinical events including heart failure hospitalizations, heart transplantation, left ventricular assist devices (LVAD) and mortality were recorded.

A vectorcardiographically derived T-wave area assessed before the start of CRT is able to strengthen the prediction, so contribute to improved patient selection. A novel, simple 12-lead ECG based score, as an early predictor, can facilitate the early evaluation, so contribute to patient-specific lead positioning and therapy optimization. With coronary sinus side brach stenting, the left ventricular lead can be fixed in an anatomically unstable but electrically appropriate position and minimize lead-related complications. PR prolongation, pre-operative and follow-up hyponatremia and hypothyroidism are independently associated with an increased risk of reaching hard clinical end-points and less likely therapy-response, that can refine risk stratification and can draw attention to the importance of multidisciplinary patient care. Our results show that device diagnostic measures of averaged physical activity correlate well with 6MWTs and could serve as a surrogate for assessment of CRT patients.

DOI:10.14753/SE.2017.2002

8. Összefoglalás

A reszinkronizációs terápia (cardiac resynchronization therapy, CRT) manapság már széleskörűen elterjedt kezelési lehetőség a szívelégtelen betegek számára, de a betegek egy részénél nem tapsztalható javulás, ők az úgy nevezett non-responderek.

Vizsgálataink célja az volt, hogy a terápia hatékonyságát és a betegek hosszútávú klinikai állapotát előrejelző elektrokardiográfiai és komorbiditási prediktorokat találjunk.

Retrospetív elemzéseinket egy centrum 569 konszekutív betegéből álló populáción végeztük, akik 2004 és 2010 között részesültek reszinkronizációs kezelésben és ugyanezen központ multidiszciplináris csapata végezte utógondozásukat. A terápiás választ az echocardiográfia során mért bal kamrai ejekciós frakció javulásaként definiáltuk. Vizsgálati végpontként az akut cardialis dekompenzációt, szívtranszplantációt, bal kamrai keringéstámogató eszköz beültetését és az összmortalitást rögzítettük.

A CRT előtt, vektorkardiográfia során nyert T-hullám area javíthatja a terápiás válasz predikcióját, így hozzájárul az eredményesebb betegszelekcióhoz. Egy új és egyszerű 12 csatornás elektrokardiogramon alapuló rizikóstratifikációs score, már igen korán, akár a beültetés során is segítheti a terápiás hatékonyság becslését, így az egyénre szabott elektródapozícionálást és a reszinkronizáció optimalizálást. A bal kamrai elektróda stenttel való rögzítésével egy instabil, de az ingerlés szempontjából optimális pozícióban stabilizálható az elektróda, így csökkenthető a diszlokációs szövődmények aránya. A PR megnyúlás, a pre- és posztoperatív hyponatraemia és a hypothyreosis a kemény klinikai végpontok elérésének és a terápiás válasz elmaradásának független prediktorai, így finomíthatják a betegek hosszútávú gondozását, valamint felhívják a figyelmet a multidiszciplináris teammunka jelentősségére. Eredményeink alapján a pacemaker készülékek által mért fizikai aktivitás jól korrelál a 6 perces járás teszttel és helyettesítheti azt a betegek állapotfelmérésében és utánkövetésében.

9. References

1. Cazeau S, Ritter P, Bakdach S, Lazarus A, Limousin M, Henao L, Mundler O, Daubert JC, Mugica J. (1994) Four chamber pacing in dilated cardiomyopathy. Pacing Clin Electrophysiol, 11 Pt 2: 1974-9.

2. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P, Klein H, Kramer A, Ding J, Salo R, Tockman B, Pochet T, Spinelli J. (1999) Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. Circulation, 23: 2993-3001.

3. Bakker PF, Meijburg HW, de Vries JW, Mower MM, Thomas AC, Hull ML, Robles De Medina EO, Bredee JJ. (2000) Biventricular pacing in end-stage heart failure improves functional capacity and left ventricular function. J Interv Card Electrophysiol, 2: 395-404.

4. Altman RK, Parks KA, Schlett CL, Orencole M, Park MY, Truong QA, Deeprasertkul P, Moore SA, Barrett CD, Lewis GD, Das S, Upadhyay GA, Heist EK, Picard MH, Singh JP. (2012) Multidisciplinary care of patients receiving cardiac resynchronization therapy is associated with improved clinical outcomes. Eur Heart J, 17: 2181-8.

5. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM, Comparison of Medical Therapy P, Defibrillation in Heart Failure I. (2004) Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med, 21: 2140-50.

6. Abraham WT. (2002) Cardiac resynchronization therapy for heart failure: biventricular pacing and beyond. Curr Opin Cardiol, 4: 346-52.

7. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L, Cardiac Resynchronization-Heart Failure Study I. (2005) The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med, 15: 1539-49.

8. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA, 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W,

Investigators M-CT. (2009) Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med, 14: 1329-38.

9. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial I. (2010) Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med, 25: 2385-95.

10. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J, Evaluation MSGMIRC. (2002) Cardiac resynchronization in chronic heart failure. N Engl J Med, 24: 1845-53.

11. Birnie DH, Tang AS. (2006) The problem of non-response to cardiac resynchronization therapy. Curr Opin Cardiol, 1: 20-6.

12. McAlister FA, Ezekowitz J, Hooton N, Vandermeer B, Spooner C, Dryden DM, Page RL, Hlatky MA, Rowe BH. (2007) Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. JAMA, 22: 2502-14.

13. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J, 3rd, St John Sutton M, De Sutter J, Murillo J. (2008) Results of the Predictors of Response to CRT (PROSPECT) trial. Circulation, 20: 2608-16.

14. Fornwalt BK, Sprague WW, BeDell P, Suever JD, Gerritse B, Merlino JD, Fyfe DA, Leon AR, Oshinski JN. (2010) Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. Circulation, 18: 1985-91.

15. Daubert JC, Saxon L, Adamson PB, Auricchio A, Berger RD, Beshai JF, Breithard O, Brignole M, Cleland J, Delurgio DB, Dickstein K, Exner DV, Gold M, Grimm RA, Hayes DL, Israel C, Leclercq C, Linde C, Lindenfeld J, Merkely B, Mont L, Murgatroyd F, Prinzen F, Saba SF, Shinbane JS, Singh J, Tang AS, Vardas PE, Wilkoff BL, Zamorano JL. (2012) 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. Heart Rhythm, 9: 1524-76.

16. Exner DV, Auricchio A, Singh JP. (2012) Contemporary and future trends in cardiac resynchronization therapy to enhance response. Heart Rhythm, 8 Suppl: S27-35.

17. Blendea D, Singh JP. (2011) Lead positioning strategies to enhance response to cardiac resynchronization therapy. Heart Fail Rev, 3: 291-303.

18. Landolina M, Gasparini M, Lunati M, Iacopino S, Boriani G, Bonanno C, Vado A, Proclemer A, Capucci A, Zucchiatti C, Valsecchi S, Ricci RP, Santini M. (2011) Long-term complications related to biventricular defibrillator implantation: rate of surgical revisions and impact on survival: insights from the Italian Clinical Service Database. Circulation, 22: 2526-35.

19. Ploux S, Whinnett Z, Lumens J, Denis A, Zemmoura A, De Guillebon M, Ramoul K, Ritter P, Jais P, Clementy J, Haissaguerre M, Bordachar P. (2012) Acute hemodynamic response to biventricular pacing in heart failure patients with narrow, moderately, and severely prolonged QRS duration. Heart Rhythm, 8: 1247-50.

20. Auricchio A, Stellbrink C, Butter C, Sack S, Vogt J, Misier AR, Bocker D, Block M, Kirkels JH, Kramer A, Huvelle E, Pacing Therapies in Congestive Heart Failure IISG, Guidant Heart Failure Research G. (2003) Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. J Am Coll Cardiol, 12: 2109-16.

21. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, Daubert JP, Eldar M, Gold MR, Goldberger JJ, Goldenberg I, Lichstein E, Pitschner H, Rashtian M, Solomon S, Viskin S, Wang P, Moss AJ, MADIT-CRTI. (2011) Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation, 10: 1061-1072.

22. Seo Y, Ito H, Nakatani S, Takami M, Naito S, Shiga T, Ando K, Wakayama Y, Aonuma K, investigators JC. (2011) The role of echocardiography in predicting responders to cardiac resynchronization therapy. Circ J, 5: 1156-63.

23. Sweeney MO, van Bommel RJ, Schalij MJ, Borleffs CJW, Hellkamp AS, Bax JJ. (2010) Analysis of ventricular activation using surface electrocardiography to predict left ventricular reverse volumetric remodeling during cardiac resynchronization therapy. Circulation, 5: 626-634.

24. Vernooy K, Cornelussen RN, Verbeek XA, Vanagt WY, van Hunnik A, Kuiper M, Arts T, Crijns HJ, Prinzen FW. (2007) Cardiac resynchronization therapy cures dyssynchronopathy in canine left bundle-branch block hearts. Eur Heart J, 17: 2148-55.

25. Tian Y, Zhang P, Li X, Gao Y, Zhu T, Wang L, Li D, Wang J, Yuan C, Guo J. (2013) True complete left bundle branch block morphology strongly predicts good response to cardiac resynchronization therapy. Europace, 10: 1499-506.

26. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, Daubert JP, Eldar M, Gold MR, Goldberger JJ, Goldenberg I, Lichstein E, Pitschner H, Rashtian M, Solomon S, Viskin S, Wang P, Moss AJ. (2011) Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation, 10: 1061-72.

27. Linde C, Gold MR, Abraham WT, St John Sutton M, Ghio S, Cerkvenik J, Daubert C. (2013) Long-term impact of cardiac resynchronization therapy in mild heart failure: 5-year results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. Eur Heart J, 33: 2592-9.

28. Mascioli G, Padeletti L, Sassone B, Zecchin M, Lucca E, Sacchi S, Boggian G, Tondo AL, Belvito C, Bakhtadze N, Borrelli A, Sinagra G. (2012) Electrocardiographic criteria of true left bundle branch block: a simple sign to predict a better clinical and instrumental response to CRT. Pacing Clin Electrophysiol, 8: 927-34.

29. Kandala J, Upadhyay GA, Altman RK, Parks KA, Orencole M, Mela T, Kevin Heist E, Singh JP. (2013) QRS morphology, left ventricular lead location, and clinical outcome in patients receiving cardiac resynchronization therapy. Eur Heart J, 29: 2252-62.

30. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE. (2013) 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace, 8: 1070-118.

31. Gorcsan J, 3rd, Oyenuga O, Habib PJ, Tanaka H, Adelstein EC, Hara H, McNamara DM, Saba S. (2010) Relationship of echocardiographic dyssynchrony to long-term survival after cardiac resynchronization therapy. Circulation, 19: 1910-8.

32. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Gorcsan J, 3rd, Gras D, Krum H, Sogaard P, Holzmeister J. (2013) Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med, 15: 1395-405.

33. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. (2002) Cardiac resynchronization in chronic heart failure. N Engl J Med, 24: 1845-53.

34. Chalil S, Foley PW, Muyhaldeen SA, Patel KC, Yousef ZR, Smith RE, Frenneaux MP, Leyva F. (2007) Late gadolinium enhancement-cardiovascular magnetic resonance as a predictor of response to cardiac resynchronization therapy in patients with ischaemic cardiomyopathy. Europace, 11: 1031-7.

35. Ypenburg C, Schalij MJ, Bleeker GB, Steendijk P, Boersma E, Dibbets-Schneider P, Stokkel MP, van der Wall EE, Bax JJ. (2007) Impact of viability and scar tissue on response to cardiac resynchronization therapy in ischaemic heart failure patients. Eur Heart J, 1: 33-41.

36. Singh JP, Klein HU, Huang DT, Reek S, Kuniss M, Quesada A, Barsheshet A, Cannom D, Goldenberg I, McNitt S, Daubert JP, Zareba W, Moss AJ. (2011) Left ventricular lead position and clinical outcome in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) trial. Circulation, 11: 1159-66.

37. Foley PW, Chalil S, Ratib K, Smith R, Prinzen F, Auricchio A, Leyva F. (2011) Fluoroscopic left ventricular lead position and the long-term clinical outcome of cardiac resynchronization therapy. Pacing Clin Electrophysiol, 7: 785-97.

38. Ypenburg C, van Bommel RJ, Delgado V, Mollema SA, Bleeker GB, Boersma E, Schalij MJ, Bax JJ. (2008) Optimal left ventricular lead position predicts reverse remodeling and survival after cardiac resynchronization therapy. J Am Coll Cardiol, 17: 1402-9.

39. Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O'Halloran D, Elsik M, Read PA, Begley D, Fynn SP, Dutka DP. (2012) Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. J Am Coll Cardiol, 17: 1509-18.

40. Singh JP, Fan D, Heist EK, Alabiad CR, Taub C, Reddy V, Mansour M, Picard MH, Ruskin JN, Mela T. (2006) Left ventricular lead electrical delay predicts response to cardiac resynchronization therapy. Heart Rhythm, 11: 1285-92.
41. Morales MA, Startari U, Panchetti L, Rossi A, Piacenti M. (2006) Atrioventricular delay optimization by doppler-derived left ventricular dP/dt improves 6-month outcome of resynchronized patients. Pacing Clin Electrophysiol, 6: 564-8.
42. Whinnett ZI, Davies JE, Willson K, Manisty CH, Chow AW, Foale RA, Davies DW, Hughes AD, Mayet J, Francis DP. (2006) Haemodynamic effects of changes in atrioventricular and interventricular delay in cardiac resynchronisation therapy show a consistent pattern: analysis of shape, magnitude and relative importance of atrioventricular and interventricular delay. Heart, 11: 1628-34.
43. van Deursen CJ, Strik M, Rademakers LM, van Hunnik A, Kuiper M, Wecke L, Crijns HJ, Vernooy K, Prinzen FW. (2012) Vectorcardiography as a tool for easy optimization of cardiac resynchronization therapy in canine left bundle branch block hearts. Circ Arrhythm Electrophysiol, 3: 544-52.
44. Birnie D, Lemke B, Aonuma K, Krum H, Lee KL, Gasparini M, Starling RC, Milasinovic G, Gorcsan J, 3rd, Houmsse M, Abeyratne A, Sambelashvili A, Martin DO. (2013) Clinical outcomes with synchronized left ventricular pacing: analysis of the adaptive CRT trial. Heart Rhythm, 9: 1368-74.
45. Gasparini M, Auricchio A, Metra M, Regoli F, Fantoni C, Lamp B, Curnis A, Vogt J, Klersy C. (2008) Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrio-ventricular junction ablation in patients with permanent atrial fibrillation. Eur Heart J, 13: 1644-52.
46. Mullens W, Grimm RA, Verga T, Dresing T, Starling RC, Wilkoff BL, Tang WH. (2009) Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program. J Am Coll Cardiol, 9: 765-73.
47. Schnittger I, Appleton CP, Hatle LK, Popp RL. (1988) Diastolic mitral and tricuspid regurgitation by Doppler echocardiography in patients with atrioventricular block: new insight into the mechanism of atrioventricular valve closure. J Am Coll Cardiol, 1: 83-8.
48. Appleton CP, Basnight MA, Gonzalez MS. (1991) Diastolic mitral regurgitation with atrioventricular conduction abnormalities: relation of mitral flow velocity to transmitral pressure gradients in conscious dogs. J Am Coll Cardiol, 3: 843-9.

49. Barold SS, Ilercil A, Leonelli F, Herweg B. (2006) First-degree atrioventricular block. Clinical manifestations, indications for pacing, pacemaker management & consequences during cardiac resynchronization. J Interv Card Electrophysiol, 2: 139-52.
50. Pires LA, Abraham WT, Young JB, Johnson KM, Miracle, Investigators M-I. (2006) Clinical predictors and timing of New York Heart Association class improvement with cardiac resynchronization therapy in patients with advanced chronic heart failure: results from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) trials. Am Heart J, 4: 837-43.
51. Olshansky B, Day JD, Sullivan RM, Yong P, Galle E, Steinberg JS. (2012) Does cardiac resynchronization therapy provide unrecognized benefit in patients with prolonged PR intervals? The impact of restoring atrioventricular synchrony: an analysis from the COMPANION Trial. Heart Rhythm, 1: 34-9.
52. Lee YH, Wu JH, Asirvatham SJ, Del Carpio Munoz F, Webster T, Brooke KL, Hodge DO, Wiste HJ, Friedman PA, Cha YM. (2014) Effects of atrioventricular conduction delay on the outcome of cardiac resynchronization therapy. J Electrocardiol,
53. Gervais R, Leclercq C, Shankar A, Jacobs S, Eiskjaer H, Johannessen A, Freemantle N, Cleland JG, Tavazzi L, Daubert C, investigators C-H. (2009) Surface electrocardiogram to predict outcome in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE-HF trial. Eur J Heart Fail, 7: 699-705.
54. Gheorghiade M, Abraham WT, Albert NM, Gattis Stough W, Greenberg BH, O'Connor CM, She L, Yancy CW, Young J, Fonarow GC, Investigators O-H, Coordinators. (2007) Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. Eur Heart J, 8: 980-8.
55. Klein L, O'Connor CM, Leimberger JD, Gattis-Stough W, Pina IL, Felker GM, Adams KF, Jr., Califf RM, Gheorghiade M, Investigators O-C. (2005) Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. Circulation, 19: 2454-60.

56. Baldasseroni S, Urso R, Orso F, Bianchini BP, Carbonieri E, Ciro A, Gonzini L, Leonardi G, Marchionni N, Maggioni AP, Investigators I-C. (2011) Relation between serum sodium levels and prognosis in outpatients with chronic heart failure: neutral effect of treatment with beta-blockers and angiotensin-converting enzyme inhibitors: data from the Italian Network on Congestive Heart Failure (IN-CHF database). J Cardiovasc Med (Hagerstown), 10: 723-31.

57. Gheorghiade M, Rossi JS, Cotts W, Shin DD, Hellkamp AS, Pina IL, Fonarow GC, DeMarco T, Pauly DF, Rogers J, DiSalvo TG, Butler J, Hare JM, Francis GS, Stough WG, O'Connor CM. (2007) Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. Arch Intern Med, 18: 1998-2005.

58. Rodondi N, Bauer DC, Cappola AR, Cornuz J, Robbins J, Fried LP, Ladenson PW, Vittinghoff E, Gottdiener JS, Newman AB. (2008) Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure - The Cardiovascular Health Study. Journal of the American College of Cardiology, 14: 1152-1159.

59. Nanchen D, Gussekloo J, Westendorp RGJ, Stott DJ, Jukema JW, Trompet S, Ford I, Welsh P, Sattar N, Macfarlane PW, Mooijaart SP, Rodondi N, de Craen AJM, Grp P. (2012) Subclinical Thyroid Dysfunction and the Risk of Heart Failure in Older Persons at High Cardiovascular Risk. Journal of Clinical Endocrinology & Metabolism, 3: 852-861.

60. Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, Bauer DC. (2005) Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Arch Intern Med, 21: 2460-2466.

61. Hyland KA, Arnold AM, Lee JS, Cappola AR. (2013) Persistent Subclinical Hypothyroidism and Cardiovascular Risk in the Elderly: The Cardiovascular Health Study. Journal of Clinical Endocrinology & Metabolism, 2: 533-540.

62. Perez AC, Jhund PS, Stott DJ, Gullestad L, Cleland JG, van Veldhuisen DJ, Wikstrand J, Kjekshus J, McMurray JJ. (2014) Thyroid-stimulating hormone and clinical outcomes: the CORONA trial (controlled rosuvastatin multinational study in heart failure). JACC Heart Fail, 1: 35-40.

63. Ascheim DD, Hryniewicz K. (2002) Thyroid hormone metabolism in patients with congestive heart failure: the low triiodothyronine state. Thyroid, 6: 511-5.

64. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. (2009) 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation, 14: 1977-2016.

65. Forman DE, Fleg JL, Kitzman DW, Brawner CA, Swank AM, McKelvie RS, Clare RM, Ellis SJ, Dunlap ME, Bittner V. (2012) 6-min walk test provides prognostic utility comparable to cardiopulmonary exercise testing in ambulatory outpatients with systolic heart failure. J Am Coll Cardiol, 25: 2653-61.

66. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, DiSalvo TG. (1996) The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. Chest, 2: 325-32.

67. Roul G, Germain P, Bareiss P. (1998) Does the 6-minute walk test predict the prognosis in patients with NYHA class II or III chronic heart failure? Am Heart J, 3: 449-57.

68. Alahdab MT, Mansour IN, Napan S, Stamos TD. (2009) Six minute walk test predicts long-term all-cause mortality and heart failure rehospitalization in African-American patients hospitalized with acute decompensated heart failure. J Card Fail, 2: 130-5.

69. Beatty AL, Schiller NB, Whooley MA. (2012) Six-minute walk test as a prognostic tool in stable coronary heart disease: data from the heart and soul study. Arch Intern Med, 14: 1096-102.

70. Guyatt GH, Pugsley SO, Sullivan MJ, Thompson PJ, Berman L, Jones NL, Fallen EL, Taylor DW. (1984) Effect of encouragement on walking test performance. Thorax, 11: 818-22.

71. Singh JP, Rosenthal LS, Hranitzky PM, Berg KC, Mullin CM, Thackeray L, Kaplan A. (2009) Device diagnostics and long-term clinical outcome in patients receiving cardiac resynchronization therapy. Europace, 12: 1647-53.

72. Whellan DJ, Ousdigian KT, Al-Khatib SM, Pu W, Sarkar S, Porter CB, Pavri BB, O'Connor CM. (2010) Combined heart failure device diagnostics identify patients at

higher risk of subsequent heart failure hospitalizations: results from PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) study. J Am Coll Cardiol, 17: 1803-10.

73. Braunschweig F, Mortensen PT, Gras D, Reiser W, Lawo T, Mansour H, Sogaard P, Stegemann B, Bruns HJ, Linde C. (2005) Monitoring of physical activity and heart rate variability in patients with chronic heart failure using cardiac resynchronization devices. Am J Cardiol, 9: 1104-7.

74. Shoemaker MJ CA, Vangsnes E, Dickinson MG, Paul R. (2012) Analysis of daily activity data from implanted cardiac defibrillators: The minimum clinically important difference and relationship to mortality/life expectancy. World Journal of Cardiovascular Diseases, 129-135.

75. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. (2004) Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med, 21: 2140-50.

76. Gras D, Bocker D, Lunati M, Wellens HJ, Calvert M, Freemantle N, Gervais R, Kappenberger L, Tavazzi L, Erdmann E, Cleland JG, Daubert JC, Committee C-HSS, Investigators. (2007) Implantation of cardiac resynchronization therapy systems in the CARE-HF trial: procedural success rate and safety. Europace, 7: 516-22.

77. Leon AR, Abraham WT, Curtis AB, Daubert JP, Fisher WG, Gurley J, Hayes DL, Lieberman R, Petersen-Stejskal S, Wheelan K. (2005) Safety of transvenous cardiac resynchronization system implantation in patients with chronic heart failure: combined results of over 2,000 patients from a multicenter study program. J Am Coll Cardiol, 12: 2348-56.

78. Ailawadi G, Lapar DJ, Swenson BR, Maxwell CD, Girotti ME, Bergin JD, Kern JA, Dimarco JP, Mahapatra S. (2010) Surgically placed left ventricular leads provide similar outcomes to percutaneous leads in patients with failed coronary sinus lead placement. Heart Rhythm, 5: 619-25.

79. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA, 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. (2009) Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med, 14: 1329-38.

80. Borleffs CJ, van Bommel RJ, Molhoek SG, de Leeuw JG, Schalij MJ, van Erven L. (2009) Requirement for coronary sinus lead interventions and effectiveness of endovascular replacement during long-term follow-up after implantation of a resynchronization device. Europace, 5: 607-11.

81. van Gelder BM, Scheffer MG, Meijer A, Bracke FA. (2007) Transseptal endocardial left ventricular pacing: an alternative technique for coronary sinus lead placement in cardiac resynchronization therapy. Heart Rhythm, 4: 454-60.

82. Gellér L SS, Róka A, Merkely B. (2005) Coronary sinus sidebranch stenting as a tool for coronary sinus lead dislocation in patients with heart failure and left bundle branch block. Eur Heart J, 52/P486.

83. Szilagyi S, Merkely B, Roka A, Zima E, Fulop G, Kutyifa V, Szucs G, Becker D, Apor A, Geller L. (2007) Stabilization of the coronary sinus electrode position with coronary stent implantation to prevent and treat dislocation. Journal of Cardiovascular Electrophysiology, 3: 303-7.

84. Kowalski O, Lenarczyk R, Prokopczuk J, Pruszkowska-Skrzep P, Zielinska T, Sredniawa B, Musialik-Lydka A, Pluta S, Kukulski T, Szulik M, Polonski L, Kalarus Z. (2006) Effect of percutaneous interventions within the coronary sinus on the success rate of the implantations of resynchronization pacemakers. Pace-Pacing and Clinical Electrophysiology, 10: 1075-1080.

85. Cesario DA, Shenoda M, Brar R, Shivkumar K. (2006) Left ventricular lead stabilization utilizing a coronary stent. Pacing Clin Electrophysiol, 4: 427-8.

86. Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE, Naccarelli GV, Schoenfeld MH, Silka MJ, Winters SL, Gibbons RJ, Antman EM, Alpert JS, Gregoratos G, Hiratzka LF, Faxon DP, Jacobs AK, Fuster V, Smith SC, Jr., American College of Cardiology/American Heart Association Task Force on Practice Guidelines/North American Society for P, Electrophysiology Committee to Update the Pacemaker G. (2002) ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). Circulation, 16: 2145-61.

87. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW, American College of Cardiology/American Heart Association Task Force on Practice G, American Association for Thoracic S, Society of Thoracic S. (2008) ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol, 21: e1-62.

88. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NA, 3rd, Ferguson TB, Jr., Hammill SC, Karasik PE, Link MS, Marine JE, Schoenfeld MH, Shanker AJ, Silka MJ, Stevenson LW, Stevenson WG, Varosy PD, American College of Cardiology F, American Heart Association Task Force on Practice G, Heart Rhythm S. (2013) 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Journal of the American College of Cardiology, 3: e6-75.

89. Del-Carpio Munoz F, Powell BD, Cha YM, Wiste HJ, Redfield MM, Friedman PA, Asirvatham SJ. (2013) Delayed intrinsicoid deflection onset in surface ECG lateral leads predicts left ventricular reverse remodeling after cardiac resynchronization therapy. Heart Rhythm, 7: 979-87.

90. Zong W, Moody GB, Jiang D. (2003) A robust open-source algorithm to detect onset and duration of QRS complexes. Computers in Cardiology 2003, Vol 30, 737-740.

91. Man S, Algra AM, Schreurs CA, Borleffs CJW, Scherptong RWC, van Erven L, van der Wall EE, Cannegieter SC, Schalij MJ, Swenne CA. (2011) Influence of the vectorcardiogram synthesis matrix on the power of the electrocardiogram-derived spatial QRS-T angle to predict arrhythmias in patients with ischemic heart disease and systolic left ventricular dysfunction. J Electrocardiol, 4: 410-415.

92. Cortez DL, Schlegel TT. (2010) When deriving the spatial QRS-T angle from the 12-lead electrocardiogram, which transform is more Frank: regression or inverse Dower? J Electrocardiol, 4: 302-309.

93. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, Berman LB. (1985) The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J, 8: 919-23.

94. Frohlich G, Steffel J, Hurlimann D, Enseleit F, Luscher TF, Ruschitzka F, Abraham WT, Holzmeister J. (2010) Upgrading to resynchronization therapy after chronic right ventricular pacing improves left ventricular remodelling. Eur Heart J, 12: 1477-85.

95. Szilagyi S, Merkely B, Zima E, Kutyifa V, Szucs G, Fulop G, Molnar L, Szabolcs Z, Geller L. (2008) Minimal invasive coronary sinus lead reposition technique for the treatment of phrenic nerve stimulation. Europace, 10: 1157-60.

96. Packard JM, Graettinger JS, Graybiel A. (1954) Analysis of the electrocardiograms obtained from 1000 young healthy aviators; ten year follow-up. Circulation, 3: 384-400.

97. Johnson RL, Averill KH, Lamb LE. (1960) Electrocardiographic findings in 67,375 asymptomatic subjects. VII. Atrioventricular block. Am J Cardiol, 153-77.

98. Bexton RS, Camm AJ. (1984) First degree atrioventricular block. Eur Heart J, 107-9.

99. Erikssen J, Otterstad JE. (1984) Natural course of a prolonged PR interval and the relation between PR and incidence of coronary heart disease. A 7-year follow-up study of 1832 apparently healthy men aged 40-59 years. Clin Cardiol, 1: 6-13.

100. Magnani JW, Wang N, Nelson KP, Connelly S, Deo R, Rodondi N, Schelbert EB, Garcia ME, Phillips CL, Shlipak MG, Harris TB, Ellinor PT, Benjamin EJ, Health A, Body Composition S. (2013) Electrocardiographic PR interval and adverse outcomes in

older adults: the Health, Aging, and Body Composition study. Circ Arrhythm Electrophysiol, 1: 84-90.

101. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, Benjamin EJ, Vasan RS, Wang TJ. (2009) Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. Jama, 24: 2571-7.

102. Minamiguchi H, Sakata Y, Ohtani T, Mizote I, Takeda Y, Mizuno H, Okuyama Y, Nakatani S, Fujita M, Watanabe T, Uematsu M, Komuro I. (2013) Usefulness of overlapping of the E and A waves of the transmitral flow as a predictor of responders to cardiac resynchronization therapy. Am J Cardiol, 11: 1613-8.

103. Hsing JM, Selzman KA, Leclercq C, Pires LA, McLaughlin MG, McRae SE, Peterson BJ, Zimetbaum PJ. (2011) Paced left ventricular QRS width and ECG parameters predict outcomes after cardiac resynchronization therapy: PROSPECT-ECG substudy. Circ Arrhythm Electrophysiol, 6: 851-7.

104. Marcus GM. (2012) The PR interval and cardiac resynchronization therapy outcomes: considering confounding, mediation, and effect modification. Heart Rhythm, 1: 40-1.

105. Nielsen JB, Pietersen A, Graff C, Lind B, Struijk JJ, Olesen MS, Haunso S, Gerds TA, Ellinor PT, Kober L, Svendsen JH, Holst AG. (2013) Risk of atrial fibrillation as a function of the electrocardiographic PR interval: Results from the Copenhagen ECG Study. Heart Rhythm, 9: 1249-56.

106. Swedberg K, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M, Metra M, Torp-Pedersen C, Poole-Wilson P. (2005) Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. Eur Heart J, 13: 1303-8.

107. Ypenburg C, van Bommel RJ, Borleffs CJ, Bleeker GB, Boersma E, Schalij MJ, Bax JJ. (2009) Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. J Am Coll Cardiol, 6: 483-90.

108. Chalil S, Stegemann B, Muhyaldeen S, Khadjooi K, Smith RE, Jordan PJ, Leyva F. (2007) Intraventricular dyssynchrony predicts mortality and morbidity after cardiac resynchronization therapy: a study using cardiovascular magnetic resonance tissue synchronization imaging. J Am Coll Cardiol, 3: 243-52.

109. Delgado V, Bax JJ. (2011) Assessment of systolic dyssynchrony for cardiac resynchronization therapy is clinically useful. Circulation, 6: 640-55.

110. Sipahi I, Carrigan TP, Rowland DY, Stambler BS, Fang JC. (2011) Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Arch Intern Med, 16: 1454-62.

111. Stavrakis S, Lazzara R, Thadani U. (2012) The benefit of cardiac resynchronization therapy and QRS duration: a meta-analysis. J Cardiovasc Electrophysiol, 2: 163-8.

112. Barold SS, Herweg B. (2011) Usefulness of the 12-lead electrocardiogram in the follow-up of patients with cardiac resynchronization devices. Part I. Cardiol J, 5: 476-86.

113. Bryant AR, Wilton SB, Lai MP, Exner DV. (2013) Association between QRS duration and outcome with cardiac resynchronization therapy: a systematic review and meta-analysis. J Electrocardiol, 2: 147-55.

114. Gold MR, Thebault C, Linde C, Abraham WT, Gerritse B, Ghio S, St John Sutton M, Daubert JC. (2012) Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. Circulation, 7: 822-9.

115. Sodi-Pallares D, Barbato E, Delmar A. (1950) Relationship between the intrinsic deflection and subepicardial activation; an experimental study. Am Heart J, 3: 387-96.

116. Sweeney MO, van Bommel RJ, Schalij MJ, Borleffs CJ, Hellkamp AS, Bax JJ. (2010) Analysis of ventricular activation using surface electrocardiography to predict left ventricular reverse volumetric remodeling during cardiac resynchronization therapy. Circulation, 5: 626-34.

117. Gold MR, Birgersdotter-Green U, Singh JP, Ellenbogen KA, Yu Y, Meyer TE, Seth M, Tchou PJ. (2011) The relationship between ventricular electrical delay and left ventricular remodelling with cardiac resynchronization therapy. European heart journal, 20: 2516-24.

118. Bonakdar HR, Jorat MV, Fazelifar AF, Alizadeh A, Givtaj N, Sameie N, Sadeghpour A, Haghjoo M. (2009) Prediction of response to cardiac resynchronization

therapy using simple electrocardiographic and echocardiographic tools. Europace, 10: 1330-7.

119. European Heart Rhythm A, European Society of C, Heart Rhythm S, Heart Failure Society of A, American Society of E, American Heart A, European Association of E, Heart Failure A, Daubert JC, Saxon L, Adamson PB, Auricchio A, Berger RD, Beshai JF, Breithard O, Brignole M, Cleland J, Delurgio DB, Dickstein K, Exner DV, Gold M, Grimm RA, Hayes DL, Israel C, Leclercq C, Linde C, Lindenfeld J, Merkely B, Mont L, Murgatroyd F, Prinzen F, Saba SF, Shinbane JS, Singh J, Tang AS, Vardas PE, Wilkoff BL, Zamorano JL. (2012) 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. Heart Rhythm, 9: 1524-76.

120. Nasir JM, Rubal BJ, Jones SO, Shah AD. (2012) The effects of body mass index on surface electrocardiograms in young adults. J Electrocardiol, 6: 646-51.

121. Hsu JC, Solomon SD, Bourgoun M, McNitt S, Goldenberg I, Klein H, Moss AJ, Foster E, Committee M-CE. (2012) Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: the MADIT-CRT (multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy) study. J Am Coll Cardiol, 25: 2366-73.

122. Brenyo A, Rao M, Barsheshet A, Cannom D, Quesada A, McNitt S, Huang DT, Moss AJ, Zareba W. (2013) QRS axis and the benefit of cardiac resynchronization therapy in patients with mildly symptomatic heart failure enrolled in MADIT-CRT. J Cardiovasc Electrophysiol, 4: 442-8.

123. Levy D, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB. (1994) Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. Circulation, 4: 1786-93.

124. Aiba T, Hesketh GG, Barth AS, Liu T, Daya S, Chakir K, Dimaano VL, Abraham TP, O'Rourke B, Akar FG, Kass DA, Tomaselli GF. (2009) Electrophysiological consequences of dyssynchronous heart failure and its restoration by resynchronization therapy. Circulation, 9: 1220-30.

125. Arshad A, Moss AJ, Foster E, Padeletti L, Barsheshet A, Goldenberg I, Greenberg H, Hall WJ, McNitt S, Zareba W, Solomon S, Steinberg JS, Committee M-CE. (2011) Cardiac resynchronization therapy is more effective in women than in men: the

MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial. J Am Coll Cardiol, 7: 813-20.

126. Zabarovskaja S, Gadler F, Braunschweig F, Stahlberg M, Hornsten J, Linde C, Lund LH. (2012) Women have better long-term prognosis than men after cardiac resynchronization therapy. Europace, 8: 1148-55.

127. Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E. (2006) Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). Circulation, 2: 266-72.

128. Dekker LR, Rademaker H, Vermeulen JT, Opthof T, Coronel R, Spaan JA, Janse MJ. (1998) Cellular uncoupling during ischemia in hypertrophied and failing rabbit ventricular myocardium: effects of preconditioning. Circulation, 17: 1724-30.

129. Potse M, Krause D, Bacharova L, Krause R, Prinzen FW, Auricchio A. (2012) Similarities and differences between electrocardiogram signs of left bundle-branch block and left-ventricular uncoupling. Europace, v33-v39.

130. Leenders GE, Cramer MJ, Bogaard MD, Meine M, Doevendans PA, De Boeck BW. (2011) Echocardiographic prediction of outcome after cardiac resynchronization therapy: conventional methods and recent developments. Heart Fail Rev, 3: 235-50.

131. Gorcsan J, 3rd. (2008) Role of echocardiography to determine candidacy for cardiac resynchronization therapy. Curr Opin Cardiol, 1: 16-22.

132. White JA, Yee R, Yuan X, Krahn A, Skanes A, Parker M, Klein G, Drangova M. (2006) Delayed enhancement magnetic resonance imaging predicts response to cardiac resynchronization therapy in patients with intraventricular dyssynchrony. J Am Coll Cardiol, 10: 1953-60.

133. Cochet H, Denis A, Ploux S, Lumens J, Amraoui S, Derval N, Sacher F, Reant P, Lafitte S, Jais P, Laurent F, Ritter P, Montaudon M, Bordachar P. (2013) Pre- and intra-procedural predictors of reverse remodeling after cardiac resynchronization therapy: an MRI study. J Cardiovasc Electrophysiol, 6: 682-91.

134. Kors JA, van Herpen G, Sittig AC, van Bemmel JH. (1990) Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. Eur Heart J, 12: 1083-92.

135. Schreurs CA, Algra AM, Man S-C, Cannegieter SC, van der Wall EE, Schalij MJ, Kors JA, Swenne CA. (2010) The spatial QRS-T angle in the Frank vectorcardiogram: accuracy of estimates derived from the 12-lead electrocardiogram. J Electrocardiol, 4: 294-301.

136. Feldman T, Childers RW, Borow KM, Lang RM, Neumann A. (1985) Change in ventricular cavity size: differential effects on QRS and T wave amplitude. Circulation, 3: 495-501.

137. Gasparini M, Galimberti P. (2013) Device therapy in heart failure: has CRT changed "the sickest benefit the most" to "the healthiest benefit the most?". J Am Coll Cardiol, 9: 945-7.

138. Rickard J, Brennan DM, Martin DO, Hsich E, Tang WH, Lindsay BD, Starling RC, Wilkoff BL, Grimm RA. (2011) The impact of left ventricular size on response to cardiac resynchronization therapy. Am Heart J, 4: 646-53.

139. Diaz-Infante E, Mont L, Leal J, Garcia-Bolao I, Fernandez-Lozano I, Hernandez-Madrid A, Perez-Castellano N, Sitges M, Pavon-Jimenez R, Barba J, Cavero MA, Moya JL, Perez-Isla L, Brugada J, Investigators S. (2005) Predictors of lack of response to resynchronization therapy. Am J Cardiol, 12: 1436-40.

140. Fried LF, Palevsky PM. (1997) Hyponatremia and hypernatremia. Med Clin North Am, 3: 585-609.

141. Schrier RW, Abraham WT. (1999) Hormones and hemodynamics in heart failure. N Engl J Med, 8: 577-85.

142. Goldsmith SR, Francis GS, Cowley AW, Jr. (1986) Arginine vasopressin and the renal response to water loading in congestive heart failure. Am J Cardiol, 3: 295-9.

143. Goldsmith SR. (2005) Current treatments and novel pharmacologic treatments for hyponatremia in congestive heart failure. Am J Cardiol, 9A: 14B-23B.

144. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. (2006) The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation, 11: 1424-33.

145. Movafagh S, Cleemann L, Morad M. (2011) Regulation of cardiac Ca(2+) channel by extracellular Na(+). Cell Calcium, 3: 162-73.

146. Arao K, Fujiwara T, Sakakura K, Wada H, Sugawara Y, Suga C, Ako J, Ishikawa SE, Momomura S. (2013) Hyponatremia as a predictor for worsening heart failure in patients receiving cardiac resynchronization therapy. Circ J, 1: 116-22.
147. Dahlstrom U. (2005) Frequent non-cardiac comorbidities in patients with chronic heart failure. Eur J Heart Fail, 3: 309-16.
148. Klein I, Danzi S. (2007) Thyroid disease and the heart. Circulation, 15: 1725-35.
149. Fazio S, Palmieri EA, Lombardi G, Biondi B. (2004) Effects of thyroid hormone on the cardiovascular system. Recent Prog Horm Res, 31-50.
150. Liu Y, Xia X, Fondell JD, Yen PM. (2006) Thyroid hormone-regulated target genes have distinct patterns of coactivator recruitment and histone acetylation. Mol Endocrinol, 3: 483-90.
151. Kinugawa K, Minobe WA, Wood WM, Ridgway EC, Baxter JD, Ribeiro RC, Tawadrous MF, Lowes BA, Long CS, Bristow MR. (2001) Signaling pathways responsible for fetal gene induction in the failing human heart: evidence for altered thyroid hormone receptor gene expression. Circulation, 8: 1089-94.
152. Tomanek RJ, Busch TL. (1998) Coordinated capillary and myocardial growth in response to thyroxine treatment. Anat Rec, 1: 44-9.
153. Liu Y, Sherer BA, Redetzke RA, Gerdes AM. (2010) Regulation of arteriolar density in adult myocardium during low thyroid conditions. Vascul Pharmacol, 3-4: 146-50.
154. Portman MA. (2008) Thyroid hormone regulation of heart metabolism. Thyroid, 2: 217-25.
155. Klein I, Ojamaa K. (2001) Thyroid hormone and the cardiovascular system. N Engl J Med, 7: 501-9.
156. Pantos C, Mourouzis I, Cokkinos DV. (2010) Thyroid hormone as a therapeutic option for treating ischaemic heart disease: from early reperfusion to late remodelling. Vascul Pharmacol, 3-4: 157-65.
157. Tang YD, Kuzman JA, Said S, Anderson BE, Wang X, Gerdes AM. (2005) Low thyroid function leads to cardiac atrophy with chamber dilatation, impaired myocardial blood flow, loss of arterioles, and severe systolic dysfunction. Circulation, 20: 3122-30.
158. Ripoli A, Pingitore A, Favilli B, Bottoni A, Turchi S, Osman NF, De Marchi D, Lombardi M, L'Abbate A, Iervasi G. (2005) Does subclinical hypothyroidism affect

cardiac pump performance? Evidence from a magnetic resonance imaging study. Journal of the American College of Cardiology, 3: 439-45.

159. Biondi B. (2007) Cardiovascular effects of mild hypothyroidism. Thyroid, 7: 625-30.

160. Hamilton MA, Stevenson LW, Luu M, Walden JA. (1990) Altered thyroid hormone metabolism in advanced heart failure. Journal of the American College of Cardiology, 1: 91-5.

161. Maia AL, Kim BW, Huang SA, Harney JW, Larsen PR. (2005) Type 2 iodothyronine deiodinase is the major source of plasma T3 in euthyroid humans. J Clin Invest, 9: 2524-33.

162. Katzeff HL, Powell SR, Ojamaa K. (1997) Alterations in cardiac contractility and gene expression during low-T3 syndrome: prevention with T3. Am J Physiol, 5 Pt 1: E951-6.

163. Brenta G, Mutti LA, Schnitman M, Fretes O, Perrone A, Matute ML. (2003) Assessment of left ventricular diastolic function by radionuclide ventriculography at rest and exercise in subclinical hypothyroidism, and its response to L-thyroxine therapy. Am J Cardiol, 11: 1327-30.

164. Esposito F, Liguori V, Maresca G, Cerrone A, De Filippo O, Trimarco B, Rapacciuolo A. (2014) Subclinical hypothyroidism: a reversible cause of complete loss of ventricular lead capture. Circ Arrhythm Electrophysiol, 1: 182-4.

165. Iervasi G, Molinaro S, Landi P, Taddei MC, Galli E, Mariani F, L'Abbate A, Pingitore A. (2007) Association between increased mortality and mild thyroid dysfunction in cardiac patients. Arch Intern Med, 14: 1526-32.

166. Biondi B, Palmieri EA, Lombardi G, Fazio S. (2002) Effects of subclinical thyroid dysfunction on the heart. Annals of Internal Medicine, 11: 904-14.

167. Jehn M, Schmidt-Trucksaess A, Schuster T, Hanssen H, Weis M, Halle M, Koehler F. (2009) Accelerometer-based quantification of 6-minute walk test performance in patients with chronic heart failure: applicability in telemedicine. J Card Fail, 4: 334-40.

168. Flynn KE, Pina IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, Kraus WE, Miller NH, Schulman KA, Spertus JA, O'Connor CM, Weinfurt KP. (2009) Effects of exercise training on health status in

patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA, 14: 1451-9.

169. Kadhiresan VA, Pastore J, Auricchio A, Sack S, Doelger A, Girouard S, Spinelli JC. (2002) A novel method--the activity log index--for monitoring physical activity of patients with heart failure. Am J Cardiol, 12: 1435-7.

170. Pressler A, Danner M, Esefeld K, Haller B, Scherr J, Schomig A, Halle M, Kolb C. (2013) Validity of cardiac implantable electronic devices in assessing daily physical activity. Int J Cardiol, 2: 1127-30.

171. Morgan JM, Delgado V. (2009) Lead positioning for cardiac resynchronization therapy: techniques and priorities. Europace, v22-8.

172. Merchant FM, Heist EK, McCarty D, Kumar P, Das S, Blendea D, Ellinor PT, Mela T, Picard MH, Ruskin JN, Singh JP. (2010) Impact of segmental left ventricle lead position on cardiac resynchronization therapy outcomes. Heart Rhythm, 5: 639-44.

173. Yu CM, Wing-Hong Fung J, Zhang Q, Sanderson JE. (2005) Understanding nonresponders of cardiac resynchronization therapy--current and future perspectives. J Cardiovasc Electrophysiol, 10: 1117-24.

174. Lau EW. (2009) Achieving permanent left ventricular pacing - Options and choice. PACE - Pacing and Clinical Electrophysiology, 11: 1466-1477.

175. Gurevitz O, Nof E, Carasso S, Luria D, Bar-Lev D, Tanami N, Eldar M, Glikson M. (2005) Programmable multiple pacing configurations help to overcome high left ventricular pacing thresholds and avoid phrenic nerve stimulation. Pacing Clin Electrophysiol, 12: 1255-9.

176. Schwierz T, Winter S, Pürerfellner H, Tomaselli F, Nesser H, Függer R. (2007) Nervus Phrenicus Stimulation bei biventrikulären Schrittmachern. . Chirurg, 1037-1040.

177. Azizi M, Castel MA, Behrens S, Rodiger W, Nagele H. (2006) Experience with coronary sinus lead implantations for cardiac resynchronization therapy in 244 patients. Herzschrittmacherther Elektrophysiol, 1: 13-8.

178. McAlister FA, Ezekowitz JA, Wiebe N, Rowe B, Spooner C, Crumley E, Hartling L, Klassen T, Abraham W. (2004) Systematic review: cardiac resynchronization in patients with symptomatic heart failure. Ann Intern Med, 5: 381-90.

179. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. (2005) The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med, 15: 1539-49.

180. Van Gelder BM, Meijer A, Basting P, Hendrix G, Bracke FA. (2003) Successful implantation of a coronary sinus lead after stenting of a coronary vein stenosis. Pacing Clin Electrophysiol, 9: 1904-6.

181. Scott PA, Chantrarat T, Roberts PR, Curzen NP. (2009) Percutaneous coronary venous stenting to facilitate placement of a left ventricular lead. Int J Cardiol, 2: e76-8.

182. Gutleben KJ, Nolker G, Marschang H, Sinha AM, Schmidt M, Ritscher G, Brachmann J. (2008) Rescue-stenting of an occluded lateral coronary sinus branch for recanalization after dissection during cardiac resynchronization device implantation. Europace, 12: 1442-4.

183. Balazs T, Merkely B, Bognar E, Geller L, Szilagyi S, Dobranszky J, Zima E. (2013) Methods for Examination an Explanted Coronary Sinus Lead Stabilized with a Coronary Stent. Pace-Pacing and Clinical Electrophysiology, 2: e27-e30.

184. Hansky B. (2008) Stenting of coronary veins: a critical comment. Europace, 12: 1363-1363.

185. Bongiorni MG DCA, Zucchelli G, Segreti L, DE Lucia R, Paperini L, Soldati E. (2010) A Modified Transvenous Single Mechanical Dilatation Technique to Remove a Chronically Implanted Active-Fixation Coronary Sinus Pacing Lead. Pacing Clin Electrophysiol. ,

186. Crossley GH, Exner D, Mead RH, Sorrentino RA, Hokanson R, Li S, Adler S. (2010) Chronic performance of an active fixation coronary sinus lead. Heart Rhythm, 4: 472-8.

187. Nagele H, Azizi M, Hashagen S, Castel MA, Behrens S. (2007) First experience with a new active fixation coronary sinus lead. Europace, 6: 437-41.

188. Hansky B, Vogt J, Gueldner H, Schulte-Eistrup S, Lamp B, Heintze J, Horstkotte D, Koerfer R. (2007) Implantation of active fixation leads in coronary veins for left ventricular stimulation: report of five cases. Pacing Clin Electrophysiol, 1: 44-9.

DOI:10.14753/SE.2017.2002

10. List of publications

Related to the thesis:

Végh EM, Engels EB, van Deursen CJM, Merkely B, Vernoy K, Singh JP, Prinzen FW. (2015) T-wave area as biomarker of clinical response to cardiac resynchronization therapy. Europace; 18(7): 1077-85.

Engels EB, Végh EM, VAN Deursen CJ, Vernooy K, Singh JP, Prinzen FW. (2015) T-wave area predicts response to cardiac resynchronization therapy in patients with left bundle branch block. J Cardiovasc Electrophysiol; 26(2): 176-83.

Januszkiewicz Ł, Vegh E, Borgquist R, Bose A, Sharma A, Orencole M, Mela T, Singh JP, Parks KA. (2015) Prognostic implication of baseline PR interval in cardiac resynchronization therapy recipients. Heart Rhythm. S1547-5271; 15: 00706-7.

Sharma AK, Vegh E, Orencole M, Miller A, Blendea D, Moore S, Lewis GD, Singh JP, Parks KA, Heist EK. (2015) Association of hypothyroidism with adverse events in patients with heart failure receiving cardiac resynchronization therapy. Am J Cardiol; 115(9):1249-53.

Sharma AK, Vegh EM, Kandala J, Orencole M, Januszkiewicz L, Bose A, Miller A, Parks KA, Heist EK, Singh JP. (2014) Usefulness of hyponatremia as a predictor for adverse events in patients with heart failure receiving cardiac resynchronization therapy. Am J Cardiol;114(1):83-7.

Vegh EM, Kandala J, Orencole M, Upadhyay GA, Sharma A, Miller A, Merkely B, Parks KA, Singh JP. (2014) Device-measured physical activity versus six-minute walk test as a predictor of reverse remodeling and outcome after cardiac resynchronization therapy for heart failure. Am J Cardiol;113(9):1523-8.

L Gellér, S Szilágyi, E Zima, L Molnár, G Széplaki, EM Végh, I Osztheimer, B Merkely. (2011) Long term experience with coronary sinus side branch stenting to stabilize left ventricular electrode position. Heart Rhythm; 8(6): 845-850.

Not related to the thesis:

Venkateswaran RV, Freeman C, Chatterjee N, Kandala J, Orencole M, Vegh EM, Parks KA, Cowburn PJ, Dec GW, Singh JP, Borgquist R. (2015) Anemia and its association with clinical outcome in heart failure patients undergoing cardiac resynchnonization therapy. J Interv Card Electrophysiol; 44(3):297-304.

Akca F, Hubay M, Zima E, Széplaki G, Végh EM, Skopál J, Lendvai Z, Theuns D, Merkely B, Szili-Torok T. (2014) High-volume lesions using a new second-generation open irrigation radiofrequency catheter are associated with the development of inhomogeneous lesions. Pacing Clin Electrophysiol; 37(7):864-73.

Vegh EM, Sood N, Singh JP. (2013) The role of ablation of the atrioventricular junction in patients with heart failure and atrial fibrillation. Heart Fail Clin; 9(4):489-99. (Review)

Akca F, Zima E, Végh EM, Széplaki G, Skopál J, Hubay M, Lendvai Z, Merkely B, Szili-Torok T. (2013) Radiofrequency ablation at low irrigation flow rates using a novel 12-hole gold open-irrigation catheter. Pacing Clin Electrophysiol; 36(11): 1373-81.

Végh EM, Széplaki G, Szilágyi S, Osztheimer I, Tahin T, Merkely B, Gellér L. (2011) Electroanatomical mapping and radiofrequency ablation of tachycardia originating in pulmonary vein in an adult patient. Orv Hetil; 152(34): 1374-8.

A. Putics, EM. Végh, P. Csermely, C. Sőti (2008) Resveratrol Induces the Heat-Shock Response and Protects Human Cells from Severe Heat Stress, Antioxidants&Redox Signaling; 10: 65-75.

DOI:10.14753/SE.2017.2002

G. Nardai, EM Végh, Z. Prohászka, P. Csermely (2006) Chaperone-related immune dysfunctions: An emergent property of distorted chaperone-networks. Trends Immunol; 27, 74-79.

DOI:10.14753/SE.2017.2002

11. Acknowledgement

I would like to thank Prof. Béla Merkely, the head of Heart and Vascular Center and Dr. László Gellér, my supervisor for admission to their research group. Thank you for providing indispensable advice, information and support on difference aspects of my project and my doctoral years.

I also would like to thank Dr. Szabolcs Szilágyi and the team of EP laboratory for the introduction and inspiration in the amazing field of electrophysiology.

I express my gratitude to Dr. Violetta Kékesi and her friendly team of the Experimental Laboratory for the helpful guidance, encouargement and patience during my learning curve in experimental cardiology and project management.

I consider it a privilage to thank Prof. Jagmeet P. Singh - and to the team of Cardiac Resynchronization Therapy Research Group of Massachusetts General Hospital - for forming my scientific vision, for whole hearted support and readiness to share his valuable time.

My final words go to equally to my family for whom I thank for their love and inestimable moral support.