THE POTENTIAL OF ELECTROCARDIOGRAPHIC MARKERS TO TUNE CARDIAC DEVICE THERAPY

S.C.WIJERS

Financial support by Abbot, Pfizer, Stichting Cardiovasculaire Biologie, Servier Nederland Farma B.V and Chipsoft Nederland B.V is gratefully acknowledged.

Cover: Sabine Krouwer
Lay-out & Printed by: ProefschriftMaken || www.proefschriftmaken.nl
Published by: ProefschriftMaken || www.proefschriftmaken.nl

ISBN: 978-94-6295-606-3

The potential of electrocardiographic markers to tune cardiac device therapy

De potentie van electrocardiografische markers voor het optimaliseren van cardiale therapie middels implanteerbare apparaten

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 11 april 2017 des middags te 4.15uur

door

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geboren op 25 augustus 1985 te Deventer

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Financial support by the Dutch Heart Foundation and the Heart & Lung foundation for the publication of this thesis is gratefully acknowledged.

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CHAPTER 1

Scope & outline of this thesis

Scope & outline of this thesis

Over the last decades, new and more invasive treatment modalities for patients with heart failure have been developed. Primary prophylactic implantable cardiac defibrillators (ICD's) are now implanted in almost every heart failure patient with a left ventricular ejection fraction (LVEF) ≤35%. To prevent sudden cardiac death (SCD) and when substantial conduction delay is present cardiac resynchronization therapy (CRT) is also often indicated. Although benefit of these devices is proven in several large clinical trials [1-5], when applied in more unselected patient populations as being present in clinical practice, results can turn out to be disappointing and therefore challenge us to be critical towards the 'evidence'. Patient groups like elderly or females are often not well represented in these large clinical trials, while the guidelines do not distinguish between these subgroups when providing their recommendations. Having more insights in the characteristics of these subpopulations, in relation to risk for ventricular arrhythmias, response to CRT and mortality, could enable a more patient-tailored approach. For example, elderly with multiple comorbidities are less likely to benefit from ICD implantation because they will more likely die from non-arrhythmic causes. Although it will be difficult to restrict the current indications, better identification of markers associated with benefit of device therapy could be of advantage as 1) to more objectively aid decisions in doubtful cases and/or 2) in earlier recognition of eligible subjects. Furthermore, these markers could be used for monitoring of arrhythmic risk or to optimize biventricular pacing in patients already implanted with a CRT device. The electrogram (ECG) is an easy and non-invasive tool that can assist in identifying patients that will benefit from cardiac device therapy. Aside from the standard measures that can be derived from the 12-lead ECG more sophisticated measures are developed to aid identification of the electrical substrate.

Part 1. Patient selection for ICD therapy (chapters 2-7)

Why improve risk stratification?
ICD therapy has showed to be very effective in patients that survived a cardiac arrest: large clinical trials demonstrated a relative reduction in all cause mortality of 27% in patients that received an ICD for secondary prophylaxis [6]. But as you can see in Figure 1 only a small proportion of the absolute number of SCD's is covered by giving these patients an ICD [7].

That's why subsequent trials focused on patients that did not experience any life-threatening arrhythmias yet, but were believed to be at higher risk due to heart failure with a reduced LVEF (primary prophylaxis). The goal of these (mostly industry driven) trials was to cover an as large as possible proportion of absolute events while keeping an acceptable number needed to treat. Thereby reduced LVEF became the most important marker that is used for risk stratification nowadays [8]. Not surprisingly subgroup analysis showed that several subpopulations did not show significant benefit of primary prophylactic ICD implantation, most importantly patients

with non-ischemic etiology of heart failure [2,9]. Furthermore, these large trials were performed over 10 years ago when therapies such as CRT were not common in clinical practice yet, further reducing the expected benefit in subgroups such as women and patients with non-ischemic cardiomyopathy. In chapter 2 adherence to the guideline for ICD implantation in clinical practice is examined and benefit in different subpopulations is assessed.

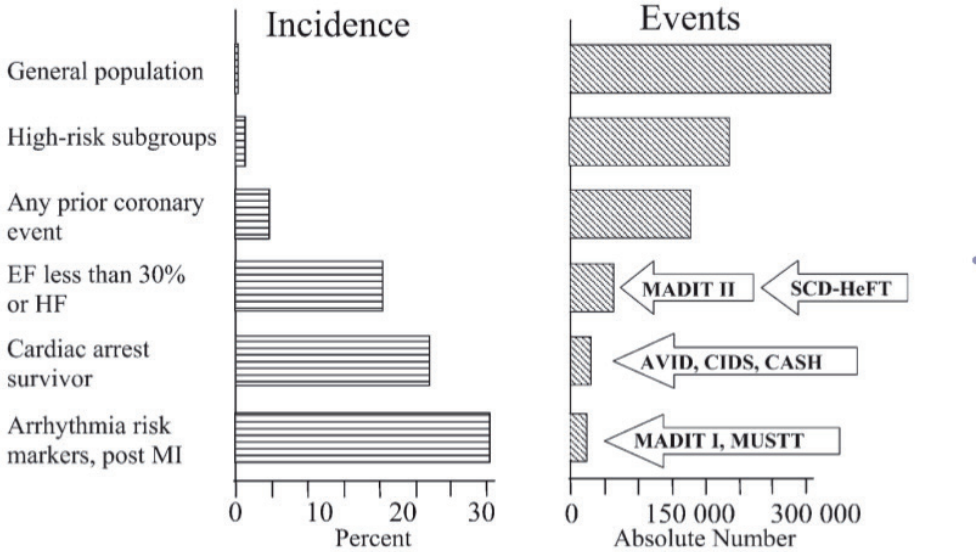

Figure 1. Incidence and absolute number of sudden cardiac deaths in general population. Adapted from Myerburg et al, Circulation 1992.

Additional risk stratification beyond LVEF and functional class of heart failure to improve benefit of ICD therapy seems necessary, especially in patients with non-ischemic etiology of heart disease. In this patient population the lower event rate leads to a substantial higher number needed to treat. An ideal marker to demonstrate ICD benefit must identify patients specifically at risk for SCD and exclude those that are more likely to die from non-arrhythmic causes. In that context electrophysiological parameters are the most obvious candidates to improve risk stratification for SCD. Electrophysiological markers predictive of ventricular arrhythmia could not only increase benefit of ICD implantation in patients with reduced LVEF, but also identify patients with preserved LVEF at risk for ventricular arrhythmias. There are various promising electrophysiological markers that could be of value in improving risk stratification (chapters 3-6). One of these potential electrophysiological markers is beat-to-beat variability of repolarization, quantified as short-term variability (STV).

At our department (Medical Physiology, University Medical Center Utrecht) comprehensive studies in the canine chronic atrioventricular block (CAVB) model showed that STV is able to identify individuals with a diminished repolarization reserve, susceptible for repolarization dependent

ventricular arrhythmias [10]. Upon AV block structural, contractile and electrical remodeling occurs that make these dogs susceptible for Torsade de Pointes arrhythmias (TdP). After anesthesia and administration of a QT prolonging drug such as dofetilide, a blocker of the rapid component of the delayed rectifier potassium outward current (I_{Kr}), 70-80% of these dogs get single and multiple ectopic beats (sEB and mEB) followed by repetitive TdP (Figure 2, panel A and B) [11]. Especially the inducible subjects show a higher electrical instability quantified as STV (temporal dispersion), which further increases before the occurrence of TdP (Figure 2, panel C) [10,12,13].

STV can be affected by several moderators of the repolarization reserve (the ability to withstand certain 'hits' on repolarization) like remodeling, I_{Kr} blockade, anesthesia, changes in filling characteristics in the remodeled heart and changes in autonomic tone [14,15]. Combinations of these moderators can cause an even greater increase of STV when repolarization reserve is decreased to such a level that arrhythmias occur. In **chapter 3** an overview of current experimental and clinical data on STV is reviewed.

Nevertheless, the onset of arrhythmias remains (at least partly) a matter of chance since it is determined by the concurrence of these multiple hits. Therefore it might well be that we are able to identify individuals at higher risk for arrhythmias but that does not mean per se that individuals will experience an arrhythmia in the relative short time of a clinical trial. Long follow up is thereby a prerequisite for trials investigating risk stratification for ventricular arrhythmias. The risk for ventricular arrhythmias can be dependent on clinical parameters such as type and stage of underlying heart disease, age or gender. To embrace the complexity of the proarrhythmic substrate we chose to combine various risk stratifying markers in the European EUTrigTreat study (FP7/2007-2013 No. HEALTH-F2-2009-241526). In this prospective multicenter trial almost 700 ICD patients (both primary and secondary indication) were included. Multiple electrophysiological tests (including STV) were performed to assess individual and combined predictive values of these markers for ventricular arrhythmias. A risk score was developed combining these electrophysiological tests and clinical parameters (**chapter 5**). In a subanalysis STV of the QT-interval was related to appropriate ICD therapy and mortality (**chapter 6**).

To be able to assess the high volumes of ECG's and extract multiple parameters, (semi-) automated analysis of digital ECG's is performed. This enables a higher resolution and a greater reproducibility compared to manual assessment of standard paper or PDF ECG's. We used 2-minute, high-resolution (1200Hz) digital 12-lead ECG's. Analysis was done offline with the fiducial segment averaging method for an accurate assessment of all time intervals. In **chapter 7** this method and its usefulness in assessing beat-to-beat changes of ECG intervals is further explained.

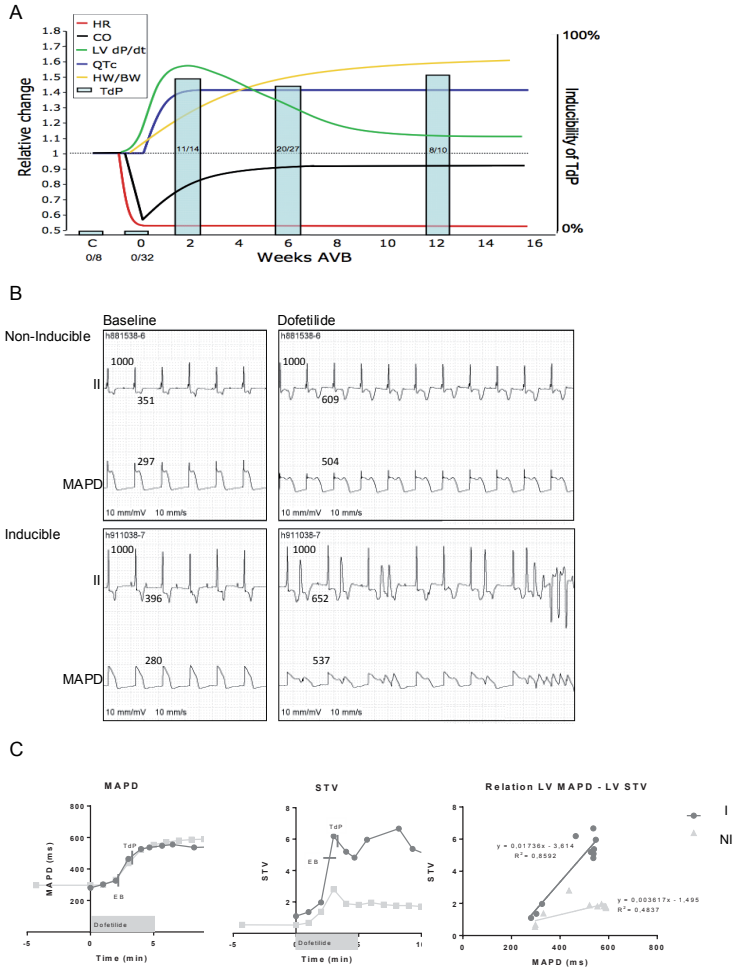

Figure 2. The canine chronic atrioventricular block (CAVB) model.
Panel A. Summary of the development of ventricular remodeling. The figure shows the relative change (left Y-axis) in heart rate (red line), cardiac output (black line), contractile remodeling expressed as in change in maximum rise in left ventricular pressure (LV dP/dt, green line), electrical remodeling expressed as change in QT interval corrected for heart rate (QTc, blue line)) and structural remodeling expressed as heart to body weight (HW/BW, yellow line). The green bars show the reproducible incidence of Torsade de Pointes arrhythmias (TdP) (right Y-axis). Figure courtesy of Bourgonje et al [38].
Panel B. ECG tracings before (baseline) and after administration of the QT prolonging drug dofetilide. The upper panel shows a dog that does not show repetitive TdP after the challenge with dofetilide (non-inducible) and the lower panel shows a dog that does (inducible).
Panel C. Changes in monophasic action potential duration in the left ventricle (LVMAPD) and short-term variability (STV) of the LVMAPD upon a challenge with dofetilide. The first panel shows a similar increase of MAPD in the LV in inducible (I) and non-inducible (NI) subjects. The second panel shows the STV of the LVMAPD, which increases both upon dofetilide, but the increase is more outspoken in the inducible subjects. The third panel shows the relationship between the LVMAPD and STV of the LVMAPD. Figure courtesy of Valerie van Weperen (unpublished).

Part 2. Monitoring of arrhythmic risk (chapters 8-9)

Although ICD's can terminate ventricular arrhythmias, additional pharmacological and electrophysiological treatment is still necessary to prevent arrhythmias and avoid (recurrent) ICD shocks. Aside from withdrawal of QT prolonging drugs, correction of potential electrolyte disturbances and beta-blockade, pacing at higher rates is known to be able to prevent (re)occurrence of TdP. Nevertheless, the exact application is not further clarified and the antiarrhythmic mechanism is not fully understood [16-19]. TdP is a repolarization dependent ventricular tachycardia that can occur in patients with long QT syndrome but also is a feared adverse effect of medical compounds. The canine CAVB block model is developed to screen for this proarrhythmic property of certain drugs but also gives us more insight into the mechanism underlying TdP. We made use of the high inducibility and reproducibility of TdP in the canine CAVB model (Figure 2, panel A) to investigate by what mechanism pacing at higher rates (temporary accelerated pacing (TAP)) averts TdP (chapter 8) [11] and if this can be guided by measurement of increase in temporal dispersion(STV), that occurs early in the cascade leading to TdP. In chapter 9 we took an important step in translating the application of STV (as monitoring parameter to guide TAP) into clinical practice by investigating the potential of STV derived electrogram of the right ventricular lead in anesthetized and awake conditions.

Part 3. The electrical substrate in patients eligible for CRT. (chapters 10-11)

Heart failure is a leading and increasing cause of death in the Western World. It renders a poor prognosis; only half of the patients are still alive 5 years after diagnosis [20,21]. The cornerstone of treatment is medication such as beta-blockers and inhibitors of the renin-angiotensin-aldosterone system that treat the symptoms, improve LVEF and reduce mortality. In a small subset of patients with symptomatic heart failure despite optimal medical therapy and substantial (left) ventricular conduction delay, CRT can be of additional benefit. In these patients biventricular pacing shortens depolarization and optimizes the timing of atrial and ventricular contraction, which leads to reverse structural remodeling and a decrease in heart failure hospitalizations [3-5,22,23]. Unfortunately, not all patients respond to this therapy, 11-46% of patients show no clinical and/or echocardiographic benefit or even have adverse effects [24,25]. As depicted in Figure 3 adapted from Gorcsan et al., the reason for the high number of 'non-responders' is multifactorial [26]. In several studies it is shown that the magnitude of CRT benefit increases in females, in patients with non-ischemic cardiomyopathy and in patients with a wide QRS complex. Since the effect of CRT is believed to be a correction of dyssynchrony by changing the electrical activation pattern, the electrical substrate is proven to be an important determinant of response. Lately there have been great efforts to improve the indication for CRT by sharpening the criteria of severity and type of conduction delay [27-31].

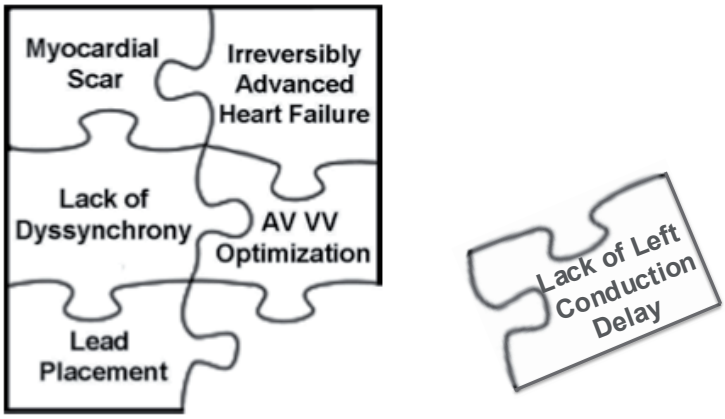

Figure 3. The puzzle of non-response. Adapted from Gorcsan et al, Circulation 2011

Left bundle branch block (LBBB) is now a prerequisite for a class I indication for CRT [32]. With the advent of CRT the interest in the vectorcardiogram (VCG) has revived because it gives a better reflection of degree and direction of conduction delay. With the possibility to derive the VCG from the 12-lead ECG it has gained renewed interest as a non-invasive and easy applicable tool with promising value for the patient selection for CRT. The department of physiology in Maastricht led by Prof F.W. Prinzen conducted several experimental and small or retrospective patients studies demonstrating the value of the VCG in the context of CRT [33-37]. We used this knowledge to confirm their results in a large prospective cohort as ECG core lab in the national multicenter Markers and Response to CRT therapy (MARC) study (part of CTMM COHFAR: the Center for Translational Molecular Medicine (www.ctmm.nl), project COHFAR (grant 01C-203), and supported by the Dutch Heart Foundation). We analyzed which electrocardiographic and vectorcardiographic markers are related to (non-) response to CRT in the context of other biomarkers (chapter 10). Furthermore, we critically reviewed the applicability of LBBB definition for CRT indication and propose a more objective vectorcardiographic parameter to quantify leftward ventricular conduction delay (chapter 11).

Aim of the thesis

General aims of the research presented in this thesis are threefold

1) Investigate the potential of the ECG to improve patient selection for ICD therapy.
2) Investigate the potential of the EGM to monitor arrhythmic risk and initiate TAP to prevent ventricular arrhythmias.
3) Investigate the potential of the ECG to improve patient selection for CRT therapy.

Outline of this thesis

Part I reviews the potential of the ECG to improve patient selection for ICD therapy. In chapter 2 we analyzed all patients that received an ICD over the years 2006-2011 in the UMCU to see how the guidelines are implemented in clinical practice. In chapters 3 until 6 potential electrophysiological parameters are discussed that could be used to improve patient selection for ICD implantation. Chapter 5 contains the main analysis of the large multicenter trial EUTrigTreat in which multiple novel electrophysiological parameters are investigated in over 600 patients. Chapter 6 is a subanalysis of the EUTrigTreat study that describes the value of STV of the QT-interval in this cohort. To accurately measure the proposed parameter that quantifies the beat-to-beat changes in repolarization we used a method called fiducial segment averaging for all our ECG analyses, this method and its applicability is described in chapter 7.

Part II focuses on monitoring arrhythmic risk to be able to initiate antiarrhythmic strategies such as TAP. In chapter 8 we used the canine CAVB model to show the potential of TAP to avert ventricular arrhythmias and to gain more insights into the mechanism. Furthermore, we looked for parameters to guide TAP. In chapter 9 the potential of STV derived from the intracardiac electrogram derived from the right ventricular lead to monitor arrhythmic risk was investigated under anesthetic and awake conditions.

In part III the main goal was to assess which electrocardiographic parameters identify the electrical substrate favorable for CRT. In Chapter 10 the main analysis of the MARC study shows the electrocardiographic markers that are related to response to CRT in combination with various clinical and echocardiographic parameters. Chapter 11 debates the use of descriptions of the QRS morphology (i.e. left bundle branch block) in patient selection for CRT and advocates the use of more objective markers derived from the VCG instead.

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PART I

PATIENT SELECTION FOR ICD THERAPY

CHAPTER 2

Implementation of guidelines for implantable cardioverter-defibrillator therapy in clinical practice: which patients do benefit?

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Netherlands Heart Journal 2013;21:274-283

Abstract

Purpose: Based on multiple large clinical trials conducted over the last decades guidelines for implantable cardioverter-defibrillator (ICD) implantations have been evolving. The increase in primary prophylactic ICD implantations challenges us to be critical towards the indications in certain patient populations.

Methods: We retrospectively collected patient characteristics and rates of appropriate and inappropriate ICD therapy, appropriate and inappropriate ICD shock and mortality of all patients who received an ICD in the University Medical Center Utrecht (UMCU) over the years 2006 - 2011.

Results: A total of 1075 patients were included in this analysis (74% male, mean age 61±13 years, left ventricular ejection fraction 30±13%); 61% had a primary indication and 58% had ischaemic heart disease. During a mean follow-up period of 31±17 months, 227 of the patients (21%) received appropriate ICD therapy (149 (14%) patients received an appropriate ICD shock). Females, patients with a primary prophylactic indication and/or patients with non-ischaemic heart disease experienced significantly less ICD therapy.
Only a few patients (54, 5%) received inappropriate ICD therapy; 33 (3%) patients received an inappropriate ICD shock. Fifty-five patients died within one year after ICD implantation and were therefore, in retrospect, not eligible for ICD implantation.

Conclusion: Our study confirms the benefit of ICD implantation in clinical practice. Nevertheless, certain patients experience less benefit than others. A more patient-tailored risk stratification based on electrophysiological parameters would be lucrative to improve clinical benefit and cost-effectiveness.

Introduction

For almost 30 years, implantable cardioverter defibrillators (ICD) have been used in the prevention of sudden cardiac death caused by life-threatening cardiac arrhythmias. In 1984, the first ICD implantation in the Netherlands was performed at the University Medical Center Utrecht (UMCU). Over the last decades, multiple studies, including series of randomised controlled trials, have demonstrated a beneficial effect of an ICD in the prevention of sudden cardiac death [1-8]. In particular, in patients with ischaemic heart disease and impaired left ventricular function, primary prophylactic ICD implantation was proven to be effective [3, 6, 8]. In patients with non-ischaemic cardiomyopathy, however, trials had difficulties reaching statistical significance, because of the low incidence of life-threatening tachyarrhythmias in these patients [6]. Guidelines have been evolving over the years incorporating the evidence of recent trials [9-11]. In the last decade the evidence about primary prophylactic ICD therapy produced a steep increase in the number of ICD implantations in Western Europe countries. A shift in indication from predominantly secondary to primary prophylaxis occurred due to a significantly higher number of suitable candidates, which increased further with the broadening of indications in the guidelines of 2008 [9]. However, recent reports express concerns about cost-effectiveness and the benefit-complication ratio [12-15]. The question is in which patients and in how many of them we actually prevent a sudden cardiac death. Critical articles about the sense and non-sense of ICD implantation for primary prophylaxis in certain patient populations have given rise to some doubts making it more difficult to implement and interpret guidelines accurately [16, 17]. This results in a higher number of non-evidence-based ICD implantations on one hand and a substantial number of patients eligible for ICD implantation, which are not recognised on the other.

We retrospectively collected several patient characteristics for all patients who received an ICD implant in the University Medical Center Utrecht (UMCU) over the years 2006 - 2011. In this study we give an overview of ICD implantations in this centre and present rates of, and risk factors for, appropriate and inappropriate ICD therapy, appropriate and inappropriate ICD shock and mortality. Subsequently, we evaluate the adherence to international guidelines in clinical practice and provide directions for future indications for ICD implantation.

Materials and methods

Patient population and parameters

In our tertiary centre, we retrospectively identified all new ICD implantations from 2006 until the end of 2011. In the determination of different indications, the class I or II recommendations of the 2006 and 2008 ACC/AHA/HRS guidelines were used [9, 18]. Obtained variables included patient demographics, indication for implantation, New York

Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), renal clearance, history of diabetes, documented rhythm disorders, QRS duration, medication and device settings.
The LVEF was rated by transthoracic echography, nuclear myocardial perfusion scan, or magnetic resonance imaging (MRI). If more than one modality was available, preference was given to LVEF provided by MRI. To determine renal function at baseline, serum creatinine was used to calculate the glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease (MDRD) formula [19]. History of diabetes and use of medication was also rated at baseline or at least as close as possible to the date of implantation, with a maximum of one month. To allocate the different antiarrhythmic drugs into classes, the Vaughan Williams classification was used [20]. Finally, specific information regarding device programming was retrieved from the last visit to the outpatient clinic.

Data were collected from electronic medical records and implantation reports by the first two authors. Collection of follow-up data for all patients was completed by the end of May 2012.

Implant technique and ICD programming

All devices were implanted by one of our cardiologists in the Cardiac Catheterisation Laboratory of the UMCU. No thoracotomies were performed for implantation and all patients received endocardial leads and subpectoral or subcutaneous device placement. Devices from Boston Scientific (Natick, MA, USA), Medtronic (Minneapolis, MN, USA) and St. Jude Medical (St Paul, MN, USA) were used. Programming of ventricular tachycardia (VT)/ventricular fibrillation (VF) zones, monitor zones and additional programming of antitachycardia pacing (ATP) therapy was decided by patient's cardiologist.

Definitions

Ischaemic cardiomyopathy as underlying heart condition was defined as either the presence of coronary artery disease, myocardial infarction or both. A history of atrial tachyarrhythmia was documented when patients suffered from atrial fibrillation or atrial flutter, or had experienced episodes of these arrhythmias in the past. We defined ICD therapy as delivery of either antitachycardia pacing (ATP) and/or ICD shock (cardioversion or defibrillation), which was considered appropriate when given in the presence of a ventricular tachyarrhythmia. Therapy given in the absence of a ventricular tachyarrhythmia, but triggered as a result of i.e. supraventricular tachycardia or due to technical disturbances, was defined as inappropriate ICD therapy. For the incidences of either inappropriate or appropriate ICD shock all patients who received an ICD shock were counted regardless of delivery of previous ATP. For incidences of both ICD therapy and ICD shock, each patient is counted once, regardless of the number of events in one patient.

Statistical analysis

Categorical variables were presented as absolute numbers and percentages and continuous variables were expressed as a mean with an upper and lower standard deviation. To compare differences between baseline characteristics, the independent sample t-test was used for continuous variables and the chi-square test for categorical variables.
Multivariate Cox regression analysis was used to determine independent risk factors for appropriate and inappropriate ICD therapy, appropriate and inappropriate ICD shock and mortality. Kaplan-Meier curves were constructed to determine cumulative incidence of appropriate ICD shocks. To perform these analyses, SPSS 20.0 (IBM, USA) was used.

Results

From January 2006 to December 2011, 1075 de novo ICD implantations were performed at the UMCU.

Baseline characteristics

An overview of the baseline characteristics of the 1075 patients is presented in Table 1. In 2006, 134 ICD implantations were performed; in 2011 this amount had almost doubled (229, +171%). ICDs were implanted for primary prevention in 654 patients (61%); 626 (58%) patients had ischaemic heart disease. There was a 3/1 male versus female ratio. Of all de novo implants almost 30% consisted of cardiac resynchronisation therapy – defibrillator (CRT-D) implantations. The mean age of the total population was 61±13 years, the mean LVEF 30±13%, and 78% used at least one antiarrhythmic agent, particularly beta-blockers (71%). A history of atrial arrhythmia was seen in 28% of the patients. During a mean follow-up period of 31 months (± 17 months), 155 patients died.

Ischaemic versus non-ischaemic cardiomyopathy

In Table 1, a distinction was made between patients with ischaemic cardiomyopathy (ICM) and non-ischaemic cardiomyopathy (NICM). The mean age at implant in the patients with NICM was lower (55±15 versus 66±10, $p<0.001$) and the distribution between men and women was more equal (male/female ratio of 5.3/1 versus 1.5/1). In patients with ischaemic aetiology, the mean LVEF and the GFR were significantly lower and diabetes mellitus type II more prevalent.

Primary versus secondary indication for ICD implantation

The increase in the number of ICD implantations was mainly based on the increase in primary prophylactic implants. The percentage of patients with ICM was significantly lower in the patients with an ICD implanted for primary prevention compared with secondary prevention (54% and 64%, respectively, $p<0.001$). LVEF was significantly higher in patients implanted for secondary prevention than in patients with a primary indication, 36±15% versus 27±11%, respectively ($p<0.001$).

Table 1. Overview of all de novo implantations of implantable cardioverter-defibrillators in the UMCU during the years 2006 until 2011

Characteristic	Total population (n=1075) number (%)	Ischaemic (n=626) number (%)	Non-ischaemic (n=449) number (%)	Secondary (n=421) number (%)	Primary (n=654) number (%)
Implantations					
2006/2007/ 2008/ 2009/ 2010 /2011	134/144/148/ 213/207/229	80/97/93/ 112/113/131	54/47/55/ 101/94/98	57/67/67/ 86/60/71	77/77/81/ 127/147/158
1/2/3 leads	596/165/314	379/97/150	217/68/164	281/82/58	315/83/256
Ischaemic/non-ischaemic aetiology	626(58)/449(42)	-	-	271(64)/150(36)	355(54)/299(46)*
Primary/secondary indication	654(61)/ 421(39)	355/271	299/150*	-	-
Demographics					
Age(years, mean, SD)	61±13	66±10	55±15*	62±14	61±13
Sex (male/female)	796(74)/279(26)	526(84)/100(16)	270(60)/179(40)*	337(80)/84(20)	459(70)/195(30)*
Clinical parameters					
LVEF (%; mean, SD)	30±13	28±10	33±17*	36±15	27±11*
NYHA class (I/II/ III/IV)	75/194/267/14	43/141/140/4	32/53/127/10	29/45/39/4	46/149/228/10
QRS duration (ms, mean, SD)	127±33	125±29	130±37*	120±30	132±34*
Diabetes mellitus II	204(19)	156(25)	48(11)*	66(16)	138(21)*
GFR (mean, SD)	67±22	65±20	72±23*	71±22	65±21
History of atrial tachyarrhythmia	300(28)	174(28)	126(28)	125(30)	175(27)
Loss to follow-up	116(11)	67	49	63	53*
Medication at baseline					
Antiarrhythmic agent	842(78)	520	322*	317	525*
Class II #	705(66)	436	269*	452	253
Class III #	102(9)	88	53	59	82

Mean follow-up period 31±17 months. *p<0.05, # alone or in combination with another antiarrhythmic drug. SD=standard deviation, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association, OHCA=out-of-hospital cardiac arrest, GFR= glomerular filtration rate (MDRD).

ICD settings

A single zone (VF only) was installed in 7% of the patients, two zones (VT + VF) in 80% and three zones (VT-1, VT-2 and VF) in 10%. In the VT-1, VT-2 and VF zone the mean rates installed were 180±13, 188±12, and 226±17 beats/min, respectively. In the remaining 3%, data of the ICD settings were not available. In approximately 90% ATP was programmed (either as single therapy or prior to shock therapy). VT/supraventricular tachycardia (SVT) discrimination algorithms were programmed in the VT zones in all patients. No major differences between monitor and therapy zones were observed between the different subpopulations of patients that experienced ICD therapy.

ICD therapy

In the total population of 1075 patients, 227 patients (21%) received at least one episode of appropriate ICD therapy (149 appropriate ICD shocks (14%)) during the mean follow-up period of 31±17 months. Inappropriate ICD therapy was seen in 54 patients (5%), 33 patients (3%) received an inappropriate ICD shock.

Cumulative incidence of appropriate ICD shock was 7% at one year, 16% at three years and 23% at five years. When corrected for several baseline characteristics by multivariate Cox regression analysis, a secondary indication, ICM, decreased LVEF (≤25%) and the male gender were independent predictors for appropriate ICD shock, with hazard ratios (HR) of 1.8 (95% CI: 1.3-2.5; p=0.001), 1.6 (95% CI: 1.1-2.3; p=0.023), 1.6 (95% CI: 1.2-2.3, p=0.004) and 2.3 (95% CI: 1.4-3.8; p=0.001), respectively (Figure 1).

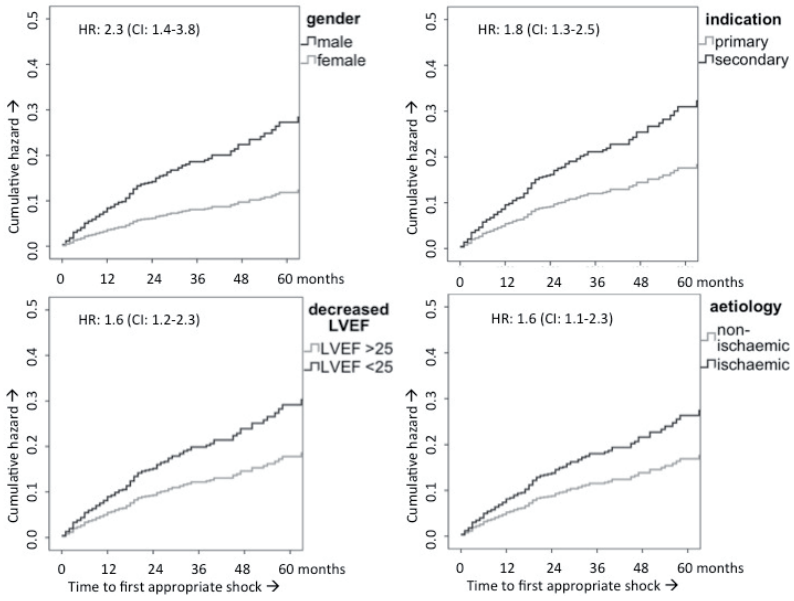

Figure 1. Cumulative hazard for appropriate shock over time divided by different subpopulations

Gender showed to be the most important risk factor for appropriate ICD shocks, with men having a more than doubled risk for appropriate ICD shock. When we only analysed patients who had an ICD implanted for primary prophylaxis, the incidences of appropriate ICD therapy and appropriate ICD shock were 17% (109 patients) and 10% (68 patients), respectively. Ischaemic aetiology and decreased LVEF (<25%) remained independent risk factors for appropriate ICD shock.
A history of atrial tachyarrhythmia was a predictor for inappropriate ICD shock (HR 4.8, 95% CI: 2.4-9.7, p<0.001).

Mortality

Of the 155 patients who died, 50 patients (5%) died within the first year after implantation. Over the follow-up period of 31±17 months, 104 patients (10%) died without receiving prior appropriate ICD therapy.
The yearly mortality rate was 5.6%. The most important risk factors for mortality were: decreased GFR (≤60) (HR 2.3, 95% CI: 1.6-3.2; p<0.001), a decreased LVEF (≤25%) (HR 2.1, 95% CI:1.5-3.0; p<0.001) and the male gender (HR 1.9, 95% CI: 1.3-3.0; p=0.004). In patients with a primary indication, a prolonged QRS duration (>130 ms) was an additional risk factor for mortality. In patients with ICM, diabetes mellitus type II, older age (>70 years) and decreased LVEF (<25%) were predictive of mortality, while the use of beta-blockers decreased the risk of mortality. In the non-ischaemic population, decreased GFR (<60) and decreased LVEF (<25%) were the most important risk factors. At baseline, decreased GFR (<60), non-ischaemic aetiology and a history of AF were predictive of mortality within one year after primary prophylactic ICD implantation.

Discussion

Interpretation of and adherence to guidelines

Baseline characteristics
The demographics of our patient population are comparable with the characteristics of patients enrolled in the large randomised controlled trials [3, 6, 8]. Since the indication for ICD therapy is determined on the basis of these large trials, this seems a logical consequence, but it is worth mentioning that patients participating in randomised controlled trials may not be representative of patients typically seen in clinical practice. Only the incidence of a history of atrial tachyarrhythmias was substantially higher in our population since this was an exclusion criterion in most of these trials.
When we divide our population on the basis of aetiology, we observed that patients with ICM were older, predominantly male and had more comorbidities. The differences seen between LVEF in the ischaemic and non-ischaemic group can be explained by the fact that in a substantial number of the patients with NICM the indication for ICD implantation was

not solely based on LVEF. A large proportion of patients with NICM have an underlying heart disease other than dilated cardiomyopathy, for whom risk factors such as unexplained syncope or hereditary taint (e.g. ARVC, LQTS) are more decisive when considering ICD implantation. Furthermore, NICM is more frequent in younger individuals and is associated somewhat more often with the female gender [21]. In our study we observed a more or less equal distribution between the two genders and a lower age at implant in the non-ischaemic population. The patients with a hereditary heart disease, such as ARVC, often receive an ICD early in life, which can attribute to the latter.

Increase in the number of implantations

As expected we observed an increase (171%) in the number of implantations over the years 2006-2011. As mentioned before, this increase in (primary indications for) implantations can be explained by the implementation of large randomised controlled trials following the latest guidelines of 2008, which led to a broadening of indications [9].

Although we see a steady increase in implantations, we would have expected an even larger increase. On one hand, we could explain the limited increase by lack of adherence to the guidelines in clinical practice, but it can also represent a critical view on evidence and interpretation of these concomitant guidelines. Therefore, knowledge of current guidelines is crucial, not only to identify those eligible for ICD implantation but also those exempt from an indication [22, 23].

In the following paragraphs we will reflect on the incidences of inappropriate and appropriate ICD therapy and inappropriate and appropriate ICD shock and mortality. We should be careful about interpreting the absolute numbers since certain variables are time dependent. For example, a larger proportion of patients who received an ICD for primary prophylactic reasons received the ICD in the last couple of years of this study; therefore the follow-up of these patients will be relatively shorter than for the patients who received an ICD for secondary prophylaxis. With the multivariate Cox regression analysis, we corrected for this by taking the time to the (first) event into account.

Appropriate ICD therapy

In the current study, 227 (21%) patients of our total population received appropriate ICD therapy after a mean follow-up of 31±17 months, which corresponds to an annual appropriate ICD therapy rate of 8.1%. This number compares well with other registries [24, 25]. We found an appropriate ICD shock rate of 14%. A secondary indication, ischaemic aetiology, a decreased LVEF and a male gender were identified as independent risk factors for appropriate ICD shock. The annual appropriate ICD shock rate of 5.4% compares well with the findings of an earlier study by Van Welsenes et al., performed in Leiden, the Netherlands, over the years 1996-2008.[24] In their population of 2134 patients with both primary and secondary indication, they found an annual appropriate ICD shock rate of 5.9%. The appropriate ICD shock rate in our primary prophylactic

population was lower with an annual appropriate ICD shock rate of 4%. In the SCD-HeFT trial (patients with a primary indication and both ischaemic and non-ischaemic heart disease) an annual appropriate ICD shock rate of 5.1% was seen. Follow-up data from the DEFINITE trial (patients with a primary indication and non-ischaemic heart disease) showed an incidence of 7% of appropriate ICD shock after 29 months of follow-up (annual appropriate ICD shock rate 2.9%). The incidence of appropriate ICD shock in our patients implanted for primary prophylaxis and non-ischaemic heart disease was 4% (annual appropriate ICD shock rate of 1.7%). The somewhat higher 'appropriate' ICD shock rates in both the SCD-HeFT trial as well as the DEFINITE trial could be explained by the ICD settings. In both trials ICDs were programmed with shock therapy only (no ATP) at a single zone of >187 beats/min and >180 beats/min, respectively. After three years of follow-up of the MADIT II study, which consisted of patients with a primary indication and ischaemic heart disease, 20% of their patients experienced an appropriate ICD shock at least once [26]. In our primary prophylactic patients with ischaemic heart disease this rate was found to be 16% after approximately 2.5 years, which might be explained by the shorter follow-up period and by the unselected nature of our patient population in contrast to the large prospective trials such as MADIT II.

When we only select the patients who received an ICD for primary prophylaxis, a lower incidence of appropriate ICD therapy and ICD shocks was seen in the subpopulation with NICM compared with the ischaemic group. The DEFINITE and SCD-HeFT failed to reach statistical significance for the benefit of ICD implantation for primary prophylaxis in the subset of patients with NICM. Nevertheless, a trend toward reduced mortality was seen [3, 6]. It should be noted that the DEFINITE trial demonstrated significant effectiveness of ICD therapy in NICM patients for preventing death from cardiac causes, but not all-cause death. The lack of statistical significance is probably due to low mortality in the NICM population that was also the reason for prematurely stopping the AMIOVIRT and CAT trial [27, 28]. Furthermore, a sub-analysis of the SCD-HeFT trial showed a relatively high mortality due to pump failure instead of arrhythmic death in patients with non-ischaemic cardiomyopathy and NYHA functional class III. This implies a relatively small absolute mortality benefit, and therefore a higher number needed to treat (25 versus 18 ICD implantations to prevent one death in two years for NICM patients and ICM patients respectively) [29]. Furthermore, if these patients receive appropriate ICD therapy, the question is: 'how many life years can be gained due to appropriate ICD therapy?' In patients with end-stage heart failure recurrent VTs can be a sign of progression of the impaired LV function. Although the ICD can successfully treat ventricular tachyarrhythmias, it cannot prevent death from pump failure. It is also important to realise that ICD shock, and certainly ICD therapy, cannot be replaced 1:1 by a prevented sudden cardiac death. Multiple trials have shown that the incidence of ICD shocks is substantially higher than the incidence of sudden cardiac death.

As described in our results the male gender was one of the independent risk factors for appropriate ICD therapy and ICD shock in our population. When we divide the population based on aetiology or indication, patients with ischaemic heart disease and patients with an ICD implanted for secondary reasons received the most appropriate ICD shocks. The male gender was more common in those subpopulations. However, when we corrected for these variables, males still had a higher probability to receive an appropriate ICD shock (HR 2.3, 95% CI: 1.4-3.8; p=0.001). The registry of Wilson et al. and the follow-up study of MADIT II also found a higher number of men in their appropriate ICD shock population [26, 30]. Moreover, the long-term follow-up study of the MADIT II cohort showed a smaller benefit of ICD implantation in women [31]. Differences in repolarisation and in arrhythmogenic substrate are suggested to cause this difference in benefit of ICD implantation [32-34]. Risk factors for appropriate ICD therapy could therefore be different in the female population. Since some studies also reported a higher complication rate in females, it could be of importance to further elucidate whether this should have consequences for patient selection and risk stratification [35].
When we exclude patients who received an ICD for secondary prophylaxis from the analysis, aetiology and decreased LVEF remained independent risk factors for appropriate ICD shock. Only gender was no longer an independent risk factor though the incidence of appropriate ICD shock in females was significantly lower than in males in patients with an ICD implanted for primary prophylaxis. The low number of females and subsequent low number of events in this subpopulation probably caused the analysis to be statistically underpowered. This supposition was supported by the fact that when we analysed the risk factors for appropriate ICD therapy (higher number of events), gender was an independent risk factor for appropriate ICD therapy.

Inappropriate ICD therapy

Inappropriate ICD therapy, and inappropriate ICD shock in particular, leads to an impaired quality of life and psychological and psychiatric effects [36, 37]. As a matter of course inappropriate ICD therapy must be prevented to the extent possible. In our population we found an inappropriate ICD shock rate of 3% after 31 ± 17 months of follow-up. This number is much lower compared with other registries or the landmark trials. In the study by Van Welsenes et al., 14% of their patients experienced an inappropriate ICD shock [24, 38]. The follow-up studies of SCD-HeFT, DEFINITE and MADIT II found inappropriate ICD shock rates of 10%, 10% and 11.5% after 45, 29 and 20 months of follow-up, respectively [3, 39, 40]. In the MADIT II study and the registry of Van Welsenes et al. prior atrial fibrillation was predictive of inappropriate ICD shock [24, 38, 40]. Our study confirms prior atrial tachyarrhythmia to be a risk factor for inappropriate ICD shock (HR 4.8, 95% CI: 2.4-9.7, p<0.001) and also patients with NICM received a higher number of inappropriate ICD shocks (HR 2.1, 95% CI:1.0-4.1, p<0.038). In other studies a

higher incidence of inappropriate ICD shocks was seen in younger patients and patients with renal dysfunction [40, 41]. Regarding the low incidence of inappropriate ICD shock in our population, it is important to emphasise that the number of inappropriate ICD shocks is greatly dependent on device settings. At the UMCU our philosophy is to program the device only for the treatment of fast VT or VF (life-threatening tachyarrhythmias); slow VTs (haemodynamically stable VTs) were treated by VT ablation or pharmacologically. Furthermore, SVT/VT discriminators are enabled in the VT zones of all patients. The more than double inappropriate ICD shock rate in the SCD-HeFT trial, for example, can be related to the fact that all ICDs were programmed with shock therapy at a single zone of >187 beats/min without discrimination between VT and SVT [3].

Risk factors for mortality

One prerequisite of ICD implantation is a life expectancy of more than 1 year. Furthermore an ICD will only be feasible if appropriate ICD therapy is delivered before the patient dies. Estimating risk at death is therefore useful and often already an important consideration in clinical practice. In our population, 50 patients died in the first year after implantation, and therefore, in retrospect, were not eligible for ICD treatment. Furthermore, 10% of the patients died without receiving appropriate ICD therapy. Different factors were associated with death in the different subpopulations. The risk factors we found were comparable with other registries [42, 43]. In our study impaired renal function was the most important risk factor for mortality.

Study limitations

In this analysis there was no control population available. Hence, we could not compare the adherence to guidelines in patients with and without ICD implantation. Furthermore, we performed a retrospective study, which entails some disadvantages. All the analysed data were retrieved from electronic medical records. Some information was not recorded in the medical records of all patients, such as NYHA class and LVEF. We noticed that in the 58 cases in which the quantification of LVEF in percentages was lacking, the LVEF was predominantly described as normal or good. This could probably cause bias. To calculate the average LVEF we used 1017 cases in which LVEF was quantified as a percentage. For the multivariate Cox regression analysis, in which we used LVEF <25 % as a variable, we used 41 more cases (1058). In these 41 cases we could be certain, based on the echocardiogram quantification and medical records, that these patients had to have an LVEF >25%. In this way the probable bias that can occur based on the abovementioned is avoided.

We collected recent data, which led to a relatively short follow-up period. The loss of follow-up was mainly caused by the fact that some patients, mostly elderly, return to their own cardiologist in the referral hospital for routine check-up.

ICD implantation: where do we go from here?

Decreased LVEF has shown to have an inverse relationship with cardiac mortality and approximately 50% of the cardiac deaths are a result of sudden death. Since no other reliable methods are available for identifying in advance those patients who are more likely to die from sudden death, LVEF is considered a valuable criterion for ICD implantation [1, 3, 44].

Due to trial designs, left ventricular dysfunction has developed into a key determinant for the selection of candidates for prophylactic ICD implantation, even though a causal relation between LVEF and the pathophysiology of ventricular arrhythmias is not clearly demonstrated. Furthermore, prior research has shown that the largest proportion of non-survivors of out-of-hospital cardiac arrest had an LVEF of 30% or higher prior to the event, and would not have been eligible for prophylactic ICD implantation [45, 46]. The relative risk for ventricular tachyarrhythmias in people with a normal LVEF is much lower and the number to treat very high. In our population the mean LVEF of patients with a secondary indication was 36 ± 15%, comparable with the three large secondary prevention trials which presented a mean LVEF after out-of-hospital cardiac arrest of 32%-45% [2, 5, 7]. Note that the patients with an ICD implanted for secondary prophylaxis had a significantly higher number of appropriate ICD shocks. On the other hand, impaired LVEF (<25%) was an independent risk factor for appropriate ICD therapy and ICD shock in the overall population and also in the subgroup of patients implanted for primary prophylaxis.

As we can see in our population, patients with NICM, patients with an ICD for primary prophylactic reasons, and women experienced the lowest number of appropriate ICD shocks, and therefore have the least benefit from ICD implantation. At the moment, ICD implantation in these groups is mainly based on the LVEF. Improvement of selection of eligible patients by electrophysiological parameters has been studied, but these studies often did not find a hazard ratio greater than two. Furthermore, electrophysiological tests are not feasible in all candidates for prophylactic ICD implantation [47, 48]. The Alternans Before Cardiac Defibrillator trial (ABCD trial [49]) was the first to suggest to combine different electrophysiological parameters to increase the predictive power to guide ICD therapy. The large prospective European multicentre study, EUTrigTreat, embraces this idea. The study enrols patients with standard indications for ICD implantation in a population consisting of both ischaemic and non-ischaemic heart disease. It is an observational trial with the aim to accurately stratify ICD patients, who are at risk for ICD shock and mortality using traditional risk markers as well as genetic markers. It compares the predictive power and temporal changes of various invasive and non-invasive electrophysiological tests such as programmed ventricular stimulation (PVS), T-wave alternans (TWA), beat-to-beat variability of repolarisation quantified as short-term variability (STV), heart rate variability (HRV) and

heart rate turbulence (HRT) to determine which patients will be at risk for life-threatening arrhythmias and will benefit of ICD implantation [50, 51].

Conclusion

As in all Western European countries we experienced an increase in the number of ICD implantations mainly based on the increase in primary prophylactic implantations. The rate of appropriate ICD shocks in our unselected population corresponds to the large clinical trials, which confirms the benefit of ICD implantation when following current guidelines. Nonetheless a significantly lower rate of appropriate ICD shocks were observed in patients implanted for primary prevention, patients with non-ischaemic cardiomyopathy and women. This implies a lower ICD benefit or at least a higher number needed to treat in these subpopulations. It would be lucrative to improve the risk stratification and patient selection for ICD implantation to accomplish optimal clinical benefit and cost-effectiveness. The prospective European multicentre study, EUTrigTreat, might contribute to this by a more patient-tailored risk stratification based on electrophysiological parameters. In our population few patients (only 3%) received an inappropriate ICD shock; we attribute this to adequate ICD programming and alternative treatment of slow VTs.

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CHAPTER 3

Beat-to-beat variability of repolarization as a new biomarker for proarrhythmia in vivo

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Heart Rhythm. 2012;9(10):1718-1726

Abstract

Pharmacological safety evaluation of (pro) drugs includes cardiac safety assessment of proarrhythmic liability in healthy tissue with emphasis on the rapid component of the delayed rectifier (I_{Kr}). The lack of 1) an arrhythmic endpoint, 2) tests in remodeled, predisposed tissue, and 3) testing chronic drug influence on channel trafficking, impairs on the drawn conclusions of these assays regarding drug safety. Moreover, the currently used human ether-à-go-go-related gene assays, action potential duration, prolongation in multicellular preparations, or the QT-interval have significant shortcomings in their prediction of an increased risk for drug-induced torsade de pointes arrhythmia.

In this review, it will be proposed that beat-to-beat variability of repolarization quantified as short-term variability can 1) discriminate between safe and unsafe drugs even under predisposed and highly arrhythmogenic conditions despite accompanying QT prolongation, and 2) identify the individual at risk for subsequent arrhythmic events.

Introduction

Pharmacological safety evaluation of (pro) drugs includes cardiac safety assessment of proarrhythmic liability with emphasis on blockade of the rapid component of the delayed rectifier (I_{Kr}) and the risk of the drug to induce torsade de pointes (TdP). TdP generally occurs in the setting of prolonged ventricular repolarization, reflected by a prolonged QT-interval on the surface ECG. The list of pharmaceuticals associated with TdP steadily increases and includes antiarrhythmics, other cardiovascular drugs as well as non-cardiovascular drugs [1] (for further information see QT drug lists www.azcert.org).

The current international guidelines, ICH-E14 and ICH-S7B, provide the recommendations regarding cardiac safety testing of newly developed drug [2,3]. Remarkably, both guidelines advocate testing of the effect of repolarization in healthy tissues, animals, and volunteers. Neither guideline recommends assessment of true proarrhythmic risk, nor testing in animal models with cardiac remodeling, including those with a reduced repolarization reserve [4]. This approach may lead to several problems: drugs designated to be safe could still induce dangerous arrhythmias in vulnerable patients groups. On the other hand, a drug with known I_{Kr}-blocking properties does not necessarily have to be associated with induction of TdP. From a drug development point of view, clinical registration of promising new drugs will thus be greatly delayed or even aborted, solely based on a perceived risk of TdP. In addition, effects of new drugs on other ion channels or channel trafficking in general are not fully incorporated.

In attempts to address these issues, huge efforts have been put into the development of various proarrhythmic animal models mimicking the vulnerable predisposed patient. Furthermore, numerous biomarkers have been proposed to possess a higher predictive value regarding proarrhythmic risk than repolarization prolongation. Beat-to-beat variability of repolarization (BVR), quantified as short-term variability (STV), is such a "surrogate parameter" that reports the temporal variability in repolarization duration between consecutive beats [5,6]. This biomarker has primarily been used in dog models, however initial studies on clinical implementation are promising.

This article presents an overview of the current experimental and clinical data, mainly emphasizing the question of whether STV enables correct prediction of a drugs's proarrhythmic potential. In this respect, a drug is defined safe or unsafe based on the arrhythmogenic outcome in the anesthetized dog with chronic complete atrioventricular block (cAVB); this designation does not apply for other safety issues. Second, the potency of baseline STV in defining individual risk for TdP will be explored.

TdP and surrogate parameters

TdP: Lessons from the congenital long QT syndrome

Congenital Long QT Syndrome (LQTS) is a heterogeneous disease, with different gene mutations affecting ionic currents of many different classes. Whereas mutations can affect

ion conduction directly, mutations can also result in aberrant intracellular channel trafficking [7]. In fact, the majority of the mutations found in LQTS2 patients affected intracellular trafficking [8]. Although clinically manifest TdP is relatively uncommon among LQTS patients, it indicates that TdP may occur by pathological mutations in different ion channel types. In contrast, reduction of I_{Kr} seems to be the central property in drug-induced TdP as nearly all of these drugs block I_{Kr} [4,9-11]. However, in analogy to the multiple channel basis of TdP occurrence in forms of congenital LQTS, it seems not unlikely that drugs that affect other cardiac ion channels may induce TdP, either by themselves or in combination with other drugs.

Although drug-induced TdP is a major point of concern in drug development, its clinical incidence is rare: less than 1 case per 10,000 or 100,000 exposures with non-antiarrhythmics [1,10]. Consequently, the first identification of a drugs' proarrhythmic potential would occur most likely during post marketing surveillance, when the number of patients exposed exceeds the ten thousands. This situation asks for potent biomarkers that can estimate drug-associated risk in much earlier performed tests. The QT-interval has been used for decades as a biomarker reflecting such proarrhythmic risk. Nonetheless, the predictive value of a prolonged QT-interval has been proven to be questionable. Similar drug-induced QT prolongation does not result in similar TdP incidence [12], and successful antiarrhythmic treatment is possible without an accompanying decrease in corrected QT-interval (QT_C) values [13-16]. Similar conclusions were made in congenital LQTS [17-19]. Since both I_{Kr} block and QT prolongation cannot be related to TdP with enough sensitivity and specificity [20,21], an independent task force concluded that human ether-à-go-go-related gene/I_{Kr} blockade and QT prolongation by themselves are no strong predictors of proarrhythmic risk [10]. Besides difficulties with the predictive value of a prolonged QT, the QT-interval itself seems to be a difficult parameter to measure adequately [22-25]. Both congenital and acquired LQTS point out that a similar exposure to culprit risk factors does not result in clinically manifest TdP consistently. Such individual differences in TdP propensity can be explained by the concept of repolarization reserve [26]. In healthy hearts, multiple mechanisms exist to ensure orderly and rapid repolarization. Therefore, reduction or block of one of these mechanisms will not directly lead to unstable repolarization. However, when challenged with multiple hits, the repolarization reserve can be compromised to such an extent that potentially dangerous arrhythmias can develop. In such conditions, insufficient repolarization strength will make repolarization labile. Biomarkers that capture instability of repolarization can include all temporal assessments irrespective of the algorithm used.

Over the years, other tests have been proposed for individual risk stratification (T-wave alternans, QT variability index) or for drug safety screening (triangulation, reverse-use dependency, instability, and dispersion), never for both. The T-wave alternans test detects subtle alterations in T-wave morphology on the ECG [4,27]. Although this technique provides a clinically applicable non-invasive measure of arrhythmogenic vulnerability, it cannot be detected by visual inspection of the ECG and the heart rate has to be elevated

to 100 beats/min. The measurement itself is derived from 3 orthogonal leads over at least 128 beats. This technique has been primarily used in the clinical setting to predict arrhythmias and sudden cardiac death among several patient populations [4,27]. Another biomarker that has mainly been applied in the clinical setting is the QT variability index [4,28]. An ECG recording of 256 seconds is needed, and the QT variability index is calculated by taking the logarithm of the ratio between normalized QT-interval variance and heart rate variance. A biomarker that can be used to assess lability of repolarization in preclinical drug evaluation is the triangulation, reverse-use dependency, instability, and dispersion concept [4,29]. It has been extensively used in the Langendorff-perfused rabbit hearts and was found to be a strong proarrhythmic predictor [29].
Although these biomarkers can reliably assess variability of repolarization, none of them includes direct beat-to-beat information or is suitable for both risk stratification and drug safety screening. Therefore, we have developed the concept of BVR [4].

BVR: Quantified as STV

BVR includes only those methods that assess changes in repolarization duration on a consecutiveness basis. BVR can simply be assessed on the basis of dimensions of a so-called Poincaré plot. Here, repolarization duration of a predetermined number of consecutive beats is plotted against the duration of each previous beat (Figure 1A). Each deviation from the line of identity, a diagonal starting from the origin that per definition indicates that each action potential is of equal duration, reports the occurrence of a difference in repolarization time between 2 subsequent beats. To compare BVR, for example in time, between subjects, or different drugs, BVR can be quantified as STV. STV, expressed in ms, represents the mean orthogonal distance to the line of identity and is calculated according to the formula $STV=\sum|D_{n+1}- D_n|/[N\times \sqrt{2}]$ where D represents repolarization duration (e.g. QT, QT_C or APD) and N is the total number of beats [5,6]. In other words, it reports the average deviation of repolarization time for a number of beats from the line of identity. In a series of beats with high repolarization lability, STV levels are higher than in a series of low lability.

STV after drug administration: Safe or unsafe drug

STV in cardiac safety testing in dogs

We previously developed and applied the concept of BVR in safety testing by using the dog with chronic atrioventricular block (cAVB dog). In this model, bradycardia associated with ventricular volume overload results in time (weeks) into contractile, structural, as well as electrical remodeling, which is associated with an increased propensity for drug-induced TdP [30,31]. The effects of the known proarrhythmic drug *d*-sotalol (Figure 1B) and amiodarone, which is rarely associated with TdP (Tables 1 and 2), were compared [5]. It was shown that despite similar QT prolongation, STV demonstrated an increase only when the animal became susceptible for TdP after *d*-sotalol (Figure 1B; Table 2). Of note is

that of all liability parameters studied, STV derived from left ventricular monophasic action potentials (STV_{LV}) was most closely correlated with TdP induction [5,44]. Over the years, this concept has been further validated in the cAVB dog model by using intravenously administered dofetilide as the gold standard in order to evaluate numerous drugs. In general, the administration of safe (pro) drugs is accompanied by an unchanged STV sometimes despite pronounced QT lengthening (amiodarone, moxifloxacin) whereas pro-arrhythmia is associated with elevated STV values (Tables 1 and 2) [5,13,14,33,34,45]. Interestingly, drug dosing-dependent TdP occurrence (eg, NS-7, sertindole) is reflected in STV behavior but not in the QT-interval. Furthermore, drugs with antiarrhythmic properties may lower baseline STV values.

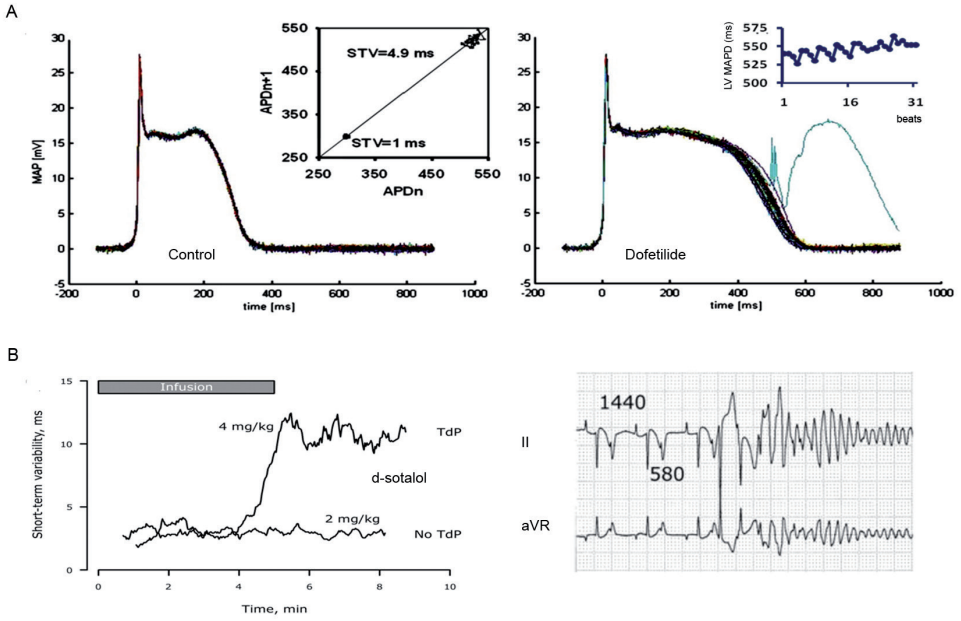

Figure 1. The concept of beat-to-beat variability quantified as STV in predicting drug-induced TdP has been illustrated in 4 plots. A: Thirty consecutive action potentials are depicted under control (left panel) and after dofetilide administration just prior to the first ectopic beat (right panel). In control, each APD corresponds to the previous APD resulting in a low STV value of 1, whereas dofetilide increased STV considerably to 4.9 (see insert left panel). The insert in the right panel shows the temporal behavior of the 30 consecutive APDs (adapted from Oros et al [30]). B: Testing of 2 dosages of d-sotalol in the same cAVB dog resulted in TdP only after administration of the higher dosage (left panel). STV behaves accordingly: A stable STV is recorded when TdP cannot be induced, while the occurrence of TdP is preceded with an increase in STV. An example of a d-sotalol induced TdP is shown in the right panel (adapted from Thomsen et al [5]): the RR interval (1440 ms) and QT interval (580 ms) just before TdP are depicted. APD = action potential duration; cAVB = chronic atrioventricular block; LV = left ventricle; MAP = monophasic action potential; MAPD = monophasic action potential duration; STV = short-term variability; TdP = torsades de pointes.

Table 1. Behavior of STV and QT_C after administration of safe drugs.

Dog model	Drugs	STV (ms)		QTc/MAPD (ms)		TdP incidence (%)	Reference
		Control	Drug	Control	Drug		
cAVB	Amiodarone	2.4±0.2	2.4±0.4	310±25	435±70*	0	5
	Amlodipine	3.8±0.6	5.0±0.7	~350	~375	0	32
	AVE0118	2.1±0.4	2.1±0.3	384±49	398±64	0	33
	Azithromycin	2.2±0.6	2.3±0.5	369±36	345±57	0	34
	Candesartan	4.1±0.8	5.2±0.9	~375	~375	0	32
	Cilnidipine	4.2±1.2	2.2±0.4†	~375	~325†	0	
	Flunarizine	1.5±0.6	1.0±0.5†	299±44	277±36	0	13
	Lidocaine	1.4±0.3	1.2±0.2	382±34	318±20†	0	14
	Moxifloxacin	2.0±0.9	3.0±1.3	394±86	515±89*	0	34
	Ranolazine	1.6±0.3	2.0±0.3	362±49	410±49	0	14
	Verapamil	1.3±0.4	1.4±0.6	332±68	328±34	0	13
Conscious cAVB	Amiodarone	3.6±0.2	3.5±0.3	253±20	N.A	0	35
	Moxifloxacin	4.5±0.8	5.9±0.6*	261±10	=	75	34,36
Conscious SR dogs	Verapamil low	3.4±0.6	3.0±0.4	237±4	=	-	37
	Verapamil high	3.7±1.1	3.9±0.8	233±3	=	-	

STV has been derived from either QT or RV/LV MAP. *Significant increase vs control. †Significant decrease vs control. cAVB = chronic atrioventricular block; LV = left ventricle; MAP = monophasic action potential; MAPD = monophasic action potential duration; QT_C = corrected QT interval; RV = right ventricle; SR = sinus rhythm; STV = short-term variability; TdP = torsades de pointes.

Apart from the anesthetized, sensitized cAVB dog model, STV has also been implemented in various other dog models ranging from conscious cAVB dogs to healthy sinus rhythm dogs [32,35-37,39-43]. In conscious cAVB dogs, the positive relation between STV derived from the QT-interval (STV_{QT}) increase and drug-induced proarrhythmia appears to be present, although much higher dosages of the orally administered drugs bepridil and terfenadine are necessary [35,39]. The relationship between STV and TdP is problematic in healthy sinus rhythm dogs; the lack of an arrhythmic endpoint in these animals makes detection of unsafe drugs difficult. In these non-remodeled, healthy hearts, TdP could never be induced with a single drug challenge. In accordance, STV does not increase (significantly). Only following the application of multiple drugs, could TdP be induced that was associated with a clear increase in STV_{QT} in conscious or anesthetized dogs. Furthermore, on the basis of STV_{QT} levels, one can discriminate between animals with and without TdP [40,42].

Table 2. Behavior of STV and QT_c after administration of unsafe drugs.

Dog model		Drugs	STV (ms)		QTc/MAPD (ms)		TdP incidence (%)	Reference
			Control	Drug	Control	Drug		
cAVB		d-sotalol low	3.5±1.5	5.5±1.6	393±39	457±49*	25	5
		d-sotalol high	3.0±0.7	8.6±3.8*	378±57	464±74*	75	
		Dofetilide	1.8±0.7	3.8±1.5*	418±75	607±139*	100	34
		Dofetilide	1.8±05	4.5±1.5*	355±35	492±53*	100	13
		Dofetilide	2.1±0.4	4.6±1.8*	384±49	481±103*	100	33
		Dofetilide	1.2±0.1	3.1±0.6*	334±27	525±34*	100	15
		NS-7 low rate	2.1±0.2	2.5±1.0	350±10	410±55*	0	38
		NS-7 high rate	2.6±0.3	6.0±1.4*	365±50	420±40*	50	
		Sertindole low	2.3±0.8	3.2±1.1	353±51	416±66*	0	15
		Sertindole high	2.3±0.7	5.1±2.1*	336±48	427±66*	78	
Conscious cAVB		Bepridil low	5.0±0.6	5.2±0.2	273±6	N.A	0	35
		Bepridil high	5.1±0.4	8.1±0.8*	282±16	N.A	75	
		Terfenadine	5.2±0.2	7.2±0.4*	224±15	↑	83	39
LQT1 SR anesthetised dog		HMR-1556	1.7±0.2	2.2±0.7	224±8	289±9*	0	40
		HMR-1556 + Isoproterenol	1.7±0.2	4.9±0.9*	224±8	292±13*	100	
Anesthetised SR dogs		Dofetilide	0.9±0.1	4.2±0.5	260±3	287±9*	0	41
Conscious SR dogs		Dofetilide high	6.5±1.5	10.4±1.6	236±5	↑*	-	37
		Dofetilide low	6.4 ±2.0	10.9±2.5	237±6	↑*	-	
		Dofetilide + HMR-1556	~5.9	~10.4*	~275	~360*	75	42
		HMR1556 + dofetilide	~6.4	~9.6	~285	~360*	50	
		Sotalol low	6.5±2.5	5.0±0.7	239±4	=	-	37
		Sotalol high	6.2±1.1	7.6±1.4	239±11	↑*	-	
SR dogs	Conscious	d,l-sotalol	4.0±2.6	3.6±1.3	254±15	296±21*	0	43
	Anesthetized	d,l-sotalol	3.0±2.8	5.4±3.6	337±35	427±64*	0	

STV has been derived from either QT or RV/LV MAP. *Significant increase vs control. cAVB = chronic atrioventricular block; LV = left ventricle; MAP = monophasic action potential; MAPD = monophasic action potential duration; QT_C = corrected QT interval; RV = right ventricle; SR = sinus rhythm; STV = short-term variability; TdP = torsades de pointes.

As can be appreciated from Tables 1 and 2, baseline (control) STV measurements differ considerably when comparing data from different animal models and/or laboratories, which is probably related to methodological differences and inherent factors of the respective model. For example, in our laboratory, the methodology to measure STV from different entities has been improved considerably over the years, resulting in lower

values in baseline and after administration of the drug. Furthermore, in the cAVB dog, STV determination based on QT-interval is hampered by those P waves that appear in the end of the T wave. When skipping such beats in the analysis, strict beat-to-beat information is lost. Gradual or (semi)abrupt change in heart rate forms another important factor that should be taken into consideration. As might be expected, STV, which is an absolute measure expressed in ms, increases also when cycle length, and thus APD, increases (Figure 2A). We consider APD dependent STV increase not to depend on enhanced repolarization lability, but on increased absolute levels of APD variation. As the administration of drugs lengthens the APD, STV may increase slightly in the absence of any proarrhythmic event (Figure 2B). STV values derived from conscious dogs are most likely influenced by heart rate variability due to respiration, which explains the higher baseline STV_{QT} values in conscious dogs as compared to their anesthetized counterparts [35,37,39-44,46]. Moreover, the presence of ectopic beats or other factors that result in large variations in cycle length will increase heart rate variability and thus STV. From these considerations, it will be clear that there is still need for improvement of determining and interpretation of BVR and its underlying components.

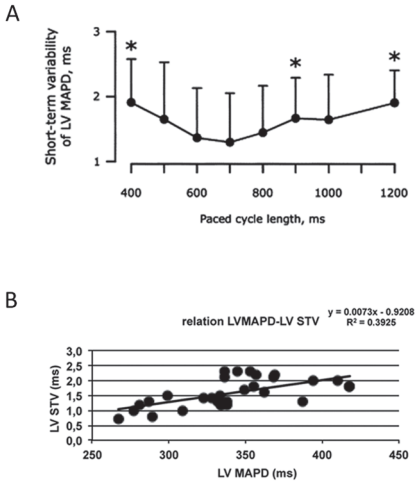

Figure 2. The relation between STV-frequency (A) and STV-APD (B) is illustrated. **A**: In anaesthetized cAVB dogs, the STV cycle length dependency is shown going from 400 to 1200 ms (x-axis). At the physiological cycle length of 600-700, STV is lowest. It increases both in bradycardic as tachycardic circumstances (adapted from Thomsen et al [15]). **B**: The STV-APD relation is calculated for a number of studies in which the administered drugs did not induce any proarrhythmic event. Please note that an increase in LV MAPD from 270 to 420 ms is accompanied by a slight increase in STV from 0.7 toward 2.3. APD = action potential duration; cAVB = chronic atrioventricular block; LV = left ventricle; MAPD = monophasic action potential duration; STV = short-term variability.

STV in cardiac safety testing in rabbits

Another widely used animal model in cardiac safety pharmacology is the anesthetized methoxamine-sensitized rabbit model. The use of STV as a surrogate parameter in this model is limited, and the results obtained are conflicting. The group from AstraZeneca R&D who originally developed this animal model showed that STV_{QT} could discriminate between safe and unsafe drugs, in contrast to QT-interval prolongation *per se* [47,48]. This has been confirmed in our hands [49]. Others failed to correlate STV and TdP in phenylephrine-sensitized rabbits [50-52]. Apart from TdP, other arrhythmias in combination with conduction abnormalities were reported both during sensitization with phenylephrine and after challenge with a class III agent. This indicates that in these rabbits arrhythmias could not exclusively be ascribed to aberrant repolarization. In fact, one study showed that dofetilide hardly prolonged QT-interval in animals suffering from drug-induced ventricular tachycardia/ventricular fibrillation [51]. Consequently, the relationship between STV and TdP-ventricular tachycardia might be affected. To what extent conduction abnormalities are affecting BVR remains to be determined. Further research is warranted in this widely used but poorly understood animal model.

The use of baseline STV values for (individual) risk stratification

STV in baseline and repolarization reserve

As mentioned, the cAVB dog possesses a high susceptibility to repolarization-dependent arrhythmias due to contractile and electrical ventricular remodeling [30,31]. Compared with acute animal models, the interplay between arrhythmogenic susceptibility, repolarization reserve, and STV can be examined as remodeling proceeds. Creation of AVB and the ensuing bradycardia did not increase STV_{LV} or STV_{QT}, whereas during progression to cAVB STV_{LV} increases, which indicates a decreasing repolarization reserve (Figure 3A) [46].

This progressive development of STV is paralleled by the development of arrhythmogenic susceptibility (Table 3): Sinus rhythm dogs and dogs with acute AVB (aAVB), in contrast to cAVB dogs, are still able to employ sufficient repolarization strength to withstand a challenge with a proarrhythmic drug (Figure 3A-B) [38,46]. Yet, not all cAVB dogs are sensitive to drug-induced arrhythmias. Interestingly, STV_{LV} is significantly lower in resistant dogs (25-35%) and does not increase on dofetilide challenge in contrast to inducible cAVB dogs (65-75%) (Figure 3A) [46]. A subset of cAVB dogs (10%) dies suddenly under conscious circumstances because of spontaneous arrhythmias. Elevated baseline STV_{LV} levels could identify these animals and thus the individual at risk (Figure 3A; Table 3) [44]. Individual risk was also considered in other AVB dog models. When investigating the effect of ventricular activation on electrical remodeling, dogs paced from the high-ventricular septum after creation of AV block were compared with control cAVB dogs kept at idioventricular rate without controlled activation. Interestingly, STV_{LV} increased only in cAVB dogs from 0 to 4 weeks after atrioventricular node ablation [54]. Another comparison in

cAVB dog was the effect of decreasing the pacing cycle length from 1000 (low heart rate) to 600 ms (high heart rate, Table 3). This acceleration in heart rate prevented dofetilide-induced TdP and reduced STV_{LV} both in baseline and after dofetilide [55].

As mentioned earlier, generally sensitization of the animal models is required and more than 1 challenge on repolarization is warranted. In our cAVB dog model, anesthesia is required for development of dofetilide-induced TdP. Baseline STV values determined from left ventricular subendocardial electrograms (STV_{EGM}) were not significantly different between conscious and anesthetized dogs, but only the latter animals developed TdP and increased STV_{EGM} values after challenge with dofetilide [56].

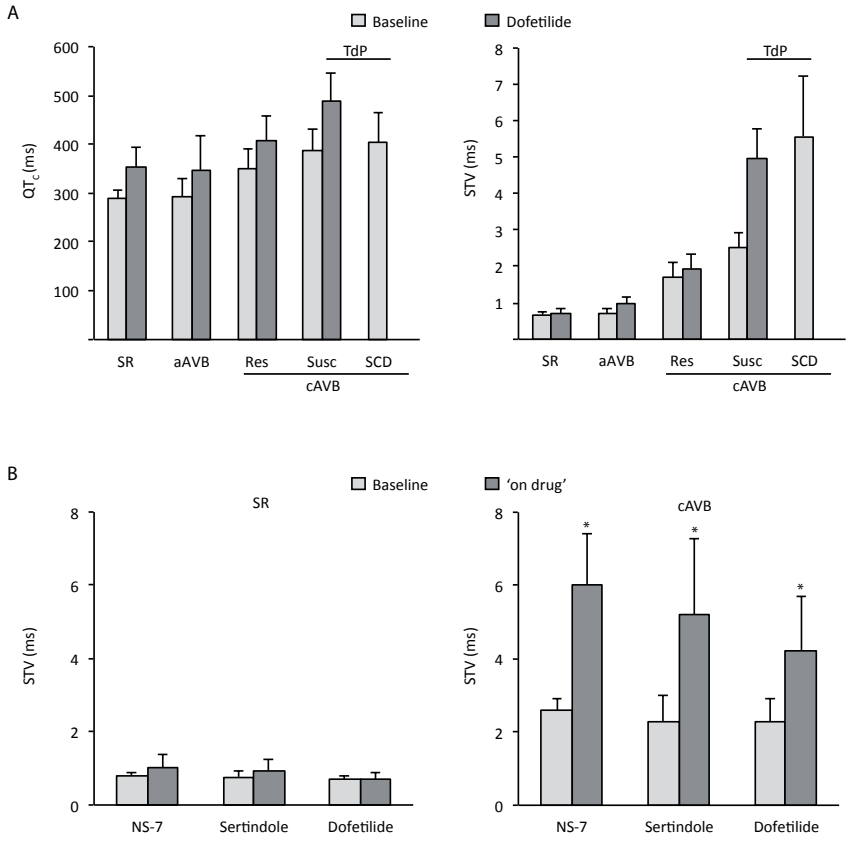

Figure 3. The concept of beat-to-beat variability quantified as short-term variability (STV) in identifying individuals at risk for repolarization dependent arrhythmias is shown. In sinus rhythm (SR), no drug is able to induce torsades de pointes (TdP) (A, B left panels) and STV remains similar. The same drugs, but now administered in remodeled chronic atrioventricular block (cAVB) circumstances, clearly increase STV prior to TdP (A,B right panels). Please note that baseline STV is much higher in cAVB circumstances than in normal SR. A similar plot with accompanying corrected QT-interval values is shown in A, but now with data of acute actrioventricular block (aAVB) (no remodeling) and a subdivision of cAVB dogs in resistant (res), susceptible (middle) and already demonstrating arrhythmias in control: sudden cardiac death (SCD). Please note that STV remains similar when no TdP can be induced by dofetilide but it increases in susceptible animals to values comparable to those in SCD animals without drug treatment. This figure contains data from Thomsen et al [15,46], Detre et al [38], and Oosterhoff et al [53].

Table 3. Behavior of STV and QT_C in baseline at different stages of remodeling.

Dog model		Drugs	STV (ms)		QT_c/MAPD (ms)		TdP (%)	Reference
			Control	Drug	Control	Drug		
cAVB	SR	Dofetilide	0.7±0.1	0.7±0.1	206±15	295±53*	0	46
	aAVB	Dofetilide	0.7±0.1	1.0±0.2	239±22	324±78*	0	
	cAVB R	Dofetilide	1.7±0.4	1.9±0.4	297±38	399±67*	0	
	cAVB I	Dofetilide	2.5±0.4†‡	5.0±0.8*	351±33	454±48*	100	
cAVB	aAVB	-	1.3±0.3	-	-	-	-	44
	cAVB	-	2.7±0.9§	-	359±54	-	-	
	SCD	-	5.4±1.4‡	-	412±70	-	-	
cAVB	SR	-	0.7±0.2	-	295±20	-	-	54
	aAVB	-	1.5±0.9	-	290±32	-	-	
	cAVB	Dofetilide	2.4±0.8†	3.0±1.4	360±45	445±65*	78	
	HSP	Dofetilide	1.4±0.4	3.1±1.0*	383±30	512±90	44	
cAVB	Low HR	Dofetilide	1.7±0.6	3.0±1.8*	320±28	427±97*	86	55
	High HR	Dofetilide	0.9±0.2	1.5±1.4	251±16	296±59	14	
cAVB	Conscious	Dofetilide	1.1±0.4	1.2±0.3	281±31	329±52*	0	56
	Anesthetized	Dofetilide	1.6±0.5	2.6±0.7*	390±71°	532±93*	70	

STV has been derived from either QT or RV/LV MAP. *Significant increase vs control. †Significant vs SR. ‡Significant vs cAVB R or cAVB. §Significant increase vs aAVB. °Significant increase vs baseline conscious. aAVB = acute atrioventricular block; cAVB = chronic atrioventricular block; HR = heart rate; HSP = atrioventricular block paced from the high ventricular septum; LV = left ventricle; MAP = monophasic action potential; MAPD = monophasic action potential duration; QT_C = corrected QT interval; RV = right ventricle; SCD = sudden cardiac death; SR = sinus rhythm; STV = short-term variability; TdP = torsades de pointes.

Clinical Studies

Over the years, a number of descriptive studies have been performed in humans to demonstrate that baseline STV_{QT} could have predictive power to identify individuals at risk for repolarization-dependent arrhythmias. Measurements of STV from QT-intervals provide a noninvasive and clinically easily applicable parameter. Hinterseer et al [57] determined STV_{QT} from paper ECGs at a speed of 50mm/s, measuring the QT-interval of 30 consecutive beats manually and plotting these values in a Poincaré plot [56]. In patients known to be at risk for drug-induced TdP, STV_{QT} was more than 2-fold higher as compared with matched controls, whereas the QT_C did not differ between the 2 groups (Table 4), indicating that baseline STV_{QT} is able to identify patients with a diminished repolarization reserve [57]. Similarly, in patients with inherited LQTS, STV_{QT} and QT_C were approximately 50 and 10% higher than in matched controls. Baseline STV_{QT} could enhance the predictive power for the diagnosis of these patients with LQTS considerably [58]. Also, in patients with documented nonischemic congestive heart failure, STV_{QT} was

increased by almost 2-fold (Table 4), while the highest values were found in patients who received an implantable cardioverter-defibrillator for secondary prevention [60].

By using a semiautomatic analysis over longer recording times, Ritsema van Eck et al demonstrated that the administration of anthracyclin-based chemotherapy, known to be cardiotoxic, resulted in a prolongation of QT_C and an increase in STV_{QT} within 24 hours of doxorubicin application [59]. STV_{QT} remained elevated during follow-up (1 month after final application). Lengyel et al [61] demonstrated an increased STV_{QT} in professional soccer players with hypertrophied hearts compared with matched controls. After exercise, the STV_{QT} was still increased in this group of young athletes despite an increase in heart rate and a decrease in heart rate variability. Finally, the finding that STV can be reliably deduced from subendocardial electrograms further emphasizes its clinical applicability [55,56,62].

Since only a limited amount of data is available, no definite conclusions can be drawn currently. However, we speculate that in clinical practice STV_{QT} could be of use for improvement of risk stratification for implantable cardioverter-defibrillator indication. Therefore, prospective studies are needed to elucidate the benefit of the benefit of the use of STV_{QT} alone or in combination in different patient groups and settings, as in the EUTrigTreat study [63]. Because of changes in heart rate variability in different patient groups, it might be useful to correct for this parameter in future studies.

Table 4. Overview clinical trials.

Population & Method	**STV_{QT}**		**QT_C**		**Reference**
	Controls	Patients	Controls	Patients	
Acquired LQTS ECG, manually 30 beats	3.6±1	8.1±4*	421±25	428±25	57
Congenital LQTS ECG, manually 30 beats	4.1±2	6.4±3*	411±32	449±41*	58
Patients receiving chemotherapy 5 min ECG, moving window. Semi-automatic	1.25	3.17*	424	451*	59
Non-ischemic heart failure ECG, manually 30 beats	4.1±2	7.8±3*	415±32	419±36	60
Soccer players ECG, semi-automatic 30 beats	3.5±1	4.8±1*	422	419	61
ICD patients EGM, semi-automatic, 60 beats	-	19.3±15.1	-	539±58	62#

* significant vs controls, # Oosterhoff et al., 2011, personal communication. ECG = electrocardiogram; EGM = electrogram; ICD = implantable cardioverter-defibrillator; LQTS = long QT syndrome; QT_C = corrected QT-interval; STV = short-term variability.

Conclusions

In conclusion, BVR, quantified as STV, has been well characterized in the cAVB dog model, and its usefulness has been confirmed in at least 1 other animal model. Compared with the QT-interval, STV is superior in assessing the proarrhythmic risk of drugs and can be used to identify individual animals at risk. Nevertheless, for now it would be most suitable to use both parameters alongside each other in safety pharmacology. Furthermore, STV_{QT} seems to be superior to QT-interval prolongation in identifying patient populations at risk for ventricular arrhythmias and might be able to accurately predict individual risk. However, no definite conclusions can be drawn yet as the studies in which STV and the QT-interval are directly compared included a limited number of patients.

Limitations

Although STV is a promising biomarker, some points need to be addressed. From a mechanistic point of view, the precise mechanism behind BVR and STV is not completely clear yet and further research is warranted. In order to reliably determine STV, ECG recordings need to be longer than clinically standard ECG recordings; to be able to calculate STV from 31 beats a recording of 2 minutes is sufficient. To derive this parameter, dedicated personnel and sophisticated tools are necessary. At the moment, the measurement of STV requires separate software to semiautomatically analyze the ECG signals. We expect to be able to automate this further in the future and implement this software in clinically used ECG equipment.

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CHAPTER 4

Microvolt T-wave alternans in an unselected heart failure population; pros and cons

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European Journal of Heart Failure 2012;14:344-347

This editorial refers to ' Profile of microvolt T-wave alternans testing in 1003 patients hospitalized with heart failure', by C.E. Jackson et al.

Currently, reduced left ventricular ejection fraction (LVEF) is the strongest predictor of life-threatening arrhythmias and used to select patients for primary prophylactic implantable cardioverter-defibrillator (ICD) implantation. However, using this measure of mechanical impaired function to predict an electrophysiological substrate will result in a relatively high number of patients to treat those susceptible. Two trials for primary prophylactic ICD implantation, Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), report a percentage of 76% and 79% of patients that did not use their device during the follow-up of 21 and 45.5 months, respectively [1,2]. On the other hand, a substantial number of sudden cardiac deaths (SCDs) occur in patients with a preserved LVEF, who are not eligible for an ICD on the basis of this risk stratifier. However, it is known that in patients with a cardiac resynchronization therapy device with defibrillator function (CRT-D), improvement of LVEF > 35% reduces the number of ICD interventions [3].

To optimize patient selection for primary prophylactic ICD implantation, electrophysiological tools for risk stratification have been tested. Microvolt T-wave Alternans (MTWA), defined as an alternation in T-wave morphology in every other heart beat reflecting spatiotemporal heterogeneity of repolarization, has been demonstrated to be a significant predictor of arrhythmic and cardiovascular death in patients with ischaemic and non-ischaemic cardiomyopathies. It is regarded as a class IIa index for stratification of fatal ventricular arrhythmias in the guidelines (ACC/AHA/ESC) 2006 [4]. Although negative predictive values were high ranging from 91.7-100%, the hazard ratio of a positive MTWA test seems to vary depending on the different populations studied (hazard ratio 1.24-6.53) [5-12].
For detection of MTWA, the spectral method requires a graded increase in heart rate (HR) usually achieved by exercise [13]. It is not possible to perform an MTWA test in patients, who are unable to exercise or have atrial fibrillation (AF). As a consequence, the studies, which investigated MTWA, have been conducted in highly selected cohorts. The number of patients excluded based on these limitations is often not mentioned; making it difficult to determine its applicability in clinical practice. Therefore it would be interesting to investigate the patients' eligibility for MTWA testing in an unselected heart failure (HF) population, as Jackson et al [14]. have done in this issue of the journal.

Ineligibility for testing

In this study [13], 2361patients with decompensated HF were screened, and 1003 were prospectively enrolled independently of LVEF. After 1 month, only 648 patients were able to perform an MTWA test. Of these 648 patients, 242 (37%) patients had to be excluded due to AF, inability to exercise (n=43 (6.6%)) or continuous ventricular pacing (n=33 (5.1%)). In only 330 patients (47%) a MTWA test was performed: 100 (30.3%) were positive, 152 (46.1%) indeterminate, and 78 (23.6%) negative.

Table 1. Number of positive, indeterminate and negative microvolt T-wave alternans (MTWA) test results for several studies that studied MTWA in ischaemic and non-ischaemic patients, patients eligible for ICD implantation and patients with heart failure.

	Patients Included	Patients Excluded	Mean LVEF (%)	MTWA tests	B-blocker	B-blocker continued	Positive	Indeter-minate	Negative
Bloomfield et al. 2006 # (5)	Ischemic/non-ischemic. LVEF ≤40%. No history of sVTE	AF, NYHA IV, Ventricular pacing. Unable to exercise	25	549	81(15%)	Yes	163(29%)	198(36%)	189(34%)
Chow et al. 2006 (6)	Ischemic. LVEF ≤35%. No history of sVTE	AF	<30	768	631(82%)	No	355(46%)	159(21%)	254(33%)
Salerno-Riarte et al ALPHA 2007 (7)	Non-ischemic. LVEF ≤40% no history of sVTE/ syncope	AF, NYHA I, IV. ICD implanted.	29.5	446	357(80%)	Yes	200(45%)	92(21%)	154(34%)
Gold et al. SCD-HeFT 2008 (8)	Ischemic/non-ischemic. Eligible for ICD implantation	AF, NYHA I, IV	24±7	490	363(74%)	No	181(37%)	201(41%)	108(22%)
Bloomfield et al. 2004 (9)	Post-MI. LVEF≤30%. No history of sVTE	AF, NYHA IV, Unable to exercise	23±6	177	131(74%)	Yes	48(27%)	73(41%)	57(32%)
Chow et al. MASTER 2008 # (10)	> 4weeks Post-MI. LVEF ≤30%. No history of sVTE	AF, NYHA IV, Unable to exercise	24±5	575*	500(87%)	Yes	293(51%)	68(12%)$	214(37%)
Klingenheben et al. 2000 (11)	CHF, LVEF ≤ 45%. No history of sVTE	AF, NYHA I, IV	28±7	107	45 (42%)	Yes?	52(49%)	22(21%)	33(31%)
Gorodeski et al. 2009 (12)	CHF, LVEF <40%	AF, ICD implanted	20-23	303	271(89%)	Yes	84(27%)	51(17%)	167(55%)
Jackson et al. 2012 (14)	Decompensated HF BNP >100pg/ml	AF, Unable to exercise	39.4	330	213(65%)	Yes	100(30%)	152(46%)	78(24%)

* Different test modalities, 78% exercise, $ After retesting, #Overlapping patient population with previous study reported by same author. LVEF: Left ventricular ejection fraction. MTWA: Microvolt T-wave alternans. sVTE: sustained ventricular tachyarrhythmic event. AF: atrial fibrillation. NYHA: New York Heart Association functional class. MI: Myocardial infarction. CHF: Congestive heart failure. ICD: implantable cardiac-defibrillator

Indeterminate test results

In the 47% of patients on which MTWA testing could be performed, a remarkably high number of indeterminate test results (49%) were reported [14], considerably higher than in previous studies, which show a range of 12-41% (median 21%) (Table 1). An indeterminate test result can be due to patient factors (failure to maintain HR between 105 and 110 b.p.m. for ≥1 minute, frequent ectopy, unsustained MTWA) or technical factors (excessive noise on electrocardiogram, rapid rise in HR through the target exercise HR range of 105-110 b.p.m.). Inability to achieve the target HR is reported as the main reason of an indeterminate result (Table 2) [14-16]. The proportion of patients on beta-blockers used in this unselected HF population is comparable to previous studies and does not seem to explain the discrepancy in the number of indeterminate tests.

Table 2. Studies that provided further information about reasons for an indeterminate test result.

Original article	Article reporting reasons for indeterminate tests	Number of MTWA tests	Number of indeterminate tests	Inability to achieve HR	Ectopic activity	Noise	USA	Other
Bloomfield et al. 2006 (5)	Kaufman et al 2006 (13)	549	191* (35%)	51.3 %	32.1%	6.4%[$]	10.2%	0%
Chow et al. 2006 (6)	Chan et al 2008 [#](14)	768	159(21%)	32%	46%	13%	9%	0%
Jackson et al 2012 (14)	Jackson et al 2012	330	152 (46%)	75%	16%	6%	2%	1%

* After retesting. [$] Including too fast increase of heart rate, [#] If more then 1 reason of indeterminate test the following hierarchy was used: 1) ectopic activity 2) IHR 3) USA 4) noise. MTWA= Microvolt T-wave alternans. HR= Heart rate. USA= Unsustained alternans.

The presented study provided further information concerning the reasons for being unable to achieve target HR: chronotropic incompetency and physical limitations. The first category consisted of patients that attained a maximum HR below 110 b.p.m, which failed to rise with further exercise. The second group discontinued exercise because of physical limitations without meeting the criteria for a positive or negative result (i.e. 59 of the total amount of 192 patients)[14].

Patients with an indeterminate test seemed to be characterized by a poorer clinical status, as shown by independent predictors such as older age and lower peak HR during exercise. Furthermore a higher log brainnatriuretic peptide (logBNP) and lower peak oxygen consumption (peakVO_2) was observed [12,14]. Therefore, the risk to die from causes other than arrhythmic death is probably higher, which may explain how MTWA reached significance in relation to total mortality but not to arrhythmic death [8]. In the results of most

trials, positive and indeterminate tests are grouped together. Therefore, it is not possible to assess to what extent the number of indeterminate tests can be attributed to these results.
In a comparable cohort of 303 patients with congestive HF [12], after adjusting for peak VO2, the predictive value of non-negative MTWA was no longer statistically significant (hazard ratio 1.18, 95% confidence interval 0.64-2.17 p <0.06). The number of indeterminate tests accounted for this, since peak VO2 was lower in the indeterminate group compared to the MTWA positive group (15.6 vs. 19.2, $p < 0.001$). This suggests that combining the results may obscure the possible predictive value of a positive result. It would therefore be interesting to assess if, and to what extent, the number of indeterminate tests influences the predictive value of MTWA in these HF patients.

Risk stratification

The current study [14] did not show any results of mortality and incidence of SCD during follow-up. Therefore, the predictive value of MTWA cannot be assessed. Nevertheless, it is important to discuss what the value of the prevention of SCD is in these patients with severe HF. In the SCD-HeFT trial, patients with an admission for HF in the previous 3 months were excluded and a sub-analysis of this trial showed no benefit of ICD implantation in patients with severe HF New York Heart Association (NYHA) class III (5-year mortality rate 48% vs. 45% in the placebo group). In risk stratification for primary prophylactic ICD, three types of HF patients are of interest: patients with 1) LVEF ≤ 35%, eligible for ICD, who will not need ICD therapy, 2) LVEF ≥ 35%, not eligible for ICD implantation, who would benefit from this, and 3) a poor prognosis more likely to die from other causes than arrhythmic death but do fulfil ICD criteria.

Conclusion

Clinical applicability of MTWA testing is limited to selected groups. In an unselected HF population, MTWA testing results in a substantial high number of indeterminate tests. Therefore, it is questionable whether MTWA alone is able to be of predictive value and for what patient population.

Future directions

With an increasing number of primary prophylactic ICD implants (LVEF of ≤ 35%), concerns rise about cost-effectiveness and the benefit/complication ratio. Investigations to improve risk stratification remain worthwhile, although many fail to reach a significant predictive value. To embrace the complexity of the various cardiac substrates underlying sudden cardiac death, combining different methods of risk stratification could be the solution. An on going multicentre trial, EU-TrigTreat, sponsored by the European Commission, enrols patients eligible for ICD implantation to compare a number of invasive and non-invasive electrophysiological risk markers (including MTWA and short-term variability) and explore their (combined) predictive value for life-threatening arrhythmias [17].

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CHAPTER 5

Separating the Risks of Appropriate Shock and Mortality in Implantable Cardioverter-Defibrillator Recipients: Targeted Stratification in the EUTrigTreat Clinical Study

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Abstract

Aims: Assessment of expected interventions and patient mortality is needed to improve effectiveness of implantable cardioverter defibrillators (ICD). We prospectively studied combinations of risk stratifiers in ICD patients.

Methods and results: In 672 patients, the following tests and parameters were collected at inclusion: left ventricular ejection fraction (LVEF), electrophysiological (EP) testing, microvolt exercise T-wave alternans (MTWA), 24-hour Holter monitoring including heart rate turbulence, cardiovascular history, as well as biomarkers hs-CRP, NT-proBNP and estimated glomerular filtration rate. Age was 63±13 years in 632 patients available for final analyses, 81% were male, 42% had ischemic cardiomyopathy, 34% had dilated cardiomyopathy. Mean LVEF was 40±14%, 20% were EP inducible, 63% had a primary prophylactic ICD. All-cause mortality and first appropriate shock were leading endpoints. During follow-up of 2.4 ± 1.2 years, n=52 (3,4%/year) died, appropriate shock occurred in n =76 (5.4%/year). In multivariate Cox analysis, age (p=0.0008), LVEF (p=0.0007), history of atrial fibrillation (AF) (p=0.0078), and NT-pro-BNP (p=0.0077) remained as mortality predictors. In contrast, LVEF (p=0.0016), EP inducibility (p=0.0098), and secondary prophylactic indications (p=0.0024) were independent predictors of appropriate shock. Separate risk scores for death and shock enabled grouping at high, intermediate or low risk of each endpoint. Higher mortality risk did not necessarily correlate with higher appropriate shock risk in a given patient.

Conclusion: In a prospective ICD cohort study combining clinical and EP parameters into a targeted risk model for mortality and shock, differentiation of these risks was observed suggesting varying benefits from ICD therapy.

Introduction

ICDs have been shown to improve survival in patients at risk of sudden cardiac death [1,2]. After widespread adoption of ICD therapy, it was noticed that a fairly large number of ICD patients do not require appropriate shocks or die prior to appropriate ICD therapy [3]. Furthermore, the majority of sudden cardiac deaths occur in patients with normal or moderately impaired LVEF [4]. Few risk stratification studies were dedicated to ICD patients, those with equivocal results were limited to ischemic cardiomyopathy using MTWA with or without EP study [5-7]. Accordingly, there is an urgent need for additional risk stratification tests to supplement LVEF including electrical markers, cardiovascular history, biomarkers, and possible combinations to be involved in ICD indications [8,9]. The EUTrigTreat Clinical Study [10] was a work package of an EU-FP7 large-scale cooperative project, designed to enroll a real-life ICD cohort and to collect carefully selected combinations of risk markers for prediction of death and shock.

Methods

Study design and baseline testing

From January 2010 through April 2014, we enrolled 672 ICD patients in four European centers. The study was registered (NCT01209494), and approved by all local ethics committees. The study design including detailed protocol and sample size calculations has been published. ICD patients with guideline primary or secondary prophylactic indications and at least 18 years of age were recruited. Baseline assessment featured LVEF, EP study, MTWA, 12-lead standard ECG and Holter monitoring including heart rate turbulence, cardiovascular history, and biomarkers high-sensitivity C-reactive protein (hs-CRP), n-terminal-pro B-type-natriuretic protein (NT-proBNP), and serum creatinine, respectively. High resolution 12-lead ECGs were also recorded for digital semi-automatic analysis using a novel ECG method, short-term variability of the QT interval [11], these results will be reported elsewhere. Expecting a wide range of indications and clinical characteristics, standard programming recommendations were agreed upon among the four participating institutions but mandatory programming was not considered possible [10].

EP study

In case of first ICD implantation, EP study was done invasively in 31 (5 %) patients, the remainder underwent non-invasive programmed stimulation via their ICD using an abbreviated protocol.[10] Inducibility of sustained ventricular arrhythmia was defined as induction of a single monomorphic VT lasting 30 sec or two polymorphic VT/VF requiring cardioversion.

MTWA testing

MTWA exercise testing (Cambridge Heart, Tewksbury/MA, USA) was done in sinus rhythm. If the patient was unable to exercise, atrial pacing was permitted. MTWA test were graded according to both A and B rules [12] by two blinded investigators from the enrolling and core centers. In case of disagreement, findings were openly discussed, with the enrolling center deciding the final grade. For statistical analysis, positive and indeterminate results were grouped as non-negative.

Holter monitoring

Holter monitoring was done for 24 hours using standard devices (Delmar Reynolds Pathfinder, Spacelabs Healthcare, Snoqualmie/WA, USA; Spiderview, Sorin Group, Paris, France; GE Mars, GE Healthcare, Milwaukee/WI, USA). Upon analysis, the number of premature ventricular complexes and non-sustained VTs were normalized to 24 hours. In case of sinus rhythm and <15% ventricular or atrial pacing, heart rate variability and heart rate turbulence were calculated using dedicated software (Librasch Calc, V1.02, Schneider R and Schmidt G, TU Munich, Germany).

Outcomes: All-cause mortality and first appropriate ICD shock

Primary endpoint was all-cause mortality [10]. From the predefined secondary endpoints, first ppropriate ICD shock was selected. As previously published [10] the endpoint did not include antitachycardic pacing. Patients were followed every 3 to 6 months. If ICD shocks occurred, EGM data were forwarded to the endpoint committee (A.T., R.W., M.Z.) for classification. Mode of death was also adjudicated by the committee.

Statistical analysis

As previously described [10] Cox regression analysis was implemented. For shocks, death was considered a censoring event [13] using competing risk adjustments proposed by Fine and Gray [14]. To select model risk parameters, a priori defined known risk factors (age, LVEF, NYHA, eGFR and gender) as well as forward selected additional risk factors qualified by $p<0.10$ were considered chosen, also using the Bayesian Information Criterion [15]. Discriminatory power of scores was evaluated using Goenen and Heller's concordance index and 10-fold cross-validation [16]. Bootstrapping was used to estimate the bias introduced by validating the model based on the same data that was used to develop the score [17]. We generated 200 bootstrap samples from the data and for each repeated the model building procedure from variable selection to determination of the score and cutoff values. Repeated comparison of incidences based on bootstrap sample and original data then allows to estimate and correct for the induced bias. Kaplan-Meier probabilities were compared by log-rank test. In 147 patients, only BNP measurements were available instead of NT-proBNP, in these cases BNP values were extrapolated [18]. No imputations were calculated. All computations were performed using the R environment for statistical computing

and graphics (http://www.r-project.org). Continuous values were expressed as mean ± standard deviation. P-values were two-tailed, an α-level of 5 % was considered significant.

Results

Patient characteristics

Of 672 patients enrolled, 632 were finally considered (Figure 1*).* First ICD implantation occurred an average of 4.0±4.0 years prior to enrollment, 31 (5%) received their implant at enrollment, 63% had primary prophylactic indications. A single-chamber ICD was implanted in 46%, dual-chamber ICD in 34%, and biventricular ICD in 20%. Manufacturer distribution was 17% Biotronik, 36% Boston Scientific, 6% St. Jude Medical, and 41% Medtronic. Mean age was 63 ± 13 years, 81 % were male. Mean LVEF was 40 ± 13 %. Sinus rhythm was basic rhythm in 507 patients (80%), AF in 80 patients (13 %), pacemaker rhythm or higher degree AV block in 45 patients (7%). Baseline parameters are shown in Table 1.

Figure 1: CONSORT graph for patient enrollment, patients not considered for final analysis and clinical endpoints.

Table 1: Clinical baseline characteristics for all patients (n=632), surviving patients (n=580), and deceased patients (n=52) (AAD = anti-arrhythmic drug, AF = atrial fibrillation, ARVC = arrhythmogenic right ventricular dysplasia, CM = cardiomyopathy, hs-CRP = high sensitivity C-reactive protein, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, NT-proBNP = n-terminal pro-brain natriuretic peptide; *=significant.

	All (n=632)	**Alive (n=580)**	**Deceased (n=52)**	**p-value**
Age (years)	63 ± 13	62 ± 13	71 ± 9	<0.001*
Male sex	512 (81 %)	468 (81%)	44 (85%)	0.584
Body mass index (kg/m²)	28.1 ± 5.3	28.2 ± 5.3	27.1 ± 5.1	0.241
LVEF	40 ± 13 %	41 ± 14	33 ± 11	<0.001*
Coronary artery disease	281 (44 %)	256 (44 %)	25 (48 %)	0.584
Ischemic CM	264 (42 %)	239 (41%)	25 (48%)	
Dilated CM	212 (34 %)	188 (32%)	24 (46%)	
Hypertrophic obstructive CM	38 (6 %)	38 (7%)	0 (0%)	
Brugada syndrome	12 (2%)	12 (2%)	0 (0%)	
Long QT syndrome	9 (1%)	9 (2%)	0 (0%)	0.005*
Other channelopathies	5 (1%)	5 (1%)	0 (0%)	
ARVC and other inheritable diseases	19 (3%)	19 (3 %)	0 (0%)	
Idiopathic arrhythmias	53 (8%)	51 (9%)	2 (4 %)	
Other (e.g. cardiac sarcoidosis, hypertensive CM)	20 (3%)	18 (3%)	1 (2%)	
NYHA class				
I	187 (30 %)	182 (31%)	5 (10%)	
I-II	83 (13 %)	78 (13%)	5 (10%)	
II	181 (29 %)	167 (29%)	14 (27%)	<0.001*
II-III	81 (13 %)	73 (13%)	8 (15%)	
III	100 (16 %)	80 (14%)	20 (38%)	
NT-proBNP (ng/L)	1363 ± 2205	1147 ± 1813	3059 ± 3771	<0.001*
hs-CRP (mg/L)	3.8 ± 5.2	3.5 ± 5.1	5.8 ± 5.9	<0.001*

AF				
Permanent	80 (13 %)	60 (11%)	20 (39%)	
Paroxysmal	135 (22 %)	123 (22%)	12 (23%)	<0.001*
No history of AF	404 (65 %)	385 (68%)	19 (37%)	
Intrinsic QRS width (ms)	122 ± 31	122 ± 31	131 ± 32	0.0002
ß-blockers	467 (85 %)	427 (85%)	40 (89%)	0.522
Class I antiarrhythmic drug	11 (2 %)	10 (2.4%)	1 (2.4%)	0.601
Class III antiarrhythmic drug	153 (29 %)	142 (29%)	11 (26%)	0.864
Digitalis glycosides	79 (15 %)	63 (13%)	16 (37%)	<0.001*
Oral anticoagulation	190 (35 %)	166 (34%)	24 (55%)	0.008*

ECG and Holter parameters

An intrinsic QRS complex was recorded in 532 patients, RV paced rhythm in 40, biventricular paced rhythm in 57, 3 patients were unclear. Mean QRS duration of intrinsic complexes was 122±31 ms, mean QT and QTc durations were 444±51 ms and 453±44 ms, respectively. Mean heart rate on Holter was 67±10 bpm, premature ventricular complexes averaged 2330±5811 per 24 hours, number of non-sustained VT episodes 2±14 per 24 hours, 144 patients (23%) exhibited at least one non-sustained VT. Mean standard deviation of normal-to-normal intervals (SDNN) was 113±43 ms, mean square root of mean of squared differences between normal-to-normal RR intervals (RMSSD) was 31±27 ms. Mean heart rate turbulence onset was -0.14±2.12 %, heart rate turbulence slope was 5.48±5.02 ms/R-R interval, and deceleration capacity (DC) was 2.09±6.56 ms, respectively.

EP study and MTWA

Sustained VT/VF was induced in 124 (20 %) patients. VF was induced in 8 %, 81 % showed monomorphic VT, and 11 % polymorphic VT, respectively. Mean cycle length of induced VT/VF was 277±55 ms.

MTWA gradings were available for final analysis in 490 patients (97%) in sinus rhythm. Of these, 345 (70 %) were performed under exercise, 145 (30 %) via atrial or biventricular stimulation. According to A rules, 29 % (n=142) were graded positive, 50 % (n=245) negative, and 21 % (n=103) indeterminate, respectively. Following B rules, 28 % (n=137) were positive, 57 % (n=279) negative, and 15 % (n=74) indeterminate, respectively.

Occurrence of Endpoints

Over a follow-up of 2.4±1.2 years, 76 (12 %) patients received a first appropriate shock (annualized rate 5.4%). The cycle length of the primary arrhythmia leading to an appropriate shock in a VT/VF episode was 255±48 ms (minimum 170 ms, maximum 385 ms), 50% (n=38) delivered in the VF zone. Mortality was 8 % (n=52, annualized rate 3.4%), and adjudicated as cardiac in n=30 (58 %), n=17 (32%) deaths were classified as non-cardiac. Information on the mode of death was incomplete in 5 cases.

Risk prediction by Cox regression and risk scores

Univariate Cox regression (*appendix Tables 1 and 2*) revealed age, LVEF, eGFR, NYHA class, history of AF, hs-CRP as predictors of mortality, SDNN, heart rate turbulence onset, heart rate turbulence slope and deceleration capacity (DC) from Holter, intrinsic QRS width and intrinsic QTc duration from 12-lead ECG as ECG predictors. Univariate predictors of appropriate shock were LVEF, eGFR, and secondary prophylactic indication. None of the ECG parameters were predictors of shock. EP inducibility and MTWA following A and B rules were significant predictors for appropriate shock but not for mortality. Assuming effects on both endpoints, multivariate Cox models were established using age, gender, LVEF, NYHA class and eGFR as basic variables. To predict mortality, history of AF, chronic obstructive pulmonary disease, and intrinsic QRS width were tested. For shock prediction, secondary prophylactic indication, leading cardiac disease, history of AF, and intrinsic QRS width were tested. Consequently, as significant parameters with $p<0.10$, secondary prophylactic indication was added to the model for appropriate shock and history of AF to the model for mortality. The two models were further refined by forward selection of additional parameters, all of which were tested separately for significance of $p<0.10$. In these steps, deceleration capacity (DC), hs-CRP, and NT-proBNP were identified as mortality predictors, EP inducibility and MTWA (A rules) as shock predictors. The final risk models for mortality and appropriate shock and their respective hazard ratios and p-values are shown in Table 2.

Hs-CRP is not shown because it was only available in 75% of the respective patients of the models (HR 1.08, CI 1.04-1.12, $p<0.001$ for all patients; HR 1.06, CI 1.01-1.11, $p<0.015$ for patients in sinus rhythm). Two models for each endpoint were derived, one applicable to all patients (sinus rhythm and AF as basic rhythms) and another for all patients in sinus rhythm. Patients were subdivided into tertiles according to lowest, intermediate and highest score values. Threshold values for this process are shown in *Appendix Table 3*. Mortality risk could be differentiated using the final model predictors age, LVEF, history of AF, and NT-pro-BNP for all patients (Figure *2A*), and LVEF, history of AF, and deceleration capacity for patients in sinus rhythm (Figure 2C). Appropriate shock risk deviated from mortality risk (Table 3B), and could be predicted using LVEF, secondary prophylaxis, and EP inducibility for all patients (Figure 2B), and LVEF, secondary prophylaxis, EP inducibility, and MTWA result in patients with sinus rhythm,

respectively (Figure 2D). With 8% (n=50) missing values for NT-pro-BNP, the final model for mortality comprised 568 patients. Missing values for all other parameters were below 3%, usually less, with the exception of hs-CRP (25%).

Table 2: Multivariate hazard ratios for prediction of all-cause mortality and appropriate shock in the respective final Cox model.

	Hazard ratio		**95 % confidence interval**		**p-value**	
n=632	**Mortality**	**Shock**	**Mortality**	**Shock**	**Mortality**	**Shock**
Age (years)	1.055		1.023-1.089		0.0008*	
LVEF (%)	0.959	0.968	0.935-0.982	0.949-0.988	0.0007*	0.0016*
History of AF	2.21		1.23-3.95		0.0078*	
NT-pro-BNP	1.00004		1.00001-1.00007		0.0077	
Secondary prophylaxis		2.09		1.30-3.36		0.0024*
EP inducibility		1.93		1.17-3.18		0.0098*
eGFR (mL/min)		0.989		0.977-1.000		0.055
Sinus rhythm only (n=507)						
LVEF (%)	0.955	0.955	0.925-0.986	0.932-0.978	0.0046*	0.0002*
History of AF	1.99		0.96-4.12		0.065	
Deceleration capacity (ms)	0.946		0.914-0.979		0.0016*	
Secondary prophylaxis		2.65		1.56-4.50		0.0003*
EP inducibility		1.78		1.03-3.07		0.038*
MTWA non-negative (A rules)		1.64		0.98-2.74		0.062

The upper half of the table shows the results for all 632 patients, the lower half for the 507 patients in sinus rhythm. (open field = not selected as model variable; * significant; AF = atrial fibrillation; eGFR = estimated glomerular filtration rate; EP = electrophysiological; LVEF = left ventricular ejection fraction; MTWA = microvolt T-wave alternans).

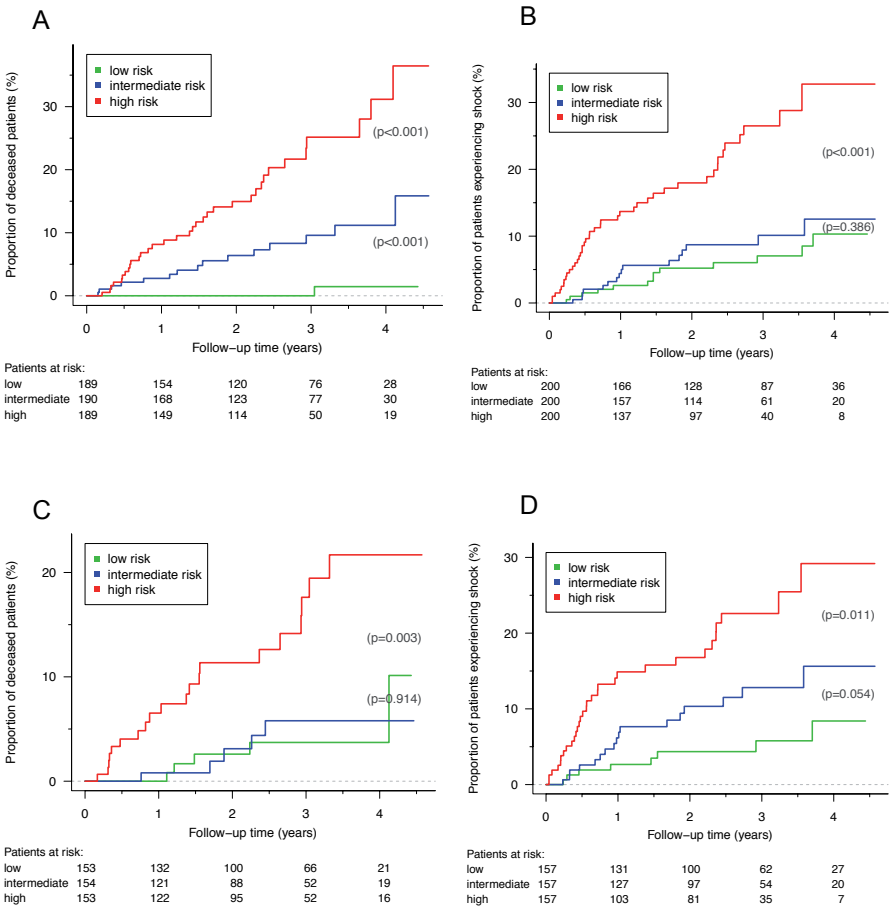

Figure 2: Kaplan-Meier cumulative event-probability curves for mortality (Panels A and C) and appropriate shock (Panel B and D) with the cohort divided into three risk groups (low, intermediate, high) defined by separate scores for the two risks. The dashed lines indicate the cumulative event-probabilities after bootstrap bias correction.
Panel A: The calculated mortality risk score provides an excellent differentiation between low, intermediate, and high mortality risks (0% to ≈8% annual mortality risk). Note that the respective shock risk of the three groups varies between 2.5% and 8.2%, and can be further differentiated within the group (see Figure 3).
Panel B: The calculated appropriate shock risk score provides good separation of high shock risk (highest tertile, annual shock risk of 9%.). Low and intermediate risks of shock (three quartiles) show small variation.
Panel C: The mortality score for patients in sinus rhythm (n=507) provides similarly good differentiation in event rates as the score for all patients in Panel A, except for the difference between low and intermediate tertiles.
Panel D: The appropriate shock score for patients in sinus rhythm (n=507) provides good differentiation in event rates for all tertiles.

The final appropriate shock models were based on 600 patients, and 471 patients with sinus rhythm, respectively. C-statistics were: c=0.745 for mortality (all), c=0.706 for mortality (sinus rhythm), c=0.681 for appropriate shock (all), c=0.716 for appropriate shock (sinus rhythm). Figure 3 shows Kaplan-Meier cumulative event incidences for the three risk tertiles. As calculated scores were normally distributed, individual patients

were identifiable with higher mortality and lower shock risks than shown in Figure 3. The tertile with low mortality risk featured annual mortalities <0.5%. These patients could be estimated with low (1.5%) and intermediate (3.2%) annual shock probabilities. Predicted intermediate annual mortality ranged between 2.4% and 4.2%. Annual risk for appropriate shock could be differentiated between 3.2% and 13.3% for group averages, and a higher spread individually. In Figure 3, highest ICD benefit can be assumed in the group with high shock risk and intermediate mortality (10% of patients) with annual shock risk of 13.3% clearly higher than the mortality risk of 4.2%. Lowest ICD benefit would occur in the low shock risk and low mortality group (21%) featuring 1.5% annualized shock risk and zero mortality. Intermediate ICD benefit can be assumed for all other groups constituting 53% of all patients. Using a single patients' score values (Appendix Table 3) the magnitudes of these risks could be further individualized.

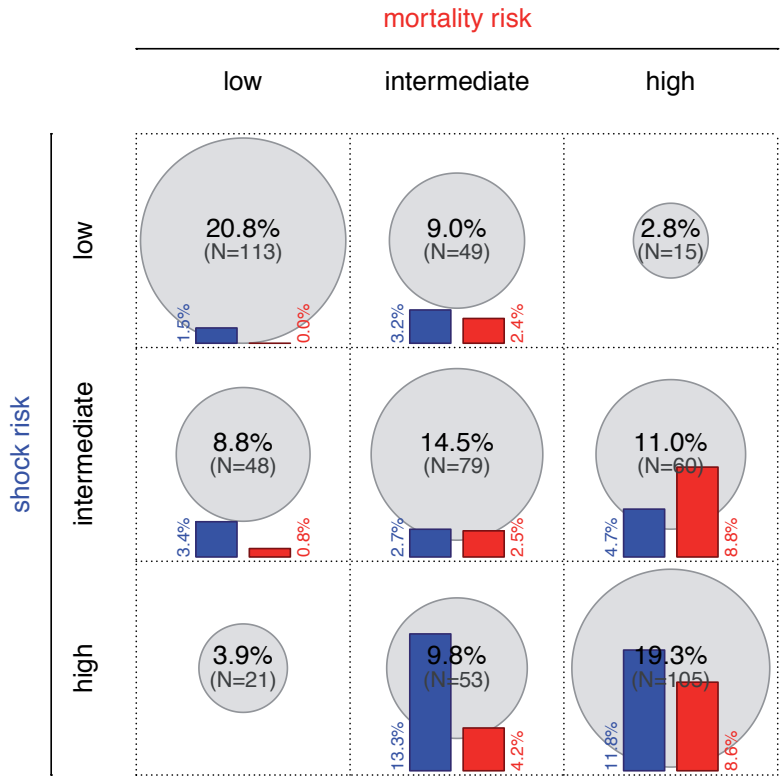

Figure 3: Distribution of patients to possible combinations of risk categories (low, intermediate, high) and their associated annualized mortality and shock risk. Grey circles denote the frequencies of patients in the various possible categories. The blue and red bars denote the actual annualized shock and mortality risks in a category, respectively.

Discussion

Main findings

This prospective study aimed for multivariate-targeted risk stratification in a large ICD patient cohort with guideline-based indications for both primary and secondary prevention of sudden death. To our knowledge, this was the first head-to-head comparison of multiple risk stratifiers in ICD patients. We identified several independent predictors of mortality as well as appropriate shocks, and developed separate risk scores that could divide the cohort into groups at high, intermediate or low risk of each endpoint. Higher mortality risk did not necessarily represent higher appropriate shock risk in a patient, and vice versa. These different combinations of mortality and shock risk suggested different ICD survival benefit.

Predictors of mortality in ICD patients

The only multivariate factor predicting both shock and mortality was LVEF, which corroborates its importance as a risk stratifier in ICD patients. Other factors adding to our final model were age and history of AF. Risk factors for mortality in ICD patients have been described in very large registries [19,20] and were confirmed in this study despite an overall low annual mortality of only 3%. However, neither of the two mentioned papers had reported shock risk, and our data demonstrates that risks of mortality and shock have to be considered separately in ICD recipients.

Predictors of appropriate shock in ICD patients

The independent predictive value of EP inducibility and MTWA testing for malignant ventricular arrhythmias is of high interest. In our study, EP stimulation was the best diagnostic test for appropriate shock prediction and could also be performed in patients with AF. This is in line with its proven value in assessing risk of sudden death in patients after myocardial infarction and with ischemic cardiomyopathy [21,22] as well as other guideline indications. Using an abbreviated protocol [10], EP testing was a very useful test in this mixed cohort of ICD patients. It was closely followed by MTWA as the second multivariate EP predictor of ICD shock. These results are in concordance with the ABCD study [7] that has reported EP testing and MTWA as predictors of events in ischemic ICD candidates, also with a study by Chow et al [5] where 50% of patients with ischemic cardiomyopathy received an ICD. In the light of other important MTWA studies [6,23] that have failed to demonstrate a predictive value, the number of indeterminate studies may have varied as well as the actual patient population. Secondary prophylaxis was the third multivariate predictor of shocks we found, featuring some of the highest hazard ratios and underscoring the strong indication of ICD therapy in these patients.

Predictors only available in sinus rhythm

As the diagnostic risk stratifiers MTWA and heart rate turbulence cannot be assessed in AF, we derived additional models applicable only for patients in sinus rhythm. While history of AF was a multivariate risk factor itself for all-cause mortality, even in patients with sinus rhythm, both MTWA and deceleration capacity added to the sinus rhythm models for mortality and shock. Deceleration capacity from Holter ECG proved to be the only electrical predictor of mortality in our cohort.

Implications for individual ICD benefit

ICD benefit may be estimated by the relative magnitudes of sudden cardiac death (i.e. malignant arrhythmias) vs. overall mortality risk. This relationship has been demonstrated in subanalyses from the MADIT-II [24] and SCD-HeFT [25]. Both reported that patients with high mortality may not derive ICD benefit because of higher proportions of non-sudden and non-cardiac deaths which is not in contradiction with long-term ICD benefit for the overall group [26]. These papers were hypothesis-generating for the current prospective study [10] which then searched for the best combination of EP risk stratification tests and clinical parameters [8,27-29]. Using separate identification of expected mortality risk and appropriate shock we aimed to estimate a distinct individual ICD benefit. It was not feasible to conduct a randomized controlled study due to ethical concerns. Higher shock risk associated with lower mortality risk means higher clinical ICD benefit. For instance, we could discern a low annual appropriate shock of 1-2% in 21% of all patients, this may in some of these patients denote only a small risk of sudden cardiac death had the patient not been implanted an ICD. We identified another group of 10% of all patients who had a 13% annual shock rate associated with only 4% annual mortality, likely resulting in a very high ICD benefit. More than 50% of all patients showed intermediate combinations of the two risks calling for individualization in each given patient. We do not know, however, whether threshold score combinations exist below which not implanting an ICD guarantees the same survival as ICD implantation. In this sense, our study is hypothesis generating and not definitive. Applying a similar concept of differential risk assessment of mortality and appropriate shock, Lee et al [30] calculated risk scores for 3445 patients of the Ontario ICD registry. Using a complete set of clinical baseline information without any dedicated diagnostic testing, these authors identified a group of 2.5% of their patients with very low expected ICD benefit as characterized by high mortality and low shock risk, as well as a group of 7.5% of their patients with low ICD benefit demonstrated by low shock risk and other than high mortality. In their final multivariate shock model, there were 11 predictors including age, male sex, AF, and serum creatinine. Shock risk was normally distributed and the range between the highest and lowest decile for shocks was approximately 8-fold, as compared to more than 30-fold for mortality deciles. We hypothesize that using EP studies and MTWA testing in large sample sizes, patient groups become better defined and larger.

In summary, risk factors for death and appropriate shocks were not equal in patients receiving ICD therapy. We tested a multitude of clinical predictors, EP parameters and risk stratification diagnostic tests. Thereby, an optimum of targeted testing was implemented, and EP study and MTWA were among the best predictors for appropriate ICD shock. Identification of distinct patients at high risk of death - who simultaneously feature a low risk of shocks - would be essential to further guide reasonable device therapy. Utilization of our scores might help to specify an individuals' benefit of ICD therapy and serve as guidance when making decisions for ICD therapy. The concept can be further advanced in larger patient numbers such as the prospective EU-CERT-ICD study (NCT02064192).

Conclusions

In this prospective, targeted risk stratification ICD cohort study, appropriate shock risk did not coincide with mortality risk. These risks could be described by a separate combination of predictors to which LVEF is common and involving diagnostic testing. Subgroups as large as 30% of all ICD patients feature higher shock risks suggesting higher ICD benefit, or combine very low shock and mortality risks suggesting a lower ICD benefit for their survival.

Funding

The research leading to the results has received funding from the European Community's Seventh Framework Programme FP7/2007-2013 under grant agreement No. HEALTH-F2-2009-241526, EUTrigTreat.

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Appendix Table 1: Univariate Cox regression for prediction of mortality (unadjusted)

Variable	Patients	p-value	Hazard ratio	Confidence intervals
Age (years)	632	<0.000001	1.0073	1.0425-1.1061
LVEF (%)	632	0.000002	0.9481	0.9264-0.9703
NYHA >2	632	0.00009	2.987	1.731-5.155
eGFR (ml/min)	620	0.00006	0.9761	0.9644-0.9880
Male gender	632	0.308	1.456	0.685-3.094
Secondary prevention	631	0.758	0.913	0.511-1.632
Ischemic vs. non-ischemic	630	0.052	1.730	0.999-2.999
History of AF	619	0.00011	2.988	1.693-5.273
COPD	632	0.0029	2.985	1.560-5.681
log NTproBNP/BNP (mg/dl)	580	0.000000073	1.728	1.410-2.118
hs-CRP (mg/dl)	476	0.0013	1.077	1.040-1.115
ICD chambers (1/2/3)	632	0.010	0.70; 2.03	0.34-1.44; 0.99-4.15
Intrinsic QRS (ms)	532	0.0005	1.0013	1.006-1.021
Intrinsic QT interval (ms)	532	0.141	1.0037	0.9989-1.0086
Intrinsic QTc interval (ms)	532	0.0021	1.0084	1.0032-1.1360
EP inducibility	613	0.233	1.491	0.789-2.816
TWA (A rules)	490	0.306	1.408	0.729-2.721
TWA (B rules)	490	0.230	1.493	0.776-2.873
Holter mean HR (bpm)	631	0.122	1.0225	0.9946-1.0512
Holter PVC/24h	629	0.272	1.000018	0.99999-1.00005
Holter nsVT/24h	629	0.590	0.9932	0.96324-1.02411
Holter SDNN (ms)	467	0.0453	0.99091	0.98173-1.00018
Holter RMSSD (ms)	470	0.686	1.00193	0.99337-1.01057
Holter DC (ms)	472	0.00233	0.9465	0.9191-0.9747
Holter HRT category (TO or TS abnormal, TO/TS abnormal)	431	0.00264	1.490; 4.443	0.540-4.109; 1.793-11.009
Holter HRT onset (%)	432	0.0253	1.186	1.034-1.360
Holter HRT slope (ms/RR-interval)	432	0.0485	0.9130	0.8250-1.0105

Appendix Table 2: Univariate Cox regression for prediction of appropriate shock (unadjusted)

Variable	n	p-value	Hazard ratio	Confidence intervals
Age (years)	632	0.098	1.0002	0.9824-1.0182
LVEF (%)	632	0.0003	0.968	0.951-0.986
NYHA >2	632	0.319	0.768	0.453-1.304
eGFR (ml/min)	620	0.007	0.986	0.976-0.996
Male gender	632	0.476	1.236	0.680-2.247
Secondary prevention	631	0.006	1.891	1.206-2.966
Ischemic vs. non-ischemic	630	0.082	1.499	0.952-2.358
History of AF	619	0.419	1.211	0.763-1.922
COPD	632	0.013	2.288	1.258-4.158
Log NTproBNP/BNP (mg/dl)	580	0.0124	1.234	1.045-1.457
hs-CRP (mg/dl)	476	0.963	0.9986	0.9424-1.0583
ICD chambers (1/2/3)	632	0.775	1.08; 1.49	0.63-1.85; 0.79-2.81
Intrinsic QRS (ms)	532	0.096	1.005	0.999-1.011
Intrinsic QT (ms)	532	0.134	1.0031	0.9991-1.0073
Intrinsic QTc (ms)	532	0.294	1.0031	0.9993-1.0084
EP inducibility	613	0.0012	2.292	1.424-3.691
TWA (A rules)	490	0.00431	2.123	1.249-3.610
TWA (B rules)	490	0.0166	1.861	1.116-3.101
Holter mean HR (bpm)	631	0.190	0.9840	0.9603-1.0083
Holter PVCs/24h	629	0.191	1.0000178	0.9999941-1.0000416
Holter nsVT/24h	629	0.940	1.000512	0.987513-1.013683
Holter SDNN (ms)	467	0.643	1.00146	0.99536-1.00758
Holter RMSSD (ms)	470	0.867	1.000742	0.992385-1.009168
Holter DC (ms)	472	0.130	0.9746	0.9454-1.0046
Holter HRT category (TO or TS abnormal, TO/TS abnormal)	431	0.341	1.552; 1.423	0.840-2.868; 0.691-2.932
Holter HRT onset (%)	432	0.177	1.0848	0.9685-1.2150
Holter HRT slope (ms/RR-interval)	432	0.388	0.9752	0.9193-1.0345

Appendix Table 3: Risk scores for both the risk of death and appropriate ICD therapy (Panel A), their threshold values and average annual group risks (Panel B). A separate risk model was calculated for patients in stable sinus rhythm. The variables "secondary prophylaxis", "inducibility" and "MTWA" are coded as binary indicator variables (i.e. secondary prophylaxis yes="1", no="0"; EP inducibility yes="1", no="0"; MTWA A-rules positive="1", non-negative="0").

Panel A:

All patients, mortality score:

0.0538 x age -0.0424 x lvef + 0.792 x afib + 0.0000409 x ntprobnp

All patients, shock score:

-0.0323 x lvef -0.0113 x egfr + 0.737 x prevention + 0.659 x inducibility

Sinus rhythm patients, mortality score:

-0.0461 x lvef + 0.686 x afib -0.0555 x holter.dc

Sinus rhythm patients, shock score:

-0.0426 x lvef -0.00823 x egfr + 0.973 x prevention + 0.576 x inducibility + 0.493 x twa(a)

Panel B:

	Low risk (mortality rate / shock rate)	**Intermediate risk** (mortality rate / shock rate)	**High risk** (mortality rate / shock rate)
Shock	< -0.464 1.5% death / **2.6% shock**	-0.464 - 0.465 3.1% / **3.9%**	>0.465 6.0% / **12.3%**
Mortality	< -0.679 **0.0% death /** 2.9% shock	-0.697 - 0.775 **3.2%** / 5.4%	>0.775 **8.6% /** 8.1%
Sinus rhythm (n=507)			
Shock	< -0.601 1.0% death / **2.0% shock**	-0.601 - 0.662 3.9% / **3.9%**	>0.662 3.7% / **12.8%**
Mortality	< -0.609 **1.4% death** / 4.3% shock	-0.609 - 0.560 **1.1%** / 2.7%	>0.560 **7.2%** / 11.5%

CHAPTER 6

Beat-to-beat variability of repolarization quantified as short-term variability of the QT-interval in the EUTrigTreat clinical study

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In preparation

Abstract

Introduction: Accurate prediction of sudden cardiac death (SCD) in individuals is still challenging. Beat-to-beat variability of repolarization, quantified as short-term variability of the QT interval (STV_{QT}) is a relatively new parameter that might be useful in the prediction of ventricular arrhythmias. In this study, we investigated the nature and the predictive value of STV_{QT} in the prospective EUTrigTreat clinical study.

Methods: 2-minute high resolution ECGs were recorded at inclusion and STV_{QT} was determined in 395 patients (sinus rhythm (SR): 323; cardiac resynchronization therapy (CRT): 45; atrial fibrillation (AF): 27). In SR patients, univariate and multivariate Cox regression analysis was performed to determine the predictive value of a dichotomized STV-QT.

Results: STV_{QT} analysis revealed different distributions of STV_{QT} among groups. Median STV_{QT} was lowest in SR patients (0.94 (0.51-2.26)), slightly higher in CRT patients (1.06 (0.53-3.18)) and severely increased in AF patients (5.09 (2.05-13.84)). During follow-up (2.4±1.2 years), 33 SR patients received an appropriate ICD shock and 15 died. In multivariate Cox regression analysis, STV_{QT} demonstrated a strong tendency to be an independent predictor for shocks (p=0.0503), but not for mortality (p=0.15).

Conclusion: Beat-to-beat variability of repolarization quantified as STV_{QT} shows a patient group dependent distribution. In SR patients, STV_{QT} strongly tended to be associated with appropriate ICD shocks and not with all-cause mortality.

Introduction

Sudden cardiac death (SCD) is a common cause of death and its incidence continues to rise. Implantable cardioverter-defibrillator (ICD) treatment is an effective way to prevent people to die from SCD [1,2]. However, according to the current guidelines, most of the people that die as a result of SCD are not eligible for ICD treatment [3]. On the other hand, the incidence of appropriate ICD shocks is low indicating that implantation of an ICD could be diverted in a large number of patients [4,5]. Several studies indicate that electrical parameters alone, or in combination can improve prediction of SCD [6,7].
The EUTrigTreat clinical study was a large European multi-center trial that aimed to risk stratify a cohort of ICD patients for appropriate ICD shock and mortality with clinical and electrical parameters [8]. Several independent predictors of mortality as well as shock were identified. Interestingly, no electrical parameters could predict mortality, while, in contrast, programmed electrical stimulation (PES) and microvolt T-wave alternans (MTWA) were able to predict appropriate ICD shock (chapter 5). These results indicate the potential of electrical parameters in risk prediction of ventricular arrhythmias.
Beat-to-beat variability of repolarization quantified as short-term variability (STV) is a relatively new electrophysiological risk parameter. This parameter has been described in a dog model with chronic complete AV-block in which STV was determined from the monophasic action potential. This parameter was able to separate animals with high and low risk for drug induced Torsade de Pointes arrhythmias [9-12]. Moreover, several small clinical trials have also shown that STV derived from the QT-interval (STV_{QT}) was highest in patients at risk for ventricular arrhythmias [13-15].
In this study, we investigated the nature of STV_{QT} and its predictive value for death and appropriate ICD shock in patients enrolled in the EUTrigTreat clinical study.

Methods

Details of the EUTrigTreat study have been described elsewhere (chapter 5). Briefly, 672 ICD patients from four European centers with either primary or secondary prophylactic ICD indications were recruited from January 2010 through April 2014. At baseline, clinical characteristics were collected including cardiovascular history. A blood sample was taken to measure high-sensitivity C-reactive protein (hs-CRP), n-terminal-pro B-type-natriuretic protein (NT-proBNP) and serum creatinine. A standard 12-lead ECG, 24 hour Holter monitoring, left ventricular ejection fraction (LVEF) by echocardiography, PES, and MTWA (exercise or pacing test) were performed as well as a 2-minute high-resolution 12-lead ECG recording for analysis of STV_{QT}.

STV_{QT}

The QT-interval was measured using fiducial segment averaging [16]. Each QRS-complex was triggered at the R-peak. Next, each fiducial point (P-onset, QRS-onset, QRS-offset and end of T-wave) was aligned separately by cross correlating the individual complex to the average of the other complexes till maximal correlation was achieved. Subsequently, visual inspection was performed and complexes were adjusted manually if necessary. The QT-interval was calculated by adding the intervals of the trigger point to the QRS-onset and the T-wave, respectively.

Using Poincaré plots, each QT-interval was plotted against the former. The mean distance of the points perpendicular to the line of identity was defined as STV_{QT} ($STV_{QT} = \sum|D_{n+1} - D_n|/(n\times\sqrt{2})$, where D represents the QT-interval and n is the number of beats, usually 30. Extrasystolic beats were detected and excluded from analysis together with the following post-extrasystolic beat.

Endpoints

All-cause mortality and the first appropriate ICD shock were defined as primary and secondary outcome, respectively. During follow up, clinical data and device interrogations were collected every 3 to 6 months. All events were reviewed by members of the endpoint committee of the EU-TrigTreat study. Cases of death and appropriate ICD shock were adjudicated using available written information and stored EGM data from the device.

Statistical analysis

Variables were analyzed by univariate Cox regression analysis. Subsequently, multivariate Cox regression models were established for prediction of both shocks and mortality using predefined risk factors (age, LVEF, New York Heart Association class (NYHA), estimated glomerular filtration rate (eGFR) and gender) as well as additional risk factors that were determined by forward selection (qualified by $p<0.10$). Kaplan-Meier curves were compared by log-rank test. P-values <0.05 were considered statistically significant.

Results

Of 632 analyzable patients in the total cohort, 395 were included for STV_{QT} analysis (Figure 1). Underlying rhythm was sinus rhythm (SR) (n=323), biventricular pacing (CRT) (n=45) or atrial fibrillation (AF) (n=27). Baseline patient characteristics of SR patients with STV_{QT} versus other patients are shown in Table 1. SR patients with STV_{QT} analysis were younger and had a higher LVEF.

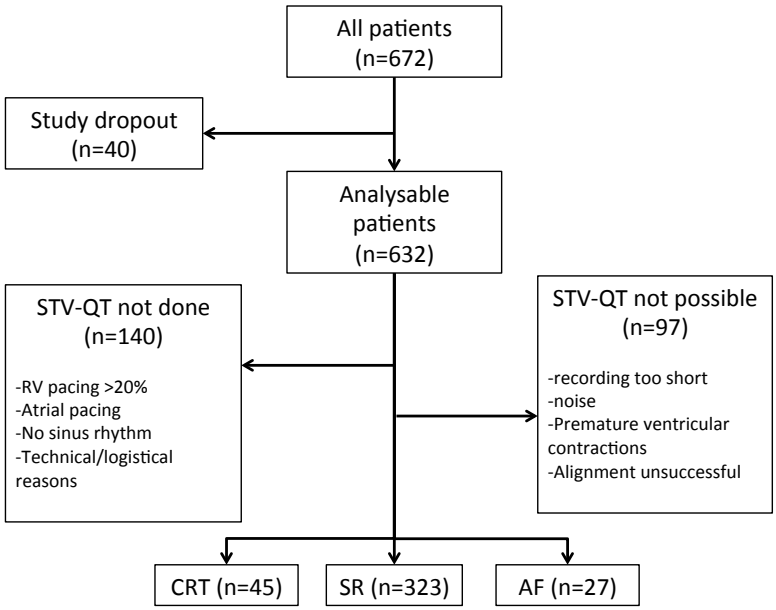

Figure 1. Flow chart of patients considered for analysis of short-term variability of the QT-interval (STV_{QT})

Table 1. Baseline characteristics of patients in sinus rhythm (SR) versus other patients.

Mean (SD) or N (%)	SR (N=323)	Other (N=309)	p-value
Age	58.96 (12.39)	66.53 (11.50)	<0.001
Gender			0.613
Female	64 (20%)	56 (18%)	
Male	259 (80%)	253 (82%)	
BMI	27.64 (4.67)	28.57 (5.84)	0.151
Leading cardiac disease			<0.001
DCM	81 (25%)	131 (43%)	
HCM	23 (7%)	15 (5%)	
ICM	133 (41%)	131 (43%)	
Other	85 (26%)	31 (10%)	
Prevention			<0.001
Primary	183 (57%)	217 (70%)	
Secondary	139 (43%)	92 (30%)	
LVEF	43.25 (13.86)	37.45 (12.66)	<0.001
NYHA			<0.001
I	135 (42%)	52 (17%)	
I-II	41 (13%)	42 (14%)	
II	85 (26%)	96 (31%)	
II-III	32 (10%)	49 (16%)	
III	30 (9%)	70 (23%)	
QRS	115.24 (26.98)	142.42 (36.09)	<0.001
QTc	443.72 (36.70)	475.15 (51.44)	<0.001

BMI = body mass index; DCM = dilated cardiomyopathy, HCM = hypertrophied cardiomyopathy, ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction, N= number; NYHA = New York Heart Association functional class; SD = standard deviation; QTc = corrected QT-interval.

Distribution of STV_{QT}

Analysis of STV_{QT} revealed different distributions of STV_{QT} among groups (Figure 2). Median STV_{QT} was lowest in SR patients (0.94 (0.51-2.26)), slightly higher in CRT patients (1.06 (0.53-3.18)) and severely increased in AF patients (5.09 (2.05-13.84)).

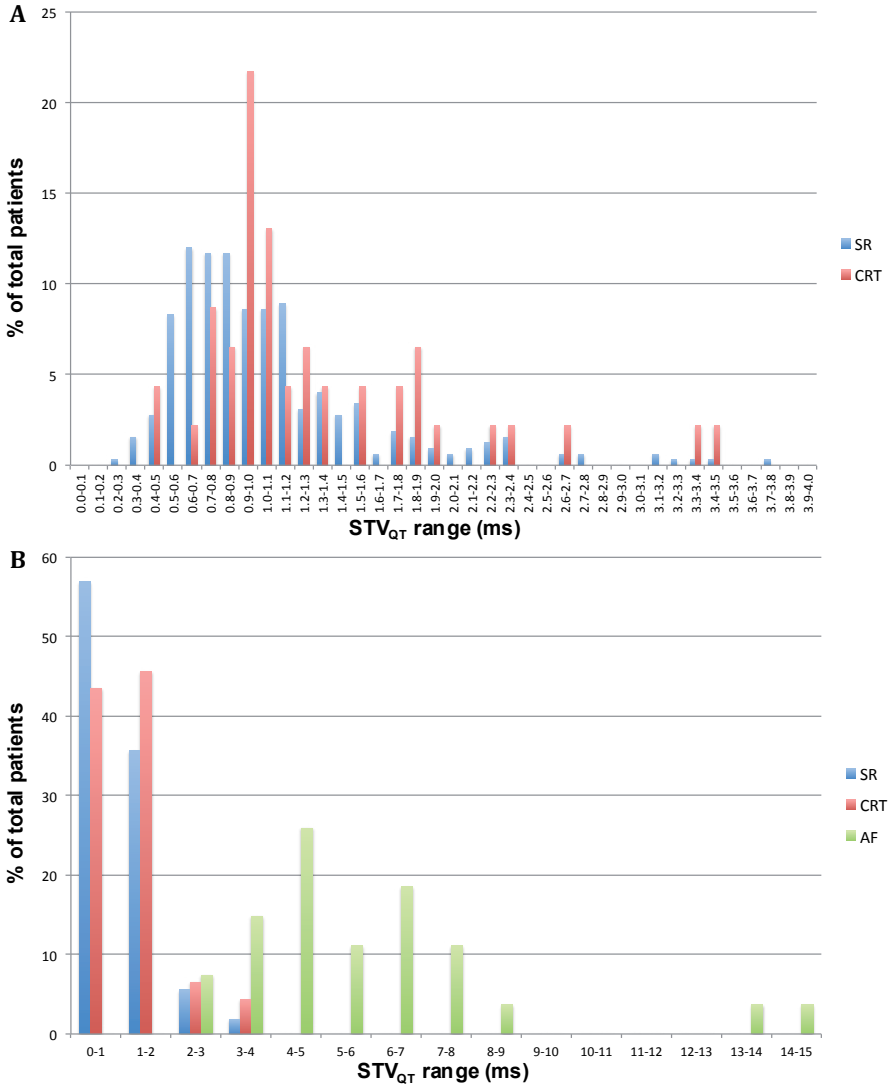

Figure 2. Distribution of STV_{QT} in patients with sinus rhythm (SR), cardiac resynchronization therapy (CRT) and atrial fibrillation (AF). A. Distribution of STV_{QT} in SR (blue bars) and CRT (red bars) patients. Vertical bars represent the STV_{QT} range for 0.1ms. Note the slight shift to the right of STV_{QT} distribution in CRT patients. B. Distribution of STV_{QT} in SR (blue bars), CRT (red bars) and AF (green bars) patients. Vertical bars represent the STV_{QT} range for 1.0ms.

Occurrence of endpoints

Over a mean follow-up of 2.4±1.2 years, 52 patients (8%, annualized rate 3.4%) died and 76 patients (12%, annualized rate 5.4%) received a first appropriate shock in the total cohort. In the subgroup of SR patients with STV_{QT}, 35 (11.3%, annualized rate 4.8%) received a first appropriate ICD shock and 15 people died (4.6%, annualized rate 2.0%). The CRT and AF patients only experienced 3 and 3 first appropriate shocks and accounted for 5 and 3 deaths, respectively.

Table 2. Baseline characteristics of low vs. high short-term variability of the QT-interval (STV_{QT}) patients dichotomized at the median of all STV_{QT} patients.

Mean (SD) or N (%)	**low STV_{QT} (N=170)**	**high STV_{QT} (N=153)**	**p-value**
Age	57.50 (12.10)	60.57 (12.55)	0.015
Gender			0.125
Female	28 (16%)	36 (24%)	
Male	142 (84%)	117 (76%)	
BMI	27.29 (4.96)	28.04 (4.30)	0.064
Leading cardiac disease			0.469
DCM	37 (22%)	44 (29%)	
HCM	13 (8%)	10 (7%)	
ICM	70 (41%)	63 (41%)	
Other	49 (29%)	36 (24%)	
Prevention			0.117
Primary	89 (53%)	94 (61%)	
Secondary	80 (47%)	59 (39%)	
LVEF	44.49 (14.18)	41.87 (13.41)	0.110
NYHA			0.010
I	87 (51%)	48 (31%)	
I-II	18 (11%)	23 (15%)	
II	39 (23%)	46 (30%)	
II-III	13 (8%)	19 (12%)	
III	13 (8%)	17 (11%)	
QRS	115.51 (26.94)	114.93 (27.12)	0.785
QTc	440.95 (36.50)	446.80 (36.79)	0.114

BMI = body mass index; DCM = dilated cardiomyopathy, HCM = hypertrophied cardiomyopathy, ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction, N= number; NYHA = New York Heart Association functional class; SD = standard deviation; QTc = corrected QT-interval.

Risk prediction by Cox regression and AUC

A detailed description of the univariate Cox regression and the establishment of the multivariate Cox models can be found in the EUTrigTreat main paper (chapter 5). The base model for adjustment consisted of age, LVEF, NYHA, eGFR and gender for both prediction of shocks and mortality. Additionally secondary prevention was added to the shock model, while atrial fibrillation and QRS width were added to the model for mortality.

STV_{QT} was dichotomized at the median and patient characteristics of both groups are shown in Table 2. The unadjusted hazard ratio revealed a significant association between a higher STV_{QT} and the first appropriate shock (hazard ratio 2.34, CI 1.15-4.72, p=0.02). Utilization of the adjustment model decreased the hazard ratio, although a higher STV_{QT} still tended to be associated with the first appropriate shock (hazard ratio 2.18, CI 1.00-4.74, p=0.05). Prediction of all-cause mortality revealed that both with (hazard ratio 2.30, CI 0.73-7.2, p=0.15) and without adjustment (hazard ratio 2.09, CI 0.74-5.88, p=0.16) the association between STV_{QT} and mortality was not significant. Figure 3 shows Kaplan-Meier curves of low and high STV_{QT} for both shocks and mortality.

The integrated area under the curve (AUC) of the ROC-curve was calculated in order to determine the discriminatory power for STV_{QT}. The AUC for appropriate shocks and mortality was 0.556 and 0.567, respectively.

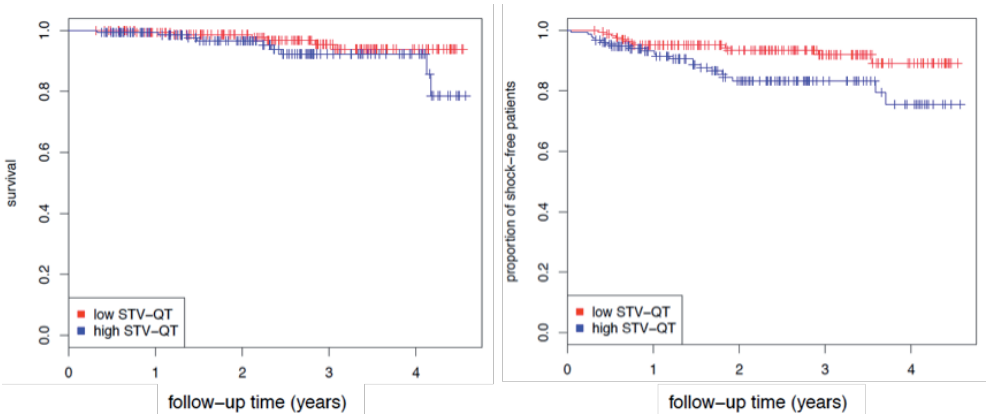

Figure 3. Kaplan-Meier curves for appropriate shock and mortality in high and low short-term variability of the QT-interval (STV_{QT}) groups. High STV_{QT} values can predict appropriate shocks independently (right panel, p=0.015) while all cause mortality (left panel) is not different between low and high STV_{QT} groups (p=0.153).

Discussion

For the first time, beat-to-beat variability of repolarization quantified as STV_{QT} has been analyzed in a large ICD patient cohort. We demonstrated different distributions of STV_{QT} in different patients groups. Despite the relative low event rate, STV_{QT} reveals a clear trend to be an independent predictor for appropriate ICD shocks in SR patients.

The rationale of beat-to-beat variability of repolarization

Identification of patients at increased risk for SCD is still a major challenge. Subtle changes in repolarization have been considered as indication for an increased risk of ventricular arrhythmias. STV_{QT} is one of the parameters that determine the instability of repolarization by measuring absolute beat-to-beat differences of the QT-interval. In the CAVB dog model, STV has been quantified from the MAP in which it was able to distinguish between remodeled and unremodeled conditions. Moreover, dogs susceptible for TdP arrhythmias could be identified with a high sensitivity and specificity [9]. Different mechanisms may underlie the increased instability of repolarization. In ventricular cardiomyocytes, it has been shown that the degree of action potential duration prolongation is associated with an increase of beat-to-beat variability of repolarization [17]. Furthermore, calcium release from the sarcoplasmic reticulum near L-type calcium channels also promotes beat-to-beat variability of repolarization [18]. In vivo, beat-to-beat variability of repolarization is associated with alterations in preload and is only present in remodeled conditions [19]. These results indicate that variability of repolarization quantified as STV can reflect instability of the action potential and the increased risk for ventricular arrhythmias. However, MAP measurements are invasive and only reflect regional repolarization conditions of the heart. Therefore, analysis of the QT interval is more elegant since it reflects global repolarization and it can be derived from the surface ECG.

Calculation of the QT-interval from the surface ECG is a delicate procedure as it is hard to define the end of the T-wave. In the present study, we used the method of fiducial segment averaging to prevent disagreement with respect to the end of the T-wave [16]. Different fiducial points (e.g. Q-onset and T-end) were semi-automatically aligned and visually inspected. After alignment, Q-onset and T-end were determined all at once, so we did not have to determine the end of T-wave for each complex separately.

Several small studies have shown that STV_{QT} in well-described populations is associated with an increased risk for ventricular arrhythmias [13-15,20]. Furthermore, STV_{QT} is increased in conditions associated with an increased arrhythmic risk such as patients treated with antracyclin [21], professional soccer players [22], acromegaly patients [23] and patients with left ventricular hypertrophy [24]. These results suggest that STV_{QT} can be increased in a wide variety of diseases that are all related to an increased risk of SCD. The strength of the EUTrigTreat clinical study was the broad scope by recruiting all kind of patients eligible for ICD therapy, regardless the underlying disease. Both, patients with primary and secondary prophylaxis were included as well as patients with low and high LVEF indicating that this cohort can be considered as the best possible representation of the general population. On the other hand, we have shown that the distribution of STV_{QT} differs between SR, CRT and AF patients, that is most probably related to the underlying rhythm or disease. The heart rhythm in patients with AF is irregular heart rhythm that may explain the increased QT-interval variability. Therefore, our results indicate that different cut-off values have to be used in different patient categories. The number of events in the present study does not allow us to determine adequate cut-off values for STV_{QT} or to perform further sub-analyses with respect to etiology.

Shocks versus mortality

Univariate analysis revealed that STV_{QT} was significantly associated with an increased risk for appropriate shocks but not for mortality. After adjustment for well-known risk factors, a strong trend remained present, indicating a possible role for STV_{QT} in prediction of shocks. The low predictive value of STV_{QT} as demonstrate by the AUC is most probably related to the low event rate for both shocks and mortality. Therefore, at the moment our results have to be interpreted with a bit caution, but it is definitely worthwhile to further investigate the predictive value of STV_{QT} for ICD shocks and mortality. Moreover, when focusing on future perspectives of the different tests that have been used in the EUTrigTreat clinical study, it is obvious that the non-invasive nature of STV_{QT} is a big advantage compared to the invasive electrophysiological study and the exercise-dependent MTWA test.

A long-term follow-up of the EUTrigTreat clinical study is planned and most probably these results will give further insight in the predictive value of STV_{QT}. Moreover, multiple regression analyses could be done in this long-term follow-up to determine the role of STV_{QT} in relation to the other electrophysiological parameters (e.g. inducibility upon PES, MTWA). Validation and further exploration of STV_{QT} should be done in trials with a large number of ICD recipients such as the ongoing, prospective EU-CERT-ICD study (NCT 02064192)

Limitations

STV_{QT} could not be determined in about one third of the patients. In most cases, technical and logistical failure (Figure 1) was the basis for the unsuccessful recording. Moreover, different distributions of STV_{QT} were found in different patient groups what prompted us to exclude CRT and AF patients. These restrictions have lead to selection bias (Table 1). However, the advantage is that our results are more applicable to the general population. The event rates in the present study were rather low and therefore the results should be interpreted with some caution. Definitely, a longer follow-up with higher event rates will give us further insight into the predictive value of STV_{QT}.

Conclusion

Beat-to-beat variability of repolarization quantified as STV_{QT} shows a patient group dependent distribution. In SR patients, STV_{QT} is associated with appropriate ICD shocks and not with all-cause mortality, suggesting its potential value in the prediction of SCD.

Funding

The research leading to the results has received funding from the European Community's Seventh Framework Programme FP7/2007-2013 under grant agreement No. HEALTH-F2-2009-241526, EUTrigTreat.

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CHAPTER 7

Fiducial segment averaging for accurate determination of the inflection points on the 12-lead surface ECG and semi automatic measurement of QT variability.

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Not published.

Introduction

Nowadays all digital ECG recorders have wave form recognition capability that enables automatic detection of fiducial points (key landmarks on the ECG like R peak and QRS onset) and calculation of the basic time intervals. Although automated analysis of the digital ECG could improve standardization and aid diagnostic classification, errors like automatic detection of ectopic beats, misinterpretation by artifacts and inaccurate fiducial point detection can occur. Furthermore some measurements on the ECG are not easy to capture in an algorithm for example measurement of the QT interval [1].
The in 2007 published AHA/ACC/HRS recommendations for the standardization and interpretation of the electrocardiogram provide a special focus on digital signal acquisition and computer-based signal processing. They emphasize that although sensitivity and specificity is improving, human over reading and confirmation of automated analyzed ECGs is still required [2]. To overcome these shortcomings semi-automatic software programs have been developed. An example of such software is Intraval, developed by Ritsema van Eck from the Rotterdam Erasmus University Medical Center and customized for use in two large clinical trials; the international EUTrigTreat trial and the national Markers And Response to Cardiac resynchronization therapy (MARC) study [3]. It enables to locate the fiducial points by the method of fiducial segment averaging [4]. This helps to overcome some of the major challenges in the analysis of the ECG: the measurement of the QT interval and of QT interval variability. In this paper the relevance and use of this method is discussed.

The digital ECG

The 12-lead resting ECG is an easily applicable, non-invasive and most used cardiovascular diagnostic tool. The electrical signal recorded at the skin has to be processed before the 3 bipolar and 6 unipolar leads can be constructed. Amplification and part of the filtering are often applied before actual storing of the signal thereafter the signal is further digitally processed. Quality of the signal depends greatly on the sampling frequency, amplitude resolution and bandwidth. A sufficient bandwidth and a high enough sampling frequency are necessary to also detect details in the electrocardiogram such as QRS notches (high frequency) and T-U waves (low frequency). A signal can be exactly reconstructed from its samples if the sampling frequency is greater than twice the highest frequency of the signal (to prevent aliasing) [5]. In practice, sampling frequency is often higher than twice the signal's limited bandwidth. In the clinical setting a bandwidth of 0.05Hz-150Hz and sampling frequency is 500Hz is most often used. For more precise measurements of especially low amplitude high frequency signals or variability measurements a higher sampling frequency is desired [6,7]. Furthermore a high amplitude resolution is necessary to get a smooth curve.

Fiducial Segment Averaging.

Fiducial segment averaging is a patented technique that improves accurate determination of the fiducial points by alignment of all separate fiducial points. The individual QRS complexes are identified with a matched filter technique. The trigger time points obtained are fine-adjusted by cross correlating in turn each individual complex with the average of the remaining complexes and then shifting the complex till maximum correlation is achieved. The process is repeated till no improvement can be attained. After identification of the trigger points all complexes are labeled normal, as ectopic or as artifact. In an overlay plot the individual fiducial points are identified and a similar fine-adjustment is made to the individual points with a segment of approximately 30 milliseconds around the fiducial point. This process is performed in turn for P onset, QRS-onset and offset, peak of T-wave and end of T-wave. The validity of the result can be assessed by visual inspection of the segment and by examining the standard deviation of the time interval measurements obtained. If necessary, manual adaptations can be made for every individual fiducial point of each complex. The values of PR-interval, QRS duration and QT-interval of each individual beat follow from the differences of their individual fiducial points in relation to the trigger point.

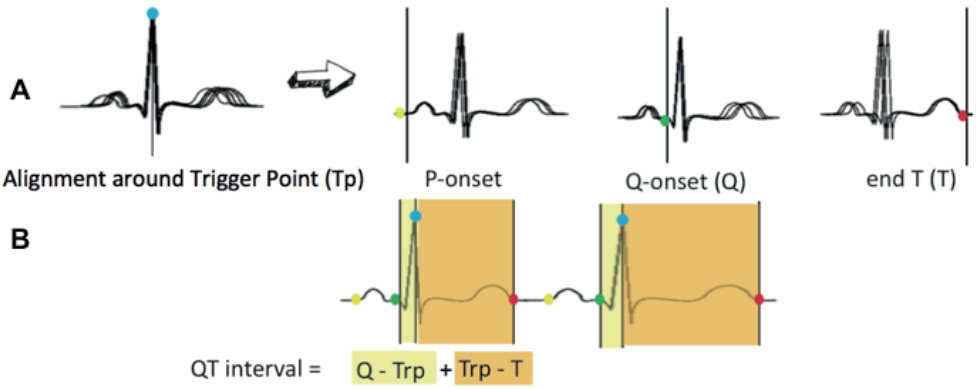

Figure 1. Interval measurement with fiducial segment averaging. Panel A: Alignment of the complexes for every fiducial point. Panel B: The QT-interval is constructed for every single beat from the individual distance from Q-onset to trigger point plus trigger point to end T.

Determination of the end of the T-wave remains a controversial issue. Differences in T wave morphology (biphasic/negative), low amplitude of the T-wave and the U-wave form the most important issues that complicate determination of the end of the T-wave [8]. When beat-to-beat variations in the QT-interval have to be assessed this problem is even further aggravated since the measurement error overestimates the actual variability because the absolute value of the differences is taken into account. This demands an

accurate determination of the QT-interval. With fiducial segment averaging the fiducial point (for example the end of the T) is determined for all complexes at the same position in the complex overhead constructed from all available leads. This eliminates the problem of defining the precise end of the T-wave and eliminates the repeated measurement error from beat-to-beat. Because the alignment is done for all fiducial points separately, the individual differences (of every beat) between fiducial points and trigger point are preserved. Therefore also the possible beat-to-beat changes in Q-onset trigger point are taken in to account (Figure 1).

QT variability

Why measure it?

A reduced left ventricular ejection fraction (LVEF) is currently the main clinical determinant of a patient's eligibility for ICD therapy although a clear relationship with the pathophysiology of ventricular arrhythmias has not been demonstrated. It does not distinguish patients who will die of arrhythmia and those who will die of heart failure, which leaves a demand for a better risk indicator. A prolonged QT-interval was, for a time, regarded as such an indicator for arrhythmic risk but the specificity of QT duration proved to be questionable [9]. QT variability has been proposed as a more promising risk indicator [10-12]. An example of a marker for QT variability is short term variability of repolarization (STV), this quantifies the beat-to-beat variations of repolarization between consecutive beats and can be calculated by the following formula: $STV = \sum|D_{n+1}-D_n| \ (N\times\sqrt{2})^{-1}$ where D represents the determinant of repolarization (i.e. QT-interval, monophasic action potential duration (MAPD)) and N the number of beats taken into account - 1. In comprehensive animal studies STV of the LVMAPD (STV_{LVMAPD}) was able to identify individuals with a diminished repolarization reserve, susceptible for repolarization dependent ventricular arrhythmias [12,13].

To translate these results into clinical practice, a number of descriptive studies have been performed in humans measuring STV of the QT-interval (STV_{QT}) (Table 1)[14-19]. These studies compare a patient population known to be at higher risk of ventricular arrhythmias to a control population. The results show that despite similar QT_C in most populations, STV_{QT} is consistently increased in the patient populations known to be at an increased risk for ventricular arrhythmias and in patients with heart failure. Therefore STV_{QT} seems superior to QT_C-interval prolongation in identifying patient populations at risk. Studies on larger datasets, preferably comparing the different markers of QT variability, are necessary to confirm these findings [20].

How to measure it?

To quantify STV_{QT} the QT-intervals of N consecutive beats are plotted against the preceding ones in a Poincaré plot. The value of STV_{QT} is defined as the mean distance of the points perpendicular to the line of identity, calculated with the formula $STV_{QT}= \sum|D_{n+1}-D_n|$

$(N\times\sqrt{2})^{-1}$ with Dn = QT interval of beat n and N=number of beats -1. Ectopic beats were detected on the basis of timing and morphology and were excluded from analysis together with the two following complexes.

Bandwidth, resolution and sampling frequency determine the faithfulness of the recorded ECG, i.e. its capability of rendering subtle high and low frequency details. For our analysis (Wijers 2012) we employed the CardioPerfect ECG module of Welch Allyn that records a 12-lead ECG at a sampling frequency of 1200Hz and uses a 10-bit A/D recorder with a range of 5mV that results in a resolution of 0.005mV.

Table 1 shows that different methods for measurement of STV_{QT} have produced similar results although at different values of STV_{QT}. This may be explained by several factors. 1) Signal quality and type of analysis 2) Determinant of repolarization. 3) Consecutiveness and time interval.

Table 1. Overview clinical studies that analyzed short-term variability of the QT-interval (STV_{QT}) in patients at risk for sudden cardiac death (SCD). $STV_{QT}30$, $STV_{QT}60$= 30 $(\sum|D_{n+1}-D_n|\ (30\times\sqrt{2})^{-1})$, respectively 60 $(\sum|D_{n+1}-D_n|\ (60\times\sqrt{2})^{-1})$ differences (Dn+1-Dn) used for calculation of STV. STV_{QT}Mean = calculation of $STV_{QT}30$ with a moving window over the full 5 min recording and then averaged. ECG = electrogram; EGM = electrogram; ICD = implantable cardioverter-defibrillator; LQTS = Long QT syndrome; QTc = corrected QT-interval.

Article	Population & Method	QT_C Controls	QT_C Patients	STV_{QT} Controls	STV_{QT} Patients
Hinterseer *Eur Heart J. 2008(14)*	*Acquired Long QT (n=20) Paper ECG, $STV_{QT}30$, manually*	421±34	428±25	3.6±1	8.1±4*
Hinterseer *Am. J. Card. 2009(15)*	*Congenital LQTS (n=40) Paper ECG, $STV_{QT}30$, manually*	411±32	449±41*	4.1±2	6.4±3*
Ritsema van Eck Comp in Card. 2009(16)	*Non-cardiovascular patients receiving chemotherapy (n=39) semi-automated 600 Hz ECG, STV_{QT}Mean*	424	451*	1.25	3.17*
Hinterseer *Am. J. Card. 2010(17)*	*Heart failure (n=60) Paper ECG, $STV_{QT}30$, manually*	415±32	419±36	4.1±2	7.8±3*
Lengyel *Plos one 2011(18)*	*Soccer players (n=76) 1000Hz ECG, $STV_{QT}30$, automated*	422	419	3.5±1	4.8±1*
Oosterhoff *Heart Rhythm 2011(19)*	*ICD patients (n=59) EGM, $STV_{QT}60$, semi-automated*	N.A	539±58	N.A	19.3±15.1
Wijers *Unpublished 2012*	*Heart failure, before CRT implantation (n=10) 1200 Hz ECG, $STV_{QT}30$, semi-automated*	429±20	518±42*	0.63±0.13	0.83±0.20*

Signal quality and type of analysis

When quantifying the QT variability with STV absolute differences are used. Because of this, there is no cancellation of measurement error. This means that the measurement error is of significant influence on the value of STV. This does not mean that a method with a higher measurement error necessarily loses its predictive value. This concept is visualized in Figure 2. It shows that the adjustment interval depends on sampling frequency and therefore the measurement error and the value of STV differ. Nevertheless the ability to distinguish between a control and a heart failure patient is not lost.

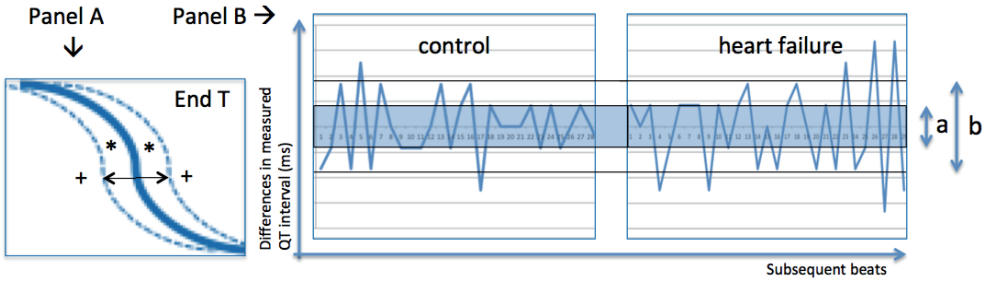

Figure 2. Influence of sampling frequency on the value of short-term variability of the QT-interval (STV_{QT}).
Panel A: No cancellation of measurement error. * = 0.83ms at 1200Hz and 1.67ms at 600Hz.
Panel B: Detection of differences in beat-to-beat QT duration in a control and a heart failure patient at different sampling frequencies. a = ±0.83ms, b = ±1.67ms

Sampling frequency will influence the value of STV up to at least 2kHz [21]. When using a paper ECG the low resolution causes a higher value of STV_{QT}. Furthermore the type of analysis is also able to influence the detail in which the variability is assessed and therefore the value of STV. For example without alignment, determination of the QT-interval has to be done for every beat separately causing repetition of the measurement error and therefore a higher STV.

Determinant of repolarization

For calculation of the STV different measures of repolarization can be used. Much of the pre-clinical research done in the canine chronic atrioventricular block (CAVB) model used the MAPD as measure of repolarization. Because of the invasive nature of this measurement and the difficulty to acquire signals of sufficient quality in humans, the QT-interval as an alternative measure of repolarization is now being studied. Another alternative could be the activation recovery interval (ARI) derived from the intracardiac EGM This measurement can be done easily in patients with a pacemaker and/or implantable cardiac defibrillator (ICD) via the right ventricular (RV) lead and will represent a more local measure of repolarization compared to the QT-interval. Compared to the MAPD the EGM has the advantage that it is possible to acquire recordings from the same location (the lead is fixed in the myocardium) at different time points (or even continuously). Since no catheter

placement is needed recordings during awake (not anesthetized) conditions can be easily performed. Oosterhoff et al showed that measurements of the LV MAPD and LV ARI are comparable in the canine CAVB model and detected a very high STV of the RV EGM in patients with ICDs [19].

Time interval

In the literature no uniform definition of "short term" is employed. Different time spans, or, alternatively, number of beats are being used for different measures of QT variability. For convenience in clinical practice a limited number of beats will be preferred.
To evaluate if the number of beats taken into account is of influence we assessed STV_{QT} in ten heart failure patients and ten age and gender matched controls in 5-minute digital ECG recordings for variously selected sequences of beats. Figure 3 demonstrates that there are no significant differences between STV_{QT} when calculated in 4 different ways. We therefore chose to use a sequence of no more than 31 beats (30 differences) in our clinical studies. With all methods a significant higher STV_{QT} was observed in the heart failure patients compared to the controls.

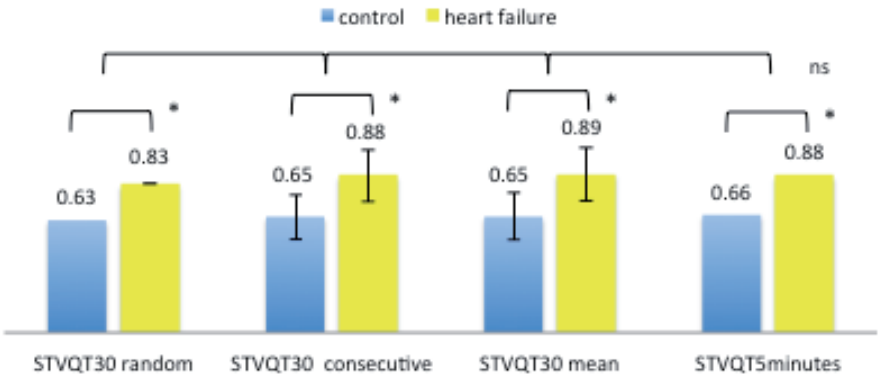

Figure 3. Values of short-term variability of the QT-interval (STV_{QT})(ms) calculated by 4 different methods. 1) $STV_{QT}30$ random = STV of 30 differences in QT interval of 31 consecutive beats randomly selected in the 5-minute recording. 2) $STV_{QT}30$ consecutive =Average of the first 31 beats (beat 1-31), second 31 beats (beat 32-62), and so on. 3) $STV_{QT}30$ mean= Average of $STV_{QT}30$ over the whole recording with a moving window: beat 1 until 31 plus the STV of beat 2 until 32 and so on. 4) $STV_{QT}5$minutes= Calculation of $STV_{QT}N$ with N number of beats -1 in the full 5 minute recording. Standard deviations (SDs) refer to the intra-individual measurements.

Additional features

Another advantage of semi-automated analysis of the ECG is that once the fiducial points are accurately identified, almost every ECG interval can be automatically extracted i.e, JT-interval, Tpeak-Tend, not only QT variability off all intervals, and also measured with different quantifications of QT variability (i.e. STV_{QT}, QTVI). Besides this we recently also

implemented the feature to extract the 12 lead derived vectorcardiogram by the Kors' regression method in the Intraval software [22].

Conclusion

In modern clinical research one cannot go without digitally acquired and analyzed ECGs. Although much progression has been made to improve accuracy of the automated analysis, the measurement of certain variables still has to be supervised and possibly adjusted by humans. Special techniques, like fiducial segment averaging, help to improve the identification of inflectional points in the ECG to the benefit of the accuracy of the (semi-automated) measurement of intervals and interval variability.

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PART II

MONITORING OF ARRHYTHMIC RISK

CHAPTER 8

Electrophysiological measurements that can explain and guide temporary accelerated pacing to avert (re)occurrence of Torsade de Pointes arrhythmias in the canine chronic atrioventricular block model.

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Heart Rhythm 2017 – In press

Abstract

Background: Pacing at higher rates is known to suppress Torsade de Pointes (TdP) arrhythmias. Nevertheless, exact application and mechanism need further clarification. In the anesthetized, canine, chronic atrioventricular block model, ventricular remodeling is responsible for a high and reproducible incidence of TdP upon a challenge with dofetilide.
Objective: We used this model to investigate by what mechanism accelerated pacing averts TdP and what repolarization parameter could be used to guide temporary applied accelerated pacing (TAP).
Methods: Ten dogs with repetitive TdP after dofetilide when paced at 60bpm were selected. In a serial experiment TAP was initiated at 100bpm after the first ectopic beat. Electrocardiogram, right and left ventricular (RV and LV) monophasic action potential (MAP) were recorded. In a subset vertical dispersion was determined with a duodecapolar catheter. Temporal dispersion was quantified as short-term variability (STV). Arrhythmias were quantified with the arrhythmia score (AS).
Results: The increase in the repolarization parameters seen after dofetilide was counteracted by TAP (e.g. LV MAPD from 381±94 back to 310±17ms*, *p<0.05). Temporal dispersion (STV_{LVMAPD}) increased from 0.69±0.37 to 2.59±0.96ms* after dofetilide and back to 1.15±0.54ms* with TAP. This was accompanied by suppression of recurrent TdP in 7/10 dogs* and a trend towards reduction in vertical (spatial) dispersion from 56±25 to 31±4ms (p=0.06). In those dogs, seconds after capture of TAP, almost all ectopy disappeared causing a decrease in AS from 21±12 to 4±3*
Conclusion: TAP is effective in averting TdP by decreasing spatial and temporal measures of repolarization. Increase in temporal dispersion (STV) can guide TAP.

Introduction

Pacing at higher rates is long known to be effective in prevention of repolarization dependent arrhythmias such as Torsade de Pointes (TdP). After withdrawal of QT prolonging drugs, correction of potential electrolyte disturbances and beta blockade, pacing at higher rates can prevent (re)occurrence of TdP [1-5]. Although a heart rate increase both due to exercise and isoproterenol infusion causes a paradoxical QT prolongation in patients with long QT syndrome (LQTS), pacing at a faster rate has shown to shorten absolute repolarization duration, reduce spatial dispersion and suppress early after depolarizations (EAD) [6-8]. All are believed to be involved in either the initiation or perpetuation of TdP, but the exact mechanisms of the effect of pacing on the control of TdP remains controversial.

Only few studies, in patients with congenital or acquired LQTS, have been performed to investigate the effectiveness and antiarrhythmic mechanism of pacing at higher rates [1-4]. These studies implicate that an implantable cardiac defibrillator (ICD) is needed as a safety net in this population because sudden deaths still occur. However, TdP is an arrhythmia that is fast but often self-limiting that could lead to unnecessary ICD shocks in these patients [9]. The question is if the programmed pacing rate (≈80 bpm) and concomitant decrease in QT-interval in these studies were sufficient to prevent TdP. Prolongation of absolute QT duration is associated with the occurrence of TdP but it is not proven that the antiarrhythmic effect of pacing at higher rates is determined by reducing the QT-interval only. Continuous pacing at higher rates could cause inconvenience for the patient and could be detrimental for cardiac function [10].

The canine chronic atrioventricular block (CAVB) model is sensitive for TdP due to structural, contractile and electrical remodeling upon AV block. After anesthesia and administration of dofetilide, a blocker of the rapid component of the delayed rectifier potassium outward current (I_{Kr}), 70-80% of these dogs get single and multiple ectopic beats (EB) followed by repetitive TdP [11]. Especially the inducible dogs show a higher electrical instability (temporal dispersion) quantified as short-term variability of repolarization (STV), which further increases before the occurrence of TdP [12,13].
The aim of this study was to investigate if temporary accelerated pacing (TAP) can avert TdP when instability of repolarization is already present, to elucidate the antiarrhythmic mechanism and to determine a repolarization marker that could guide this intervention.

Methods

Animal handling

Ten purpose-bred mongrel dogs of either sex (body weight 26±3kg, Marshall, New York) were used. Animal handling was in accordance with Dutch law on animal experiments and the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. The Animal Experiment Committee of the University of Utrecht approved all experiments.

Anesthesia

Experiments were performed under general anesthesia. Premedication consisted of methadone 0.5mg/kg, acepromazine 0.5mg/kg and atropine 0.5mg i.m. After 30 minutes anesthesia was induced with pentobarbital sodium 25mg/kg i.v. and maintained by isoflurane 1,5% in O_2 and N_2O, 1:2.

AV-block and pacemaker/ICD implantation

In an initial procedure, AV block was performed with radiofrequency ablation of the proximal His bundle. Subsequently, a pacemaker or ICD was implanted with one lead in the right ventricle (RV). After creation of the AV-block we let the dogs remodel for ≥ 2 weeks on idioventricular rhythm (IVR).

Experimental set-up

The dogs were left without cardiac pacing except during experiments. Then the pacemaker/ICD was put on a lower rate of WI60 bpm (or slowest rate with capture if IVR ≥60bpm) to control ventricular activation and prevent severe bradycardia with concomitant blood pressure drop during anesthesia. A standard 6-lead ECG was simultaneously recorded with monophasic action potential duration from the free wall of both the left and right ventricle (LV_{MAPD} and RV_{MAPD}, respectively). MAP catheters were introduced via the femoral vein and artery.

Ten dogs were selected based on inducibility upon a challenge with the I_{Kr} blocker dofetilide (25µg/kg infused over 5 minutes) (experiment 1). Inducibility was defined as ≥ 3 TdP within ten minutes of dofetilide infusion. If recurrent TdP occurred, infusion was stopped before infusion of the total dose. Defibrillation was applied if a TdP was not self-terminating within 10 seconds. In a second experiment (experiment 2) pacing frequency was gradually increased from WI60 bpm to WI100 bpm after the occurrence of the first EB.

Measurements

Arrhythmias; sEB, mEB and TdP (defined as ≥ 5 beats with QRS vector twisting around isoelectric line) were scored over 10 minutes. An EB was counted as such when occurring during the T-wave of the previous beat. Arrhythmia score (AS) was calculated using the

quantification of Stams et al [14]. ECG intervals (RR, QRS, QT, Tpeak-Tend (TpTe)) were determined offline by manual assessment in EP-TRACER software (CardioTek, Maastricht, The Netherlands) and calculated from an average of 5 consecutive beats. QT-intervals were corrected for heart rate (QTc) [15]. The MAPs were analyzed in a semi-automatic manner with the AutoMAPD software (Matlab, Natick USA). The LV MAPD and RV MAPD were measured from the steepest upstroke of the MAP until 80% of repolarization. STV of LV MAPD and RV MAPD was calculated over 31 beats using the following formula: STV $= \sum|D_{n+1} - D_n| \, (N \times \sqrt{2})^{-1}$ where D represents the determinant of repolarization (in this case MAPD) and N the number of beats taken into account – 1. Interventricular dispersion was quantified as Δ MAPD (LV MAPD - RV MAPD).

In experiment 1 and 2, measurements were done at baseline from 5 consecutive beats at the end of the 10 minutes recording and after administration of dofetilide just before the occurrence of the first EB. After initiation of TAP, measurements were performed at 1-2 minutes of TAP (TAP 1-2) and 5 minutes of TAP (TAP 5).

Multipolar electrocardiogram catheter

In a subset of dogs (n=4), endocardial unipolar electrograms (EGMs) were recorded with a duodecapolar catheter (St Jude Medical, The Netherlands). This catheter consists of 10 electrode pairs (2mm distance between electrodes, 10mm between electrodes pairs) and was positioned in the LV under fluoroscopic guidance in two planes to assure correct position. A reference electrode was placed in the right hind leg vein. Nine simultaneously recorded unipolar EGMs were derived from the most distal electrode of every of the 10 pairs. In the AutoMAPD software the activation time (AT) was measured from the pacing spike until the dV/dt minimum of the RS complex. The activation recovery interval (ARI) was calculated as the dV/dt minimum of the RS complex to the dV/dt maximum of the T-wave. Repolarization time (RT) was calculated as the sum of the AT and ARI. The ARI derived from the EGM has shown to be representative for the action potential duration (APD) [16]. Vertical dispersion was quantified as the largest difference in repolarization time between two subsequent electrodes. Measurements were done from one beat at time points described above.

Statistical analysis

Pooled data are expressed as mean ± standard deviation. All comparisons of electrophysiological data were compared with generalized estimating equations. Inducibility was compared using the McNemar test for paired proportions. Pearson correlation coefficients were calculated for linear distributed variables. Spearman rank correlation was used to determine correlations between STV values. A p-value ≤ 0.05 was considered significant. SPSS version 20.0.0 was used for the statistical analysis.

Results

After AV block the ventricular rate in awake conditions reduced from 100±26bpm to 41±7bpm. Pacing during experiments was performed at VVI60 except from one dog that had an IVR > 60 and therefore was programmed on VVI70. As expected [11], data before (baseline) and after (before the first EB) dofetilide in experiment 1 and 2 yielded similar results (data not shown). Prior to the first EB, dofetilide significantly increased all repolarization parameters (Table 1, columns 1 and 2) such as LV MAPD and RV MAPD (from 250±24ms and 231±13ms to 381±94ms and 301±39ms, respectively) but also the temporal (STV LV and STV RV) and spatial (TpTe and Δ MAPD) dispersion surrogates. Sudden acceleration from VVI60 to VVI100 seemed to induce/aggravate TdP in the first two, we therefore chose to gradually decrease cycle length in 20±9s in the remainder of experiments. Figure 1 shows a representative example of the gradual acceleration.

Table 1. Effect of dofetilide and subsequent temporary accelerated pacing (TAP) on electrophysiological markers.

n=10	Baseline	Before 1stEB	TAP 1-2	TAP 5
RR	989 ± 45	992 ± 48	605 ± 5‡	605 ± 7‡
QRS	127 ± 12	127 ± 10	134 ± 7‡	129 ± 10
QT	421 ± 38	581 ± 77†	483 ± 51‡	504 ± 30‡
QTc	422 ± 37	582 ± 77†	544 ± 55	575 ± 63
TpTe	122 ± 50	209 ± 56†	142 ± 40‡	153 ± 35‡
LV MAPD	250 ± 24	381 ± 94†	316 ± 29	310 ± 17‡
RV MAPD	231 ± 13	301 ± 39†	273 ± 19‡	283 ± 27
Δ MAPD	22 ± 18	104 ± 54†	47 ± 40‡	44 ± 54‡
STV LV MAPD	0.69 ± 0.37	2.59 ± 0.96†	2.04 ± 1.02	1.15 ± 0.54‡
STV RV MAPD	0.62 ± 0.29	1.34 ± 0.66†	1.34 ± 0.58	0.80 ± 0.27‡

Data is shown from before (baseline) and after administration of dofetilide (before the first ectopic beat (1st EB) and after initiation of TAP). TAP1-2 = 1-2 minutes after initiation of TAP, TAP 5= 5 minutes after initiation of TAP. † = p <0.05 relative to baseline. ‡ = p <0.05 relative to before the 1st EB. TpTe= Tpeak-Tend. MAPD=monophasic action potential duration. STV=short-term variability.

Figure 1. Representative example of gradual increase in pacing rate from 60 to 100 bpm. Vertical arrow depicts start of gradual acceleration of pacing rate upon the first ectopic beat. Horizontal arrows depict paced cycle length.

Timing and inducibility of arrhythmias

The first EB after administration of dofetilide occurred on an average of 2.45 minutes (165±45s) in experiment 1 and 2.48 minutes (168±48s) in experiment 2. The time to the occurrence of TdP after the first EB in experiment 1 varied between 3-177s (68±74s). TAP substantially decreased inducibility from 10/10 (100%) to 3/10 (30%) ($p<0.05$) and also practically eliminated all ectopy (Figures 2 and 3). As a result, the AS decreased from 24±12 to 9±11 ($p=0.02$) (21±12 to 4±3 in successfully treated dogs, n=7, $p=0.01$).

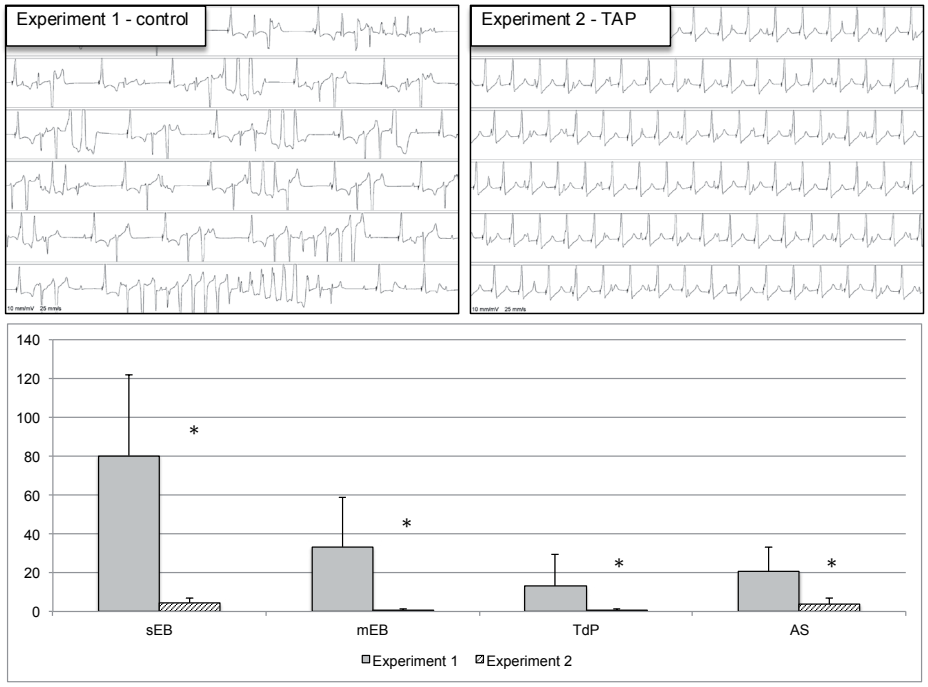

Figure 2. Quantification of arrhythmias in the 7 successfully treated dogs. In the first panel a representative ECG tracing is shown during experiment 1 and 2 at the same time point (t=323s after start dofetilide). In the lower panel single ectopic beats (sEB), multiple ectopic beats (mEB), Torsade de Pointes (TdP) and arrhythmia score (AS) are quantified (average ± standard deviation). * $p<0.05$.

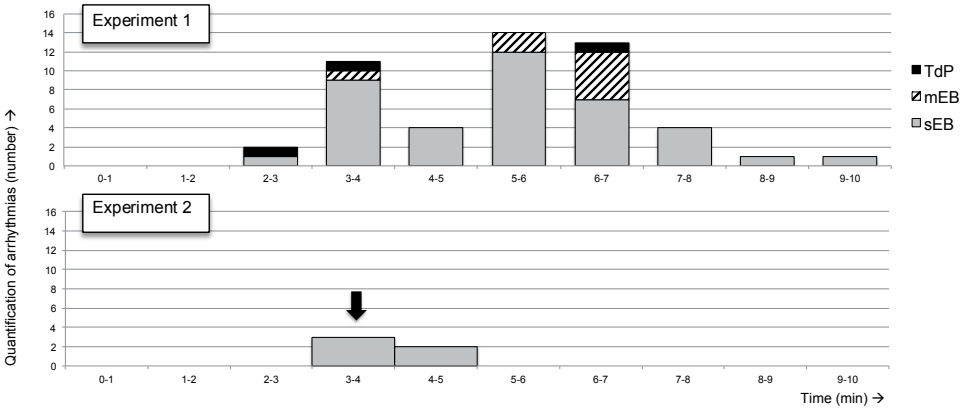

Figure 3. A representative example of difference in single ectopic beats (sEB), multiple ectopic beats (mEB) and Torsade de Pointes (TdP) between experiment 1 (upper panel) and 2 (lower panel) in the same dog. Arrow represents start of temporary accelerated pacing.

Electrophysiological effects of accelerated pacing

Upon capture of TAP, all markers of repolarization decreased significantly (Table 1, columns 3 and 4). For most parameters this effect occurred within 1-2 minutes (TAP1-2) and remained stable (TAP5). However, the decrease in LV MAPD and STV was slower and became significant at TAP5. None of the markers returned completely to baseline.

The largest increase and decrease in LV MAPD was measured in dogs were the MAP catheter was placed in an earlier activated area (Figure 4 (n=6), LV MAPD was not recorded in 4 dogs). Measurements in the non antiarrhythmic TAP experiments (n=3) were not possible due to the occurrence of excessive ectopy.

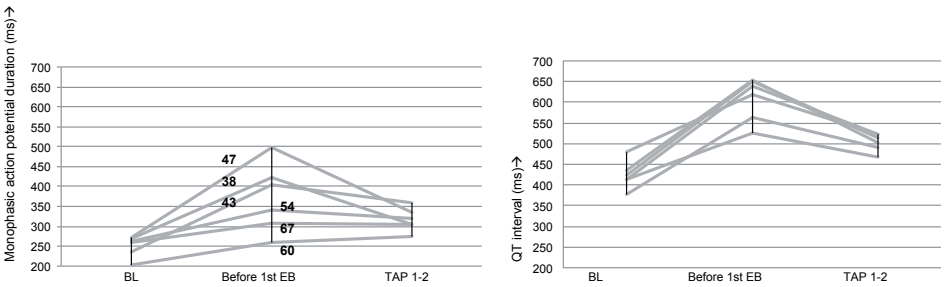

Figure 4. Effect of temporary accelerated pacing (TAP) in successfully treated dogs on left ventricular monophasic action potential duration (LV MAPD) and QT-interval in the first 1-2 minutes after initiation of TAP (TAP 1-2). Activation times for the LV MAP catheter in every dog are given.

Temporary effect of accelerated pacing

In 7 dogs, the reduction of pacing frequency to 80 bpm (n=3) or 60 bpm (n=4, Figure 5), respectively 10 and 15 minutes after infusion of dofetilide, resulted in reoccurrence of ectopic activity in 6/7 dogs and TdP in 3 dogs.

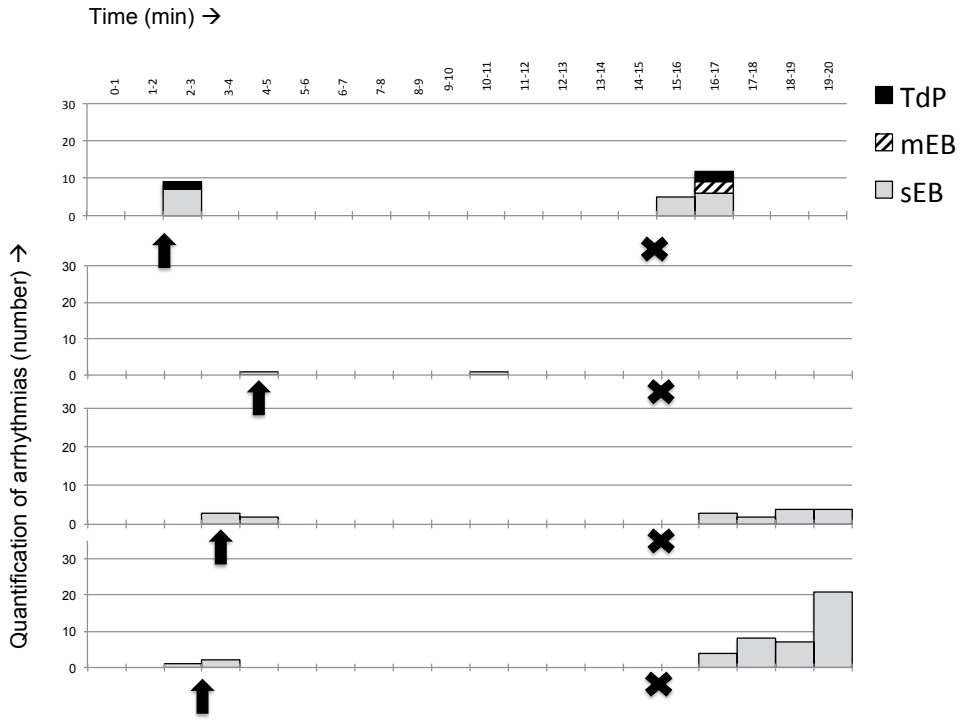

Figure 5. Temporary effect of accelerated pacing. Number of single ectopic beats (sEB), multiple ectopic beats (mEB) and Torsade de Pointes (TdP) after initiation of temporary accelerated pacing (TAP) (arrow) and cessation of TAP (cross) over time (in minutes) are depicted for 4 dogs.

Vertical Dispersion

On baseline, paced at 60 bpm, vertical intraventricular dispersion was low (21±6 ms) and not dependent on frequency shifts: 80 bpm (16±5 ms) and 100 bpm (23±3 ms). After administration of dofetilide, the ARI but also the vertical dispersion increased significantly to 48±26 ms ($p<0.05$). In 3/4 dogs TAP was successful in alienating all ectopy at 5 minutes (Figure 6) with a concomitant trend towards reduction of vertical dispersion from 56±25 to 31±4 ms ($p=0.06$).

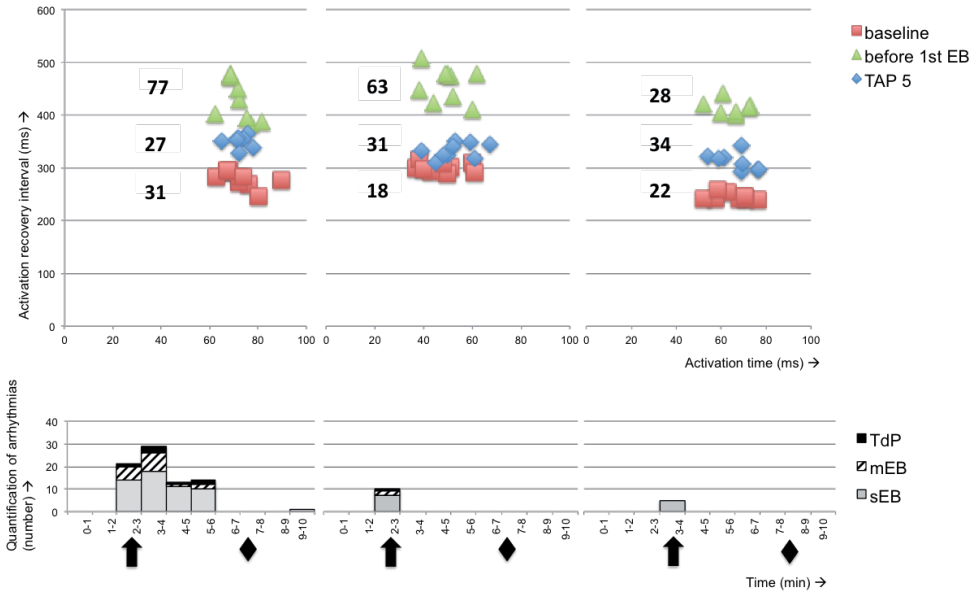

Figure 6. Vertical dispersion (VD) measured in three dogs with temporary accelerated pacing (TAP) successful in alienating ectopy at 5 minutes. In the upper panel activation time is plotted against the activation recovery intervals at three different time points during experiment 2; before (baseline) and after administration of dofetilide (before the 1st ectopic beat (EB) and at 5 minutes of TAP (TAP 5)). VD is quantified for every time point. In the lower panel number of arrhythmias during the experiment are shown over time (arrow = start TAP, diamond = TAP 5).

Discussion

In this study we show that in the canine CAVB dog model, TAP is effective in preventing TdP and even ectopy, when guided by an increase in temporal dispersion (STV_{LVMAPD}). This is accompanied by a reduction of spatial ventricular dispersion.

Efficacy of temporary accelerated pacing

To show that TAP is effective in averting TdP, we made use of the high inducibility and reproducibility in the canine CAVB model in which also the severity of arrhythmias has shown to be similar in serial experiments [11]. TAP prevented inducibility in 70% of the dogs. This is comparable to the effect of continuous pacing as shown by Oosterhoff et al [17]. In that study, pacing was initiated before the administration of dofetilide. In the current study, we show that after administration of dofetilide and subsequent increase of repolarization instability (significant increases in QT-interval and STV_{LVMAPD}), TAP is able to avert inducibility in otherwise susceptible dogs.

Antiarrhythmic mechanism of (temporary) accelerated pacing

Pacing at higher rates is expected to strengthen repolarization reserve and reduce the APD. The latter is more pronounced at slow rates (reverse rate dependence, RRD). Several

hypotheses have been postulated to explain this phenomenon [18-22]. Bányász et al [23] shows that RRD is an intrinsic property in the canine cardiac preparation but it is also described in patients receiving I_{Kr} blockade and in patients with LQTS [7,24,25].
Previous studies have shown that TdP in the canine CAVB model is dependent on the presence of these EADs, although DADs cannot be completely excluded [26]. EADs serve as a trigger but can also amplify the spatial dispersion by causing an increased heterogeneity of repolarization and thereby facilitate perpetuation. Increasing heart rate is also known to have a suppressive effect on EADs in number and in amplitude [8], which is attributed to augmentation of I_{Kr} and hastening of calcium-induced inactivation of L-type calcium current. Every event that shortens cycle length tends to reduce EAD amplitude.

Effects of (temporary) accelerated pacing on dispersion

Increased dispersion is supposed to facilitate EADs to propagate and to become an EB [27]. Since TAP not only averts TdP but also practically eliminates all EBs this could mean that it is preventing EADs/DADs to occur or to propagate by a reduction of spatial dispersion. This is supported by the fact that TAP does not cause a homogenous reduction in APD. Figure 4 shows that the decrease in LV MAPD is most pronounced in dogs with a larger measured increase of LV MAPD, this could imply that TAP mostly affects regions with a long APD located in the earlier activated areas (short activation time). These regional differences are probably depending on heterogeneous distribution of ion channels. This also holds true for interventricular differences. In the canine CAVB model, remodeling causes a reduction in density of I_{Ks} channels in both ventricles while reduction of I_{Kr} density is only seen in the LV. Therefore repolarization strength is more dependent on I_{Ks} in the RV, which could explain the more significant reduction of RV MAPD compared to LV MAPD upon TAP (when enhancement of I_{Ks} is a factor in RRD) [28].

Upon TAP, we see a significant reduction in spatial dispersion (QT, TpTe and Δ MAPD) (Table 1). Measurements with the duodecapolar catheter were done to get better insight in the LV intraventricular dispersion. Before the occurrence of the first EB, we observed a significant increase in vertical dispersion. This is in line with the findings from the detailed needle mapping study of Dunnink et al [29] who found an even more increased vertical dispersion right before the occurrence of TdP in the same model. After initiation of TAP with successful suppression of ectopy, a decreasing trend in vertical dispersion is observed, although not significant. The latter can be due to the small number of dogs and the low resolution reached with the duodecapolar catheter. Furthermore, vertical dispersion was assessed before the first EB instead of the first TdP due to the initiation of TAP upon the first EB.

Temporal dispersion of repolarization to monitor arrhythmic risk and initiate TAP

We showed TAP, initiated when instability of repolarization is already present, is just as effective in preventing TdP as continuous pacing at higher rates. To make TAP clinically

applicable we have to be able to monitor electrical instability with a marker that is not too early and not too late in the cascade that leads to TdP and is robust enough to measure adequately in a clinical setting.
An early marker such as absolute prolongation of repolarization (MAPD, QT duration) is proven not to be specific in reflecting the severity of the substrate [12]. Furthermore, the relative increase is small which makes it less robust. An increase in temporal dispersion (STV) is known to precede the occurrence of EADs and shows a significant and abrupt increase upon proarrhythmic challenge [12,13].
In this study, 50% increase in STV_{LVMAPD} would have initiated TAP adequately in 8/10 experiments in which LV MAPD was measured. 50% increase in QT duration would have only initiated TAP adequately in 5/20 experiments. Real-time measurement of STV could be implemented in devices to monitor (in)stability of repolarization and when appropriate, initiate TAP. Therefore, it should be investigated if the measurement STV_{EGM} is feasible and represents STV_{MAPD} in the canine CAVB model and subsequently patients at risk for TdP.

Rate of pacing and acceleration

For TdP to occur, the APD and heterogeneity thereof needs to reach a critical value. The latter, can be facilitated by several factors, such as bradycardia and/or a long-short cycle. Nevertheless, if dispersion is large enough, a long-short cycle is no prerequisite for the occurrence of TdP but sudden rate changes do exaggerate the substrate by causing a sharp increase in dispersion [26, 30,31]. Preventing 'pauses' with for example a rate-smoothing algorithm as suggested by Viskin et al. [32,33], can be very effective but will not prevent TdP if the substrate is severe enough. Furthermore, this algorithm does not prevent EBs and therefore sudden rate change to occur. Since already one shorter cycle length can cause TdP you would prefer to interfere earlier in this cascade. STV is known to precede occurrence of EADs and therefore EBs [11-13,30].
It is important to be aware that by increasing heart rate to (a more physiological heart rate of) 100bpm, which is sufficient to be protective in most of the dogs. The protective heart rate will depend greatly on substrate and it has a gradual effect as shown by the reoccurrence of ectopy and even TdP when pacing rate is reduced back to 80 or 60 bpm. We did not investigate an upper limit of safety but rates until 100 bpm are assumed to be safe in patients in functional class I [33,34]. Because the pacing is temporary, detrimental effects of pacing at higher rates on cardiac function will remain limited. The main issue is to prevent sudden rate changes. This is why we increased pacing rate gradually and paid attention to pacemaker settings to prevent T-wave oversensing.

Limitations

Bradycardia, as the cause of ventricular remodeling, may be much more dominant in this model as in patients with for example LQTS and therefore modulation of heart rate could

be of greater importance in this model. Whether pacing location is of influence was not taken into account in this study. Furthermore, pacing at higher rate will not prevent adrenergic induced TdP, beta-blockade will therefore remain imperative.

It would have been preferred to initiate TAP based on the actual increase in STV_{LVMAPD} but at the start of this study we were not yet able to realize real-time measurement of this parameter. We used the occurrence of the first EB as a surrogate. We were not able to assess more in depth spatial dispersion because we did not perform needle mapping.

Conclusion

TAP is very effective in averting TdP by decreasing (spatial and temporal) measures of repolarization. The effect observed is fast and reversible. The robust increase in STV, reflecting an increase in susceptibly for arrhythmias, is a suitable marker to guide TAP in a clinical setting.

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CHAPTER 9

Beat-to-beat variations in activation recovery interval derived from the right ventricular electrogram can monitor arrhythmic risk under anesthetic and awake conditions in the canine chronic atrioventricular block model.

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Abstract

Introduction: In the chronic atrioventricular block (CAVB) dog model, beat-to-beat variation of repolarization in the left ventricle (LV) quantified as short-term variability of the left monophasic action potential duration (STV_{LVMAPD}) increases abruptly upon challenge with a pro arrhythmic drug. This increase occurs before the first ectopic beat (EB), specifically in subjects that demonstrate subsequent repetitive Torsade de Pointes arrhythmias (TdP). STV could be feasible to monitor arrhythmic risk through the use of the intracardiac electrogram (EGM) derived from the right ventricle (RV) lead from pacemakers or implantable cardioverter defibrillators (ICD).

Methods: 1) In 30 anaesthetized, inducible (≥3TdP) CAVB dogs, STV between left en right ventricular monophasic action potential duration (STV_{LVMAPD} and STV_{RVMAPD}) was compared. 2) STV of the activation recovery interval (ARI) derived from the RV EGM (STV_{RVARI}) was measured in prospectively enrolled CAVB dogs implanted with an ICD with EGM recording capabilities. 2a) 10 CAVB dogs were challenged with dofetilide under anesthesia, and 2b) 8 CAVB dogs were challenged with cisapride under awake conditions.

Results: 1) Both STV_{LVMAPD} and STV_{RVMAPD} increased before the first EB (1.29±0.58 to 3.05±1.70ms and 1.11±0.53 to 2.18±1.43ms respectively (p=0.001). 2a) STV_{RVARI} increased from 2.82±0.33 to 3.77±0.69ms (p=0.001). 2b) Inducible subjects (4/8) showed an increase in STV_{RVARI} from 2.65±0.55 to 3.45±0.33ms (in the first hour, p=0.02) and 4.20±1.33 (before the first EB, p=0.04)

Conclusion: Behavior of STV from the right and the left ventricle is comparable. STV_{RVARI} increases significantly before the occurrence of an arrhythmia, in awake and anaesthetized conditions. This can be integrated in devices to monitor arrhythmic risk.

Introduction

Aside from implantable cardioverter defibrillators (ICDs) to terminate ventricular arrhythmias, additional pharmacological and electrophysiological treatments are still necessary to prevent arrhythmias and avoid (recurrent) ICD shocks. The question arises whether the ICD can also be used to monitor the risk of ventricular arrhythmias and to enable preventive strategies to intervene.

The canine chronic atrioventricular block (CAVB) model, a model made sensitive to Torsade de Pointes arrhythmias (TdP) by inducing bradycardia and subsequent ventricular remodeling, is used to test antiarrhythmic drugs but also to gain a better insight in the (cellular) mechanism of TdP. Comprehensive studies in the canine CAVB model showed that beat-to-beat variations in repolarization quantified as short-term variability of the left ventricular monophasic action potential duration (STV_{LVMAPD}) is increasing abruptly before the occurrence of the first short coupled ectopic beat (EB), specifically in subjects that demonstrate subsequent multiple EBs and repetitive TdP [1]. Therefore this parameter may be feasible 1) to monitor arrhythmic risk continuously when integrated in devices and 2) to initiate preventive strategies when necessary. For example, pacing at higher rates is applied in patients with long QT syndrome and incorporated in the guidelines for device-based therapy of cardiac rhythm abnormalities [2-6]. In the canine CAVB dog model, temporary accelerated pacing (TAP) is very effective in suppressing TdP, even when started at the moment of the first EB [7]. Therefore STV could be used to guide TAP and prevent chronic pacing at higher rates, which can be detrimental for cardiac function [8]. For this to be feasible in clinical practice, we would like to use the intracardiac electrogram (EGM) derived from the right ventricular (RV) lead to monitor STV, preferably on a 24/7 basis. To investigate if STV of the activation recovery interval (ARI) derived from the RV EGM accurately reflects arrhythmic risk, we performed: 1) A retrospective analysis to evaluate whether STV of the RV MAPD is comparable to the STV of the LV MAPD. 2) A prospective analysis to investigate the value of the STV_{RVARI} derived from the RV EGM in anesthetic (2a) and awake (2b) conditions.

Material and methods

Animal handling was in accordance with Dutch law on animal experiments and the European Directive for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (2010/63/EU). The Animal Experiment Committee of the University of Utrecht approved all experiments.

For the retrospective study (part 1), we collected recently performed experiments in 30 subjects from our database. For the prospective study (part 2) under anesthetic and awake conditions, ten purpose-bred mongrel dogs of either sex (body weight 24 ± 3kg, Marshall, New York) were instrumented and investigated.

Experiments

Anesthesia (part 1 and 2a)

Premedication consisted of methadone 0.5mg/kg, acepromazine 0.5mg/kg and atropine 0.5mg i.m. After 30 minutes complete anesthesia was induced with pentobarbital sodium 25mg/kg i.v. and maintained by isoflurane 1,5% in O2 and N2O, 1:2.

AV block and ICD implantation (part 2)

In an initial procedure, complete atrioventricular (AV) nodal block was performed with radiofrequency ablation of the proximal His bundle and subsequently a pacemaker or ICD was implanted with one lead in the RV. After creation of the AV block we let the dogs remodel for ≥ 2 weeks on idioventricular rhythm (IVR).

Part 1- comparison between electrophysiology in left and right ventricle

For this retrospective analysis, we used the ECG and MAP recordings from experiments performed in 30 subjects inducible after an i.v. challenge with the I_{Kr} (the rapid component of the delayed rectifier potassium current) blocker dofetilide (25µg/kg infused over 5 minutes). All subjects remodeled on IVR. In 16 subjects experiments were performed during IVR and 14 subjects during RV pacing at 60bpm (VVI60). Measurements were done before (baseline) and after administration of dofetilide (before the 1st EB).

Part 2a – the RV EGM for monitoring of arrhythmic risk during anesthetic conditions

Ten CAVB dogs were included in this prospective analysis.

After induction of anesthesia and introduction of the MAP catheters (Hugo Sachs Elektronik, Germany) via the femoral vein and artery. MAP recordings from the free wall of both the left and right ventricle (LV MAP and RV MAP, respectively) and a standard 6-lead surface ECG were simultaneously recorded. Measurements were done at baseline and before the 1st EB after administration of dofetilide. The subjects were paced from the RV at a rate of 60 bpm (VVI60) to stabilize focus and prevent severe bradycardia with concomitant blood pressure drop during anesthesia.

We calculated the correlations between baseline and dofetilide measurements of the RV MAPD and RV ARI and STV_{RVMAPD} and STV_{RVARI}. Subsequently we measured the increase of both RV ARI and STV_{RVARI} after administration of dofetilide, before the 1st EB, to assess the capacity of the RV EGM to monitor arrhythmic risk under anesthetic conditions.

Part 2b– the RV EGM to monitor arrhythmic risk during awake conditions

After a baseline measurement, eight subjects, inducible with dofetilide under anesthesia, received 10-20mg/kg cisapride (AST farma b.v, Oudewater, The Netherlands) orally in awake conditions. The EGM was recorded until 24 hours after administration of cisapride: 2-minute 6-lead ECGs were recorded every hour for the first ten hours. The ICD was programmed at ventricular fibrillation (VF) zone > 200bpm with a VF detection window

of 30/40 and a maximum of 3 shocks. During the experiment the subjects had IVR. In case of an arrhythmia that needed ICD intervention, pacing at higher rates was initiated at VVI80 and gradually increased until VVI100. Additionally flunarizine 2mg/kg in 2 minutes was administered intravenously.

Measurements

ECG intervals (RR, QRS, QT and Tpeak-Tend (TpTe)) and MAP signals were recorded with EP Tracer (Cardiotek, Maastricht, The Netherlands) (sampling frequency 1000Hz). ECG intervals were calculated from an average of 5 consecutive beats. The MAPs were analyzed in a semi-automatic manner with the AutoMAPD software in which the MAPD was determined using a user-defined template to assess the relevant fiducial points. The LV and RV MAPD were measured from the steepest upstroke of the MAP until 80% repolarization. The unipolar EGM (sampling frequency 250Hz, band pass filter 0.5-50Hz) was derived from the RV lead between can and tip, resampled to 400Hz and analyzed offline with custom-made Matlab software (Bakken Medtronic, Maastricht, The Netherlands and Mathworks, Natick, USA). This software uses an overlay plot to discard deviating waveforms and aligns all complexes separately around the ARI onset and offset using the fiducial segment averaging method [9]. The ARI was measured from the minimum dV/dt from the derivative of the QRS complex to the maximum dV/dt of the first derivative of the T wave. The STV of both MAPD and RV ARI over 31 beats were calculated using the following formula: $STV = \sum|D_{n+1} - D_n| \, (N \times \sqrt{2})^{-1}$ where D represents the determinant of repolarization (in this case the MAPD and ARI respectively) and N the number of beats taken into account – 1. Inducibility was defined as ≥ 3 TdP and/or one or more non self-limiting TdP that needed to be treated with defibrillation in a set timeframe after administration of the drug. An EB was considered short coupled when couplings interval was <500ms.

Statistical Analysis

Pooled data are expressed as mean ± standard deviation. All comparisons of electrophysiological data were compared with a paired T-test. Correlation coefficients were calculated to measure the association between both baseline as the values prior to the first EB after administration of dofetilide. Pearson's correlation coefficients were calculated for linear distributed variables and Spearman's rank correlation coefficients for non-linear distributed variables. A p-value equal to or smaller than 0.05 was considered significant. SPSS version 20.0.0 was used for the statistical analysis.

Results

Part 1: Comparison between the electrophysiology of the left and right ventricle.

In the 30 inducible CAVB dogs, LV and RV MAPD at baseline were 282±52ms and 252±38ms respectively. After administration of dofetilide these values increased to 416±107ms and 337±83ms ($p<0.001$). STV_{LVMAPD} increased from 1.29±0.58 to 3.05±1.70ms and STV_{RVMAPD} from 1.11±0.53 to 2.18±1.43ms ($p=0.001$). In Figure 1 (panel A), significant correlations between the MAP's (left panel: Pearson's $r^2 = 0,79$ ($p<0.001$) and the $STV's_{MAP}$ (right panel: Spearman's $r^2 = 0,62$ ($p <0.01$) in the left and right ventricle are shown.

Part 2a: ARI derived from RV EGM compared to RV MAP

In each of the ten included subjects two experiments under anesthesia were performed. Of these 20 experiments, 13 could be used for this analysis. Experiments were excluded because RV ARI was not recorded (n=6) and RV MAP analysis (n=1) was not possible. For all 13 experiments one baseline and one dofetilide (before the first EB) measurement were done for RV MAPD and RV ARI at the same time.

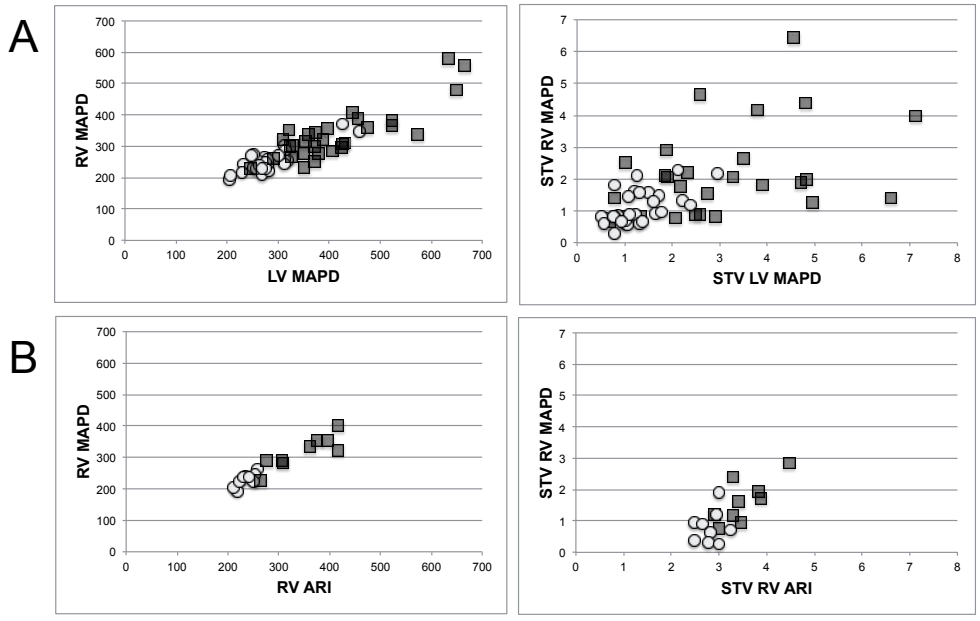

Figure 1. Panel A: Correlations between monophasic action potential duration (MAP) in the left ventricle (LV) and right ventricle (RV). In the left panel, RV MAP is plotted against LV MAP. In the right panel beat-to-beat variations in RV MAP and LV MAP are plotted, quantified as short-term variability (STV). **Panel B:** Correlations between measurements from the MAP catheter and intracardiac electrogram (EGM) in the RV. In the left panel RV MAP is plotted against activation recovery interval (ARI) in the RV. In the right panel STV RV MAP and STV RV ARI are plotted. Correlation coefficients are shown in the left upper corner; P r^2 = Pearson's correlation coefficient, S r^2 = Spearman's correlation coefficient. Grey circles = baseline, black squares = before the 1st EB after administration of dofetilide.

After administration of dofetilide, RV MAPD increased from 231±22 to 309±51ms ($p<0.001$) and STV_{RVMAPD} from 0.85±0.49 to 1.47±0.65ms ($p=0.01$). RV ARI increased from 237±18 at baseline to 341±56ms ($p<0.001$) and STV_{RVARI} increased from 2.82±0.33 to 3.77±0.69ms ($p=0.001$).
The correlation coefficient between the RV MAPD and RV ARI was 0.89 (Pearson's r^2,$p<0.001$) and for STV_{RVMAPD} and STV_{RVARI} 0.42 (Spearman's r^2,$p=0.05$) (Figure 1, panel B)

Part 2b: Awake

In total 4/8 subjects were inducible with cisapride (10-20mg/kg). First EB occurred 1.15±0.63 hours after administration of cisapride, the first TdP occurred after 3.57±1.84 hours. Figure 2 shows a representative impression of the EGM tracings with STV_{RVARI} values at baseline (top panel), before the first EB (middle panel) and first TdP (lower panel).

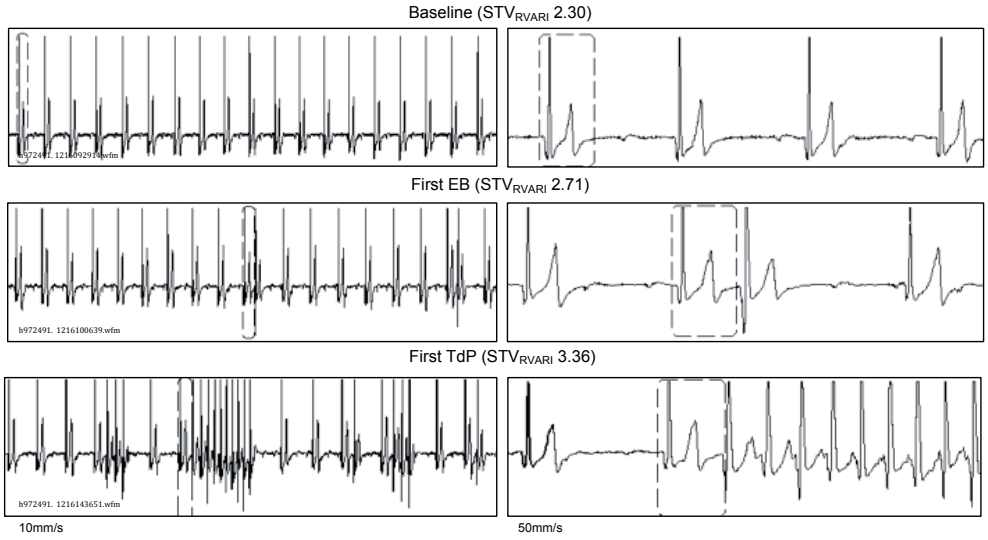

Figure 2. Representative intracardiac electrogram (EGM) tracings of one subject on baseline and after administration of cisapride before the first ectopic beat (EB) and before the first Torsade de Pointes arrhythmia (TdP). Values of short term variability (STV) of the right ventricle (RV) activation recovery interval (ARI) of that subject at those time points.

In Table 1, an overview of electrophysiological parameters after administration of cisapride is given. Panel A shows that cisapride caused an increase in repolarization duration (QT) and spatial dispersion (TpTe) in all subjects after one hour of administration of cisapride. Only in the inducible subjects STV_{RVARI} increased significantly in the first hour after administration of cisapride and before the first EB (Table 1 (panel C), and Figure 3). The ARI remained similar 213±34 and 207±29ms ($p=0.315$).

Table 1. Electrophysiological measurements after administration of cisapride in the awake condition.

Panel A	Baseline	First hour
RR	1543±345	1523±354
QRS	105±22	111±18
QT	333±32	362±37*
TpTe	69±22	83±27*
RV ARI	211±26	208±39
STV_{RVARI}	2.63±0.41	2.98±0.56

Panel B	Baseline	First hour
RR	1487±260	1353±286
QRS	112±23	116±15
QT	324±7	351±15
TpTe	62±9	70±13
RV ARI	208±20	208±53
STV_{RVARI}	2.61±0.30	2.50±0.21

Panel C	Baseline	First hour	First EB	First TdP
RR	1599±449	1694±365	-	-
QRS	98±22	105±21	-	-
QT	343±46	373±52*	-	-
TpTe	77±29	97±33*	-	-
RV ARI	213±34	207±29	204±34	219±82
STV_{RVARI}	2.65±0.55	3.45±0.33*	4.20±1.33*	5.10±2.46

In the first panel (A) all 8 subjects are included. In panel B the 4 non-inducible subjects are included and in the lower panel (C) the 4 inducible subjects. Measurements were done at baseline and after the first hour in all subjects and also before the first ectopic beat and first TdP in de inducible subjects. ARI = activation recovery interval; EB = ectopic beat; RV = right ventricle; STV = short –term variability; TdP = torsades de pointes arrhythmia; TpTe = T peak – T end. Values are provided as mean ± standard deviation. * $p \leq 0.05$.

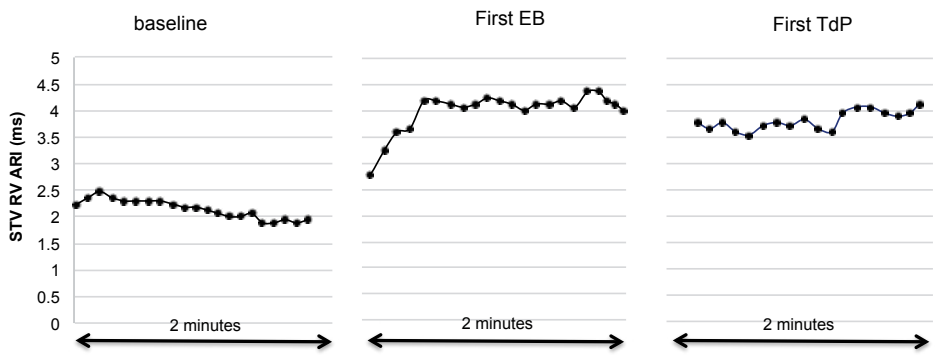

Figure 3. Short-term variability (STV) of the right ventricle (RV) activation recovery interval (ARI) on different time points in an inducible subject. Consecutive STV_{RVARI} values over 2 minutes are plotted on before (baseline) and after cisapride (before the first (short-coupled) ectopic beat (First EB) and before the first Torsade de Pointes arrhythmia (First TdP)).

Discussion

Previous studies already showed the capability of the intracardiac EGM to reflect repolarization instability [10-12]. Nevertheless, its application is not further elaborated. In this study, it is shown that 1) measurement of repolarization instability quantified as STV is comparable in the left and right ventricle, and 2) STV_{RVARI} derived from the intracardiac EGM increases upon a pro-arrhythmic challenge in anesthetized and awake conditions. Since the RV EGM is a stable and continuous available signal, it is a particular suitable tool to use for monitoring arrhythmic risk. This gives us the opportunity to act upon a detected increased susceptibility with appropriate anti-arrhythmic therapy, for example TAP.

Electrophysiology in the left and right ventricle: relevance of location

Our first step to translate the use of STV_{RVARI} for monitoring arrhythmic risk to clinical practice was to show that beat-to-beat variations in repolarization are comparable between the LV and RV. In the retrospective analysis of the 30 subjects that were inducible after a dofetilide challenge, we show that not only STV_{LVMAPD} but also STV_{RVMAPD} increases before the occurrence of TdP (Table 1). Although the increase in the RV is less pronounced, it is significant. This does not mean that the electrophysiological adaptations in the left and right ventricle are similar; they're only comparable. In the CAVB dog, it is known that the RV MAPD is shorter than the LV MAPD, which causes the interventricular difference (Δ MAPD). This can be explained by a difference in distribution of repolarizing ion channels; in the RV there is more I_{Ks} and I_{to}. Nevertheless, they both seem capable to detect increased arrhythmic risk. Although all dogs remodeled at IVR, some of them were paced during the experiments at VVI60. This was done 1) to be able to completely control ventricular focus and 2) prevent severe bradycardia with concomitant blood pressure drop upon induction of anesthesia. Dunnink et al [13] showed that although baseline repolarization measures were lower in the subjects paced at VVI60 during the experiments, a similar increase in electrophysiological values and TdP inducibility was seen.

RV EGM based monitoring of arrhythmic risk

For calculation of STV different measures of repolarization can be used. In the canine CAVB model, MAPD has been used as measure of ventricular repolarization. Nevertheless, this determinant of repolarization is not suitable for clinical practice because of the invasive nature of this measurement and the difficulty to acquire signals of sufficient quality in humans. An attractive alternative is the intracardiac EGM quantified by the ARI. This measurement can be done easily in patients with a pacemaker and/or ICD via the RV lead. Compared to the MAPD, the EGM has the advantage to acquire recordings from the same location (the lead is fixed in the myocardium) and continuously (24/7). Since no transvenous catheter placement is needed, recordings during awake conditions can be easily performed.

Oosterhoff et al. showed that measurements of the MAPD and ARI in the LV are comparable in the canine CAVB model [14]. For better clinical applicability, we used the EGM of the RV and also found a positive correlation between the STV_{RVARI} and STV_{RVMAPD} (Figure 1B, right panel).
That the correlation is not very strong can be explained by the fact that the unipolar EGM reflects a larger region in the heart than the MAPD, which is a bipolar measurement representing only the cells around the MAP catheter tip. Several studies studied the relationship between the unipolar derived ARI and the MAPD, and suggested that the highest correlation is achieved when Q onset of the ARI is measured as minimum dV/dt and end T is measured at the maximum dV/dt [15,16]. With the latter, it is tried to exclude remote repolarization, but still the unipolar EGM is more influenced by more distant events in the myocardium [17]. This does not automatically mean that the potential to detect repolarization instability is less, as represented by the significant increase in STV_{RVARI} before the 1st EB upon a challenge with dofetilide (2.82±0.33 tot 3.77±0.69ms (p=0.001). Furthermore, differences in absolute value of STV can be explained by difference in method of analyzing and sampling frequency between the MAP recording (1000Hz) and the EGM recording (400Hz).

Susceptibility for TdP in awake conditions

We also challenged the subjects under awake conditions to determine the potential of STV_{RVARI} for monitoring electrical instability since anesthesia has major effect on repolarization and also sensitivity to TdP [18]. Dunnink et al. serially investigated the effect of anesthesia in different regiments in the CAVB dog model. Under awake conditions, inducibility with dofetilide was absent (0/10), while 7/10 dogs showed reproducible TdP under anesthetic conditions. Furthermore, they showed a significant difference in QT duration between the anesthetized and awake experiments (281±31 and 390±71ms, p<0.05). The increase of QT duration after administration of dofetilide was only significant under anesthetic conditions (+48±52ms, ns and +190±71ms, p<0.05) [18].
We made use of the gastroprokinetic drug cisapride, a selective sertonine 5-HT4 receptor agonist that also acts indirectly as a parasympaticomimetic. It was developed by Janssen Pharmaceutica in 1980's and withdrawn in most countries in 2000 because of QT prolonging side effects and ventricular arrhythmias. We chose to use cisapride because it is shown to be a potent I_{Kr} blocker.
The previous studies investigating cisapride in the canine CAVB model tell us that 1) remodeling is a prerequisite for susceptibility [19], 2) absence of anesthesia reduces total incidence of TdP (Winckels et al. 2007, not published), 3) different routes of administration cause different timing of TdP corresponding with the maximum plasma concentration [20,21], and 4) there is a difference in susceptibility between species [21]. In *supplemental Table 1* you can find a schematic overview of these studies.

Electrophysiological changes preceding awake induced TdP

In our study, a significant increase in QT in all subjects is seen after administration of cisapride. Only in the 4 inducible subjects this is accompanied by a significant increase in STV_{RVARI}, reflecting increased instability of repolarization. This significant increase is seen in the first hour and before the occurrence of the first EB, minutes to hours before occurrence of the first TdP. Because in awake conditions more compensation mechanisms are still in place to strengthen repolarization reserve, this situation (an increase in STV) can occur when instability of repolarization is present minutes to hours before the actual occurrence of TdP. This gives a large window of opportunity to interfere.

24/7 monitoring of arrhythmic risk

To be able to monitor repolarization instability continuously automated analysis of the ARI is necessary. We therefore created a software algorithm especially for this purpose in cooperation with Medtronic using MatLab. To exclude artifacts and deviating waveforms (such as ectopic activity) an overlay plot was applied which was also used to align the QRS onset and end T separately with the fiducial segment averaging method [9]. This method provides an accurate measurement of beat-to-beat changes since determination of the fiducial point only has to be performed once for all waveforms. This prevents measurement error from beat-to-beat, which is especially relevant in measuring beat-to-beat changes in repolarization intervals since the end of T is often difficult to determine.

Clinical implications and future directions

Several studies have shown that the RV EGM can be used to predict risk for ventricular arrhythmias in patients [11,22]. Also Oosterhoff et al. showed that a high STV 'QT' derived from the intracardiac bipolar EGM and corrected for heart rate (STV ratio) can identify patients at risk for ventricular arrhythmias [10]. We now show that in this experimental set-up, STV increases before the occurrence of an arrhythmia and can be monitored by the EGM derived from the RV lead of a pacemaker and/or ICD, both in anesthetized as in awake conditions. STV_{RVARI} could be used to monitor arrhythmic risk and initiate preventive strategies such as TAP. The next step for translation into clinical practice should be fully automated analysis of STV from (pre-arrhythmia) intracardiac EGMs.

Limitations

The canine CAVB model is a model made sensitive for TdP; results therefore cannot be directly extrapolated to other types of arrhythmias.
Using the unipolar EGM, interference of P-waves could not be prevented. This is particular the case in the canine CAVB model and is not to be expected in humans (without AV block).

Conclusion

In the canine CAVB model, behavior of STV derived from the RV is comparable to the LV. STV_{RVARI} increases significantly when instability of repolarization becomes present, before the occurrence of TdP, in awake and anaesthetized conditions. Continuous measurement of STV_{RVARI} could be integrated in devices to 24/7 monitor arrhythmic (in)stability and guide antiarrhythmic therapies.

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PART III

THE ELECTRICAL SUBSTRATE IN PATIENTS ELIGIBLE FOR CRT

CHAPTER 10

Refining success of cardiac resynchronization therapy using a simple score predicting the amount of reverse ventricular remodeling – Results from the Markers And Response to CRT (MARC) study

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Accepted for publication in Europace 2017

Abstract

Aims: Cardiac resynchronization therapy (CRT) reduces morbidity and mortality in systolic heart failure patients with ventricular conduction delay. Variability of individual response to CRT warrants improved patient selection. The Markers And Response to CRT (MARC) study was designed to investigate markers related to response to CRT.

Methods: We prospectively studied the ability of 11 clinical, 11 electrocardiographic, 4 echocardiographic and 16 blood biomarkers to predict CRT response in 240 patients. Response was measured by the reduction of indexed left ventricular end-systolic volume (LVESVi) at 6 months follow up. Biomarkers were related to LVESVi change using log-linear regression on continuous scale. Covariates that were significant univariately were included in a multivariable model. The final model was utilized to compose a response score.

Results: Age was 67±10yrs, 63% were male, 46% had ischemic etiology, LV ejection fraction was 26±8%, LVESVi was 75±31ml/m2, and QRS was 178±23msec. At 6 months LVESVi was reduced to 58±31 ml/m2 (relative reduction of 22±24%), 130 patients (61%) showed ≥ 15% LVESVi reduction. In univariate analysis 17 parameters were significantly associated with LVESVi change. In the final model age, QRS_{AREA} (using vectorcardiography) and two echocardiographic markers (intraventricular mechanical delay and apical rocking) remained significantly associated with the amount of reverse ventricular remodeling. This CAVIAR (**C**RT-**A**ge-**V**ectorcardiographic QRS_{AREA} -**I**nterventricular Mechanical delay-**A**pical **R**ocking) response score also predicted clinical outcome assessed by heart failure hospitalizations and all-cause mortality.

Conclusions: The CAVIAR response score predicts the amount of reverse remodeling after CRT and may be used to improve patient selection.

Introduction

Cardiac resynchronization therapy (CRT) is an established therapy for patients with systolic heart failure despite optimal medication and inter- and intraventricular conduction delay. CRT reduces heart failure hospitalizations and mortality and improves exercise capacity and quality of life [1-6]. Despite the success of CRT, a significant number of patients show no clinical improvement [4]. Several factors influence response to CRT including etiology of heart failure, QRS morphology and duration, and mechanical dyssynchrony [5,7]. In addition, optimal delivery of CRT and targeted lead position are essential for response to CRT [8]. One of the best parameters to define reverse remodeling is reduction of indexed left ventricular end systolic volume ($LVESV_i$). Reverse ventricular remodeling is closely correlated with clinical endpoints such as all-cause mortality and heart failure hospitalizations [9].
In the landmark trials the selection of patients was mainly based on QRS duration [2,3,6]. Retrospective analyses have shown that patients with left bundle branch block (LBBB) ECG morphology may have a higher chance to respond to CRT [10]. As a consequence, both QRS duration and morphology are mentioned in the most recent guidelines, refining identification of the electrical substrate [1,11]. However, there are several definitions of LBBB, making this marker operator-dependent [12]. Echocardiographic markers of dyssynchrony may also have predictive value but many are notoriously difficult to reproduce with high intra- and interobserver variability [13]. Only limited data is available on the predictive value of blood biomarkers for CRT response and outcome [14].
To improve prediction of the beneficial effects of CRT we prospectively investigated the prognostic value of a set of clinical, electrical, structural, and blood biomarkers to predict reverse remodeling assessed as a decrease in $LVESV_i$ in patients with an indication for CRT according to the guidelines.

Methods

More extensive description of the methods can be found in the supplemental information.

Study design

The Markers and Response to CRT (MARC) study was a prospective, multicenter, observational study performed in The Netherlands designed to identify a set of biomarkers that can predict the magnitude of reverse left ventricular (LV) remodeling. In total, 240 patients with an indication for CRT according to the current guidelines [1,11] including patients with LBBB and non-specific intraventricular conduction delay (IVCD) but without right bundle branch block were included in 6 participating centers between February 2012 and November 2013. Total follow-up was 12 months. The study was initiated and coordinated by the 6 centers within the framework of the Center for Translational Molecular

Medicine (CTMM), project COHFAR (grant 01C-203), and additionally financially supported by Medtronic Inc., Minneapolis, MN, USA. Study monitoring was done by Medtronic Bakken Research Center, Maastricht, The Netherlands, data management, validation, and statistical analysis by the investigators in collaboration with Medtronic (BG). The study was approved by the institutional review boards of all participating centers. All patients gave written informed consent. The trial was registered at clinicaltrials.gov: NCT01519908.

Study participants

Inclusion criteria were an indication for CRT according to the guidelines at the time of inclusion. All patients had a *de novo* indication for CRT according to the most recent ESC and American guidelines [1,11] New York Heart Association (NYHA) class II or III, stable sinus rhythm (no documented atrial arrhythmias lasting > 30 seconds during the last 2 weeks prior to inclusion), for class II patients an intrinsic QRS-width ≥ 130 ms with LBBB or ≥ 150 ms with non-specific IVCD, for NYHA class III an intrinsic QRS-width ≥ 120 ms with LBBB or ≥ 150 ms with non-specific IVCD, and on optimal heart failure oral medical therapy. Exclusion criteria included severe renal insufficiency with a glomerular filtration rate (GFR) <30ml/min/1.73m^2, an upgrade from a bradycardia pacemaker or CRT-P to CRT-D, permanent atrial fibrillation (AF) or flutter or tachycardia, right bundle branch block, and permanent 2nd or 3rd degree atrioventricular block. Patients were seen at the outpatient department at baseline, 1, 6 and 12 months after CRT-D implantation.

Device settings and optimalization

After implantation devices were programmed to DDD mode with a sensed atrioventricular (AV) delay of 90ms and a paced AV delay of 130ms. Left-to-right (VV) ventricular delay was set to 0ms. After one month, AV and VV delays were optimized echocardiographically to the discretion of the local investigator. Devices were programmed to rate response mode after one month unless good chronotropic response was observed at device check-up utilizing device rate histograms.

Biomarkers

Biomarkers assessed in the MARC study included 11 clinical parameters, 11 electrocardiographic parameters including beat-to-beat variability and vectorcardiography (VCG), 4 echocardiographic parameters assessing cardiac function and structure, and 16 blood biomarkers. These parameters were chosen on the basis of earlier implication as response predictors from prospective or retrospective analyses.

Electrocardiography and vectorcardiography

A 12-lead digital electrocardiogram (ECG) was recorded at baseline. All parameters were analyzed in the ECG core lab (SW, MV). LBBB was defined as a slurred/notched R-wave in I, aVL and V6, an absent Q in I, V5, V6, a R-peak time > 60ms in V6 and no R-wave

or R-wave of <60ms in V1-V3. VCGs were synthesized from pre-procedural digital 12 lead ECGs. A VCG consists of three orthogonal leads X, Y and Z, which together form a 3D vector loop. The QRS_{AREA} and T_{AREA} were calculated from the VCG. RR and QT Short-Term Variability (STV_{RR} and STV_{QT}) were assessed from beat-to-beat variability during >2min ECG recording. An illustration demonstrating QRS conversion to VCG and QRS_{AREA} can be found in the online supplement (*Supplementary Figure 2*).

Echocardiography

Echocardiograms were obtained before and 6 months after implantation and analyzed by the echocardiography core lab (JS, MJC) using vendor specific software. Images were deemed not analyzable if image quality was unsuitable for reliable assessment. All echocardiographic parameters were measured on three separate beats and averaged. Left ventricular end-diastolic diameter (LVEDD), end-diastolic (LVEDV) and end-systolic volume (LVESV), and ejection fraction (LVEF) were measured using the biplane Simpson's method by two experienced observers. If image quality of the apical two-chamber view (AP2CH) was deemed unsuitable for reliable biplane volume assessment, solely the apical four-chamber volume (AP4CH) was used. Volumetric response ($\Delta LVESV_i$) was calculated as the change of log-transformed $LVESV_i$ between baseline and 6-month follow-up. Apical rocking was defined as a short systolic septal to lateral rocking motion of the apex. It results from short initial septal contraction and inward motion of the septum, pulling the apex towards the septum [15], followed by delayed activation of the lateral wall, pulling the apex laterally while stretching the septum. Septal flash was defined as a rapid contraction and subsequent stretching of the septum during the isovolumetric contraction period. Interventricular mechanical delay (IVMD) was defined as the timing difference between left and right ventricular pre-ejection intervals. All dyssynchrony parameters were assessed by an observer blinded for volumetric response. Mitral valve insufficiency was visually assessed and scored.

Blood biomarkers

Parameters were chosen to cover pathophysiological domains that could be involved in CRT response: neurohormones, renal function parameters, inflammation, structural myocardial markers, and collagen turnover. Within each pathophysiological domain, parameters were chosen depending on earlier implication in CRT response by previous prospective or retrospective analyses. Blood was collected at implant from peripheral blood and the coronary sinus. The collagen markers (Procollagen Type III N-terminal Peptide (P3NP), C-terminal Telopeptide of Type I Collagen (ICTP), C-terminal PICP, Matrix Metallo Proteinase 9 (MMP-9), Tissue Inhibitor of Metallopeptidase 1 (TIMP-1), and Aldosterone) were sent to an independent laboratory (Centre d'Investigation Clinique – Plurithematique Pierre Drouin CHU de Nancy, Nancy, France) for analysis. ST2, Growth Differentiation Factor 15 (GDF-15), Galectin-3, N-terminal Prohormone Brain Natriuretic Peptide (NT-proBNP), high-sensitive troponin T (TnT), creatinine, blood urea nitrogen (BUN), high-sensitive C-reactive

protein (hsCRP) and Interleukin-6 (IL-6) were measured in the University Medical Center Groningen (MK, AHM). The laboratories were blinded to the clinical history.

Statistical analysis

The MARC study was designed to assess the relation between biomarker variables measured at baseline and reverse remodeling at 6 months after CRT initiation. The pre-specified analysis was to perform an analysis of covariance (ANCOVA) on logarithm-transformed $LVESV_i$ measurements for each of the biomarker variables. The PROSPECT study (13) showed that $LVESV_i$ has a log-normal distribution, and with transformation the model results can be interpreted on a relative scale. We planned to enroll 240 patients in order to have at least 200 patients with paired baseline and 6 month $LVESV_i$ measurements, which would give 90% power to show significance on a predictor with predictive ability similar to IVMD in PROSPECT [13]. Each marker was tested separately in an ANCOVA model with the marker and baseline $LVESV_i$ as covariates. Continuous markers were standardized. Significant markers were included in a multivariable model and backward elimination was used to determine a final multivariable model. Patients with incomplete covariate data were excluded from the analysis. The predictive value of the response score in prespecified subgroups was depicted in a forest plot. Confidence intervals for the increase in relative $LVESV_i$ change with a one-point increase on the response score were derived from ANCOVA models restricted to the subgroup. Interaction p-values were derived from models with the subgroup indicator and response score as covariates. The relation between response score and incidence of the composite endpoint of all-cause death and hospitalization for worsening heart failure was assessed using Cox proportional hazards regression. The Kaplan-Meier method was used to estimate incidence in patient groups defined by tertiles of the response score. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA), and a p-value <0.05 was considered statistically significant in all analyses. Results are presented as mean ± standard deviation unless indicated otherwise.

Results

Patient characteristics

A total of 240 patients were included. For 213 patients paired $LVESV_i$ measurements were available. These 213 patients were analyzed for the primary endpoints. Reasons for absence of paired $LVESV_i$ measurements were 2 failed implants, 5 implants not attempted, 4 deaths, 4 withdrawn consent, 1 missed visit, 11 unperformed or unreadable echocardiogram studies. Baseline characteristics are shown in Table 1. Mean age was 67±10 years, 63% were male. Heart failure was of ischemic origin in 46% of patients and one third was in NYHA class III. Main comorbidities were diabetes mellitus (27%) and chronic obstructive pulmonary disease (13%). The majority of patients had LBBB (57%), QRS duration was 179±23ms. Atrioventricular conduction was preserved in most patients

with a PR interval of 195±41ms. Echocardiographically measured IVMD was 46±29 ms, and apical rocking was present in 60% of patients.

Table 1. Baseline characteristics.

Baseline Characteristic	All patients (N = 240)	Patients with paired $LVESV_i$ (N = 213)
Demographics		
Age - years	67 ± 10	66 ± 10
Male sex - no. (%)	151 (63)	132 (62)
Medical history - no. (%)		
Ischemic etiology of heart failure	111 (46)	90 (42)
History of atrial fibrillation	32 (13)	27 (13)
Left bundle branch block (per investigator)	209 (87)	187 (88)
Left bundle branch block (ECG core laboratory*)	137 (57)	129 (61)
Diabetes	65 (27)	56 (26)
Renal dysfunction	15 (6)	10 (5)
Chronic obstructive pulmonary disease	31 (13)	26 (12)
Baseline status		
Left ventricular ejection fraction** - %	26 ± 8	26 ± 7
Left ventricular end systolic volume index** - mL/m^2	74 ± 30	75 ± 31
QRS duration* - ms	178 ± 23	179 ± 23
PQ interval* - ms	195 ± 41	192 ± 37
NYHA class - no. (%)		
I	1 (0.4)	1 (0.5)
II	150 (63)	133 (62)
III	89 (37)	79 (37)
IV	0 (0)	0 (0)
Vectorcardiography and Echocardiography		
QRS_{AREA}* - µVs	131 ± 47	136 ± 47
Inter-ventricular mechanical delay** - ms	46 ± 29	47 ± 29
Apical rocking** - no. (%)	143 (60)	135 (63)
Blood biomarkers – median (IQR)		
Procollagen Type III N-terminal Peptide (P3NP) - µg/l	3.3 (2 - 5)	3.3 (2 - 5)
Blood Urea Nitrogen (BUN) - mmol/l	7.5 (6 - 10)	7.3 (6 - 9)
Creatinine - µmol/l	87 (72 - 111)	85 (70 - 109)
N-terminal Prohormone Brain Natriuretic Peptide (NT-proBNP) - ng/l	966 (437 - 1839)	974 (440 - 1815)
TIMP Metallopeptidase Inhibitor 1 (TIMP1) - ng/ml	177 (146 - 238)	175 (145 - 234)
Galectin 3 - ng/ml	17 (14 - 22)	17 (14 - 21)
C-Propeptide of Type I Procollagen (PICP) - ng/ml	82 (63 - 108)	81 (63 - 108)
Matrix Metallopeptidase 9 (MMP9) - ng/ml	228 (153 - 350)	235 (148 - 361)

Baseline Characteristic	All patients (N = 240)	Patients with paired $LVESV_i$ (N = 213)
C-terminal Telopeptide of Type I Collagen (ICTP) - µg/l	5.3 (4 - 9)	5.2 (4 - 9)
Aldosterone - pg/ml	65 (33 - 127)	63 (30 - 132)
High-sensitivity C-reactive Protein (hsCRP) - mg/l	2.1 (1 - 5)	2.0 (1 - 5)
High-sensitivity Troponin T - ng/l	22 (15 - 31)	22 (14 - 30)
Interleukin 6 (IL6) - ng/ml	2.7 (2 - 5)	2.7 (2 - 5)
ST2 - ng/l	25 (19 - 33)	25 (19 - 33)
Growth differentiation factor 15 (GDF15) - ng/l	290 (198 - 469)	283 (196 - 454)
PICP/ICTP ratio	15 (9 - 26)	15 (9 - 27)
Baseline medication - no. (%)		
ACE inhibitor or ARB	225 (94)	200 (94)
Aldosterone Antagonist	116 (48)	105 (49)
Beta-blocker	201 (84)	181 (85)
Diuretic	170 (71)	152 (71)
Statin	142 (59)	120 (56)

* ECG core laboratory. ** Echo core laboratory. Plus-minus values are mean ± standard deviation. ACE = angiotensin-converting-enzyme; ARB = angiotensin receptor blocker; IQR = interquartile range; NYHA = New York Heart Association

Lead positions

Transvenous LV lead implantation was successful in 233 (97%). 8 patients received an epicardial LV lead by surgical approach. LV lead position was lateral in 67% and postero-lateral in 23% of 211 patients with implant fluoroscopic images. The RV lead was placed in the apex in 85%.

Atrial fibrillation during follow-up

During follow-up atrial high rate episodes lasting > 6 minutes were detected in 56 patients (23%). Only 9 of them had AF ≥ 23 hours and only 2 patients longer than 1 month.

Echocardiographic outcome at 6 months

For 213 patients paired $LVESV_i$ measurements were available. At 6 months $LVESV_i$ was reduced from 75±31 ml/m^2 at baseline to 58±31 ml/m^2 (relative reduction 22±25%). In total, 130 patients (61%) had a reduction ≥ 15% of $LVESV_i$. Unadjusted associations of each individual marker with $LVESV_i$ reduction are reported in *Supplementary Table 1*. A multivariable model was built using backward selection of all markers except JTc with a significant unadjusted association (Table 2). The final model included the following independent markers: age, QRS_{AREA}, interventricular mechanical delay, and apical rocking. Advancing age was inversely related with $LVESV_i$ reduction. The other three markers, one electro- and two echocardiographic markers, were positively related with $LVESV_i$ reduction; larger QRS_{AREA} and longer interventricular mechanical delay, and presence of apical rocking were associated with larger LV reverse remodeling.

Table 2. Univariable and multivariable prediction of $LVESV_i$ reduction.

Covariate Biomarker		Unadjusted models			Multivariable model		
Marker	**Patients with paired $LVESV_i$ (N = 213) – no(%)**	**Effect Estimate***	**95% Confidence Interval**	**P-value**	**Effect Estimate***	**95% Confidence Interval**	**P-value**
Female Gender	81 (38)	-12.2%	(-20.1%, -3.7%)	0.006			
Age	66 ± 10	5.7%	(1.1%, 10.7%)	0.016	4.6%	(0.1%, 9.3%)	0.043
Ischemic Cardiomyopathy	90 (42)	25.8%	(15.3%, 37.3%)	< 0.0001			
NYHA class (I/II)	134 (63)	-12.2%	(-20.0%, -3.5%)	0.007			
LBBB	129 (61)	-20.2%	(-27.1%, -12.7%)	< 0.0001			
Blood Urea Nitrogen (BUN) - ng/ml	8 ± 4	5.6%	(0.9%, 10.5%)	0.019			
Creatinine - ng/ml	93 ± 33	6.2%	(1.5%, 11.2%)	0.009			
Galectin 3 - ng/ml	18 ± 6	5.6%	(0.8%, 10.5%)	0.021			
ST2	28 ± 13	7.4%	(2.5%, 12.5%)	0.003			
PQ interval - ms	192 ± 37	6.1%	(1.3%, 11.1%)	0.012			
JTc interval - ms	368 ± 42	5.6%	(0.8%, 10.5%)	0.020			
QT Short-Term Variability (STV QT) - ms	0.79 ± 0.35	5.2%	(0.3%, 10.3%)	0.038			
QRS_{AREA} - μVs	136 ± 47	-13.9%	(-17.7%, -9.8%)	< 0.0001	-10.4%	(-14.9%, -5.8%)	< 0.0001
T wave area - μVs	93 ± 36	-11.2%	(-15.5%, -6.6%)	< 0.0001			
Inter-Ventricular Mechanical Delay - ms	47 ± 29	-12.1%	(-15.9%, -8.1%)	< 0.0001	-5.5%	(-10.2%, -0.7%)	0.026
Apical rocking	135 (63%)	-19.6%	(-26.5%, -12.0%)	< 0.0001	-11.8%	(-19.8%, -2.9%)	0.010
Septal flash	102 (48%)	-18.0%	(-25.3%, -10.0%)	< 0.0001			

* Effect Estimate for continuous variables is for 1 standard deviation (s.d.) change. For example, for age the s.d. is 10 years and the effect estimate is 4.6%, which means that a patient who is 10 years older had on average 4.6% increase of $LVESV_i$ (i.e. less reverse remodeling).

LVESVi response score.

The final model calibration is illustrated by Figure 1. Based on the significant markers in the multivariable model we constructed the CAVIAR (CRT-Age-Vectorcardiographic QRS area-Interventricular mechanical delay-Apical Rocking) scoring system for $LVESV_i$ reduction with CRT (Table 3a). The CAVIAR predicted and average actual change of $LVESV_i$ are shown in Table 3b.

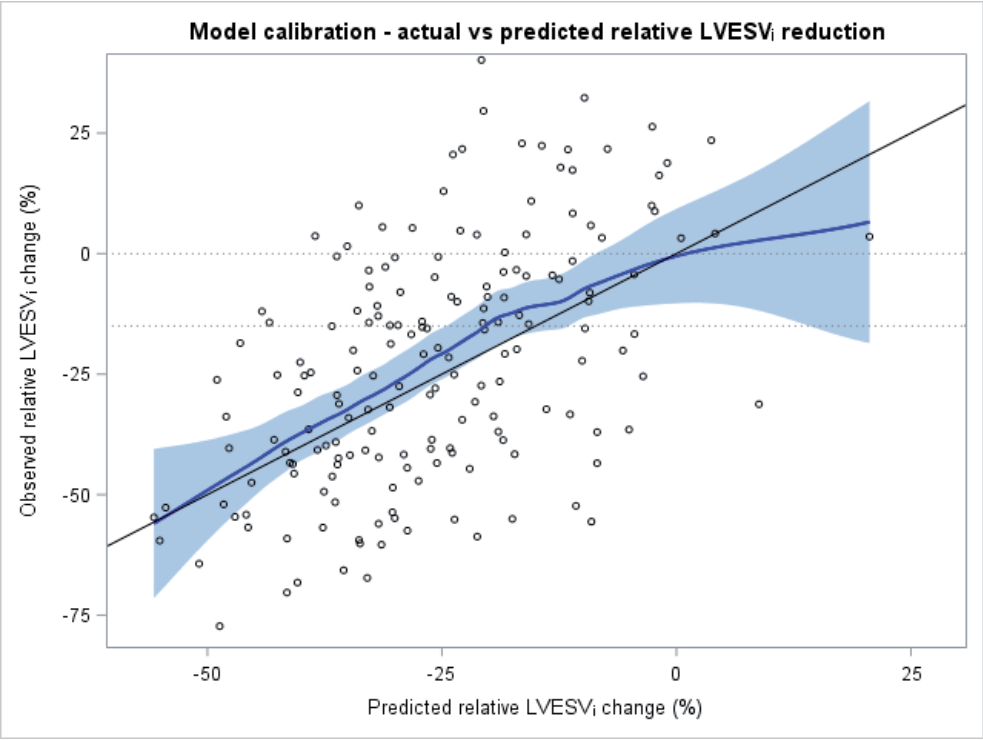

Figure 1. Scatter plot of actual versus predicted relative reduction of $LVESV_i$. The diagonal black line is the line of equality. The blue curve and band are a LOESS fit with 95% confidence band.

Table 3a. Response score for factors associated with $LVESV_i$ reduction.

Variable	Value range	Score
Age - yr	< 60	1
	60 - 74	0
	≥ 75	-1
Vectorcardiographic QRS_{AREA} - μVs	< 80	-2
	80 - 99	-1
	100 - 119	0
	120 - 139	1
	140 - 159	2
	160 - 179	2
	180 - 199	3
	200 - 219	4
	≥ 220	5
Inter-Ventricular Mechanical Delay - ms	< 15	-1
	15 - 44	0
	45 - 74	1
	≥ 75	2
Apical **R**ocking	Absent	0
	Present	2

The CAVIAR (**C**RT-**A**ge-**V**ectorcardiographic QRS area-**I**nterventricular mechanical delay-**A**pical **R**ocking) score is the sum of the applicable values in column "Score" with minimum -2 and maximum 9.

Table 3b. Predicted and average actual change of $LVESV_i$ assigned to the response score.

Response Score	Patients - n (%)	Predicted $LVESV_i$ change - %	Average actual $LVESV_i$ change - %
-2	12 (7)	-1.3	-5.3
-1	14 (8)	-7.1	-14.9
0	15 (8)	-12.5	8.2
1	19 (11)	-17.6	-12.9
2	18 (10)	-22.4	-19.6
3	23 (13)	-26.9	-22.5
4	20 (11)	-31.2	-32.3
5	19 (11)	-35.2	-29.6
6	15 (8)	-38.9	-36.1
7	9 (5)	-42.5	-46.9
8	6 (3)	-45.8	-45.6
9	7 (4)	-49.0	-47.4

Figure 2 illustrates how the response score predicts reverse remodeling in selected subgroups. Shown is the percent-wise relative change of $LVESV_i$ that corresponds to a one point increase on the response score. Only female gender was associated with more reverse remodeling at comparable CAVIAR scores.

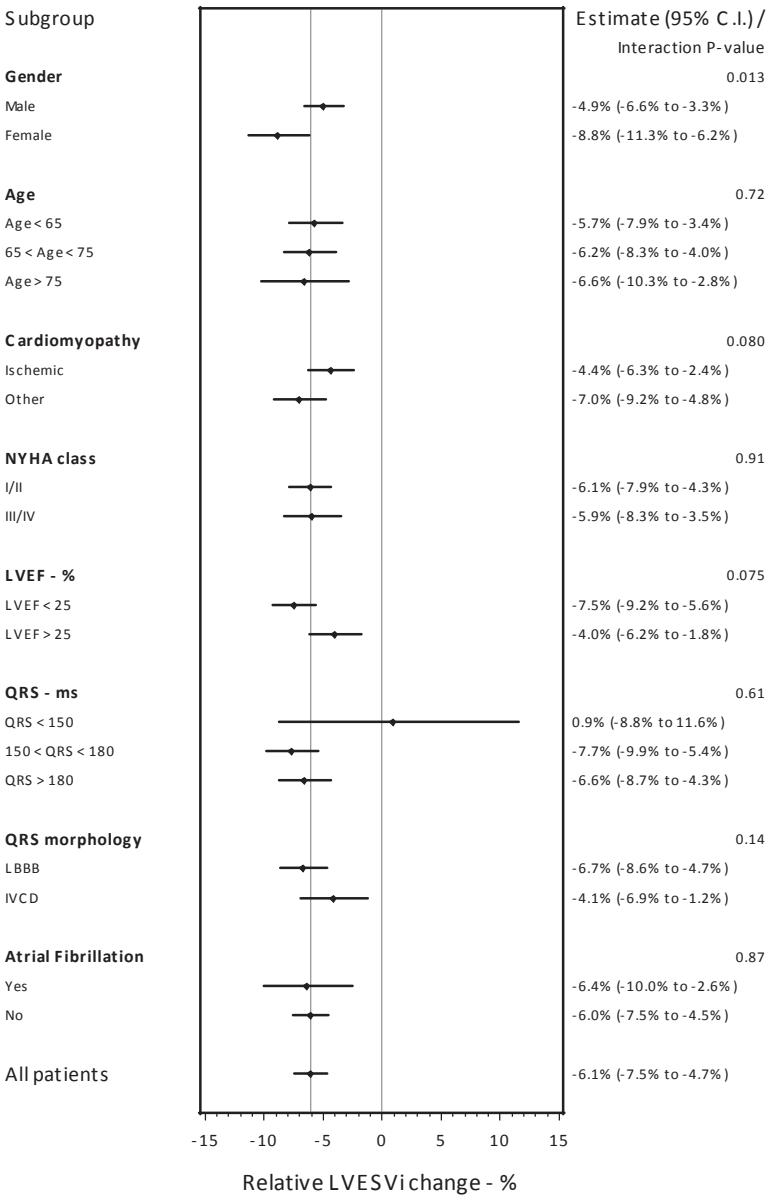

Figure 2. Forest plot for predicted difference in relative $LVESV_i$ change corresponding to a one point increase of the response score, according to pre-specified subgroups. The right side shows predicted difference and confidence interval, and interaction p-values.

Figure 3 illustrates that QRS_{AREA} predicted $LVESV_i$ change better than QRS duration. Comparing a model for $LVESV_i$ reduction including QRS duration and QRS morphology to a model including QRS duration, QRS morphology and QRS area, the likelihood ratio (LR) test for comparison has a chi-square value of 25.1 ($p<0.0001$), indicating that the QRS_{AREA} adds significantly to just QRS duration and morphology. Similarly for the incidence of all-cause mortality and hospitalization for worsening heart failure, the LR chi-square is 10.6 (p-value of 0.0011).

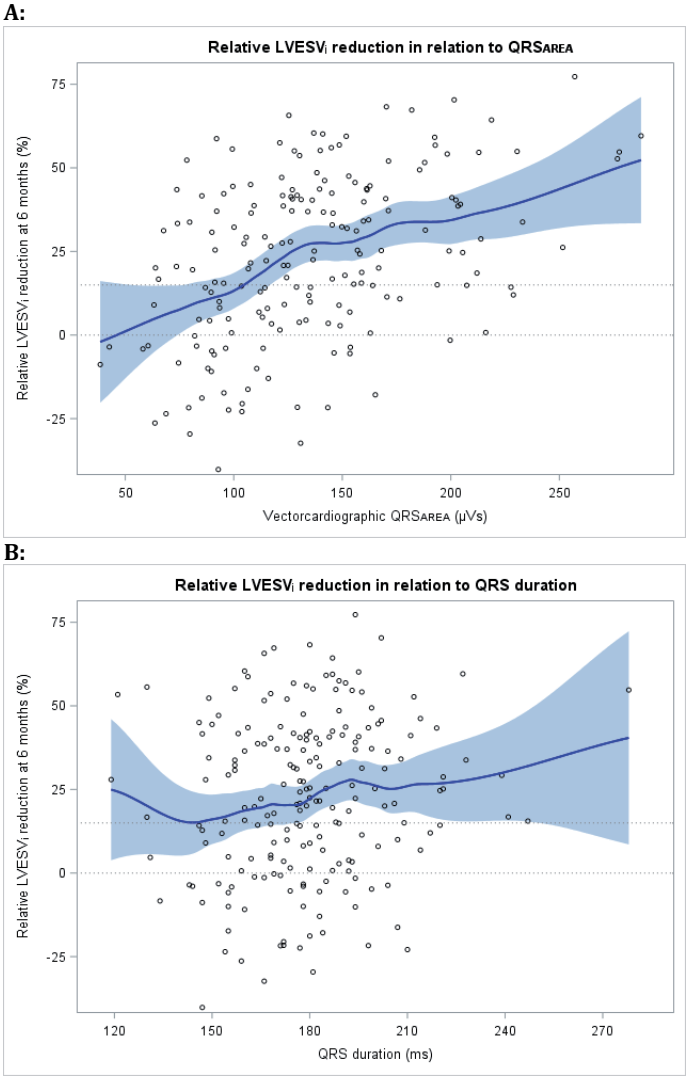

Figure 3. Scatter plot of reduction in $LVESV_i$ and QRS_{AREA} (A) or QRS duration (B). The blue curve and band are a LOESS fit with 95% confidence band

Relation of reverse remodeling at 6-months and cardiovascular events.
During 1-year follow-up, 11 deaths and 29 hospitalizations for worsening heart failure occurred in 23 patients. Ten patients had an event after the 6-month visit. Cox regression analysis identified a significant relation between reverse LV remodeling at 6 months and the post-6-months incidence of combined endpoint of all-cause death or hospitalization for worsening heart failure (p=0.0083). A higher CAVIAR score was significantly associated with lower incidence of the combined endpoint (hazard ratio 0.72; 95% confidence interval 0.59 to 0.87; p=0.0006). In Figure 4 the Kaplan-Meier estimates are depicted for the incidence of the combined endpoint, according to CAVIAR score tertiles (score -2 to 1, 2 to 4, and 5 to 9) for all patients. In *supplemental Figure 2* only patients with a LBBB are included.

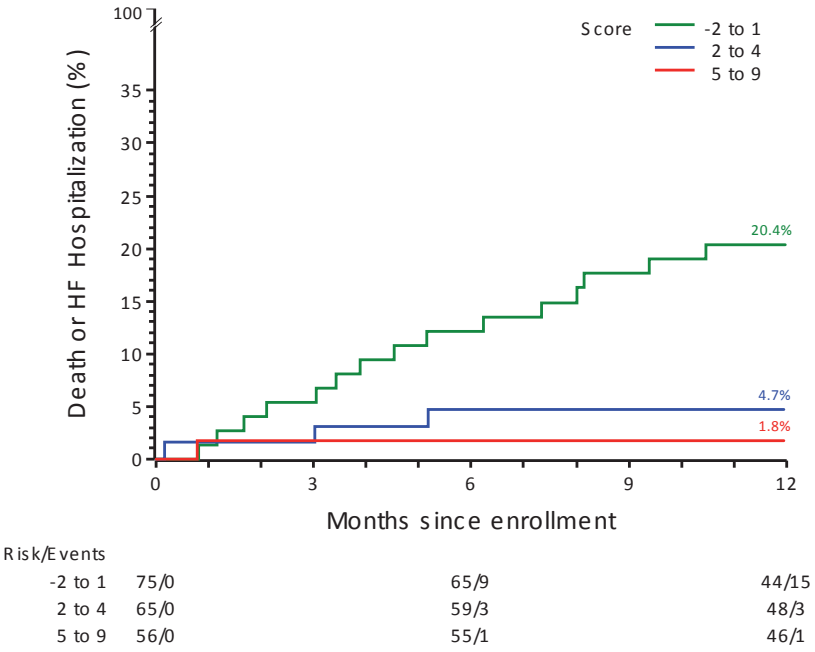

Figure 4. Kaplan-Meier estimates for the incidence of the combined endpoint of all-cause death and hospitalization for worsening heart failure, for patients grouped by response score tertile. A lower score is associated with a significantly increased event incidence (p=0.0006 with score as a continuous variable).

Discussion

This prospective study was primarily designed to determine markers for response in patients with a guideline indication for CRT. Independent predictors of response were younger age, larger QRS_{AREA}, longer interventricular mechanical delay and presence of apical rocking, all represented in the CAVIAR score. QRS morphology and duration, and several blood biomarkers were predictors in univariate analysis but did not add to the response prediction score after

multivariate analysis. Interestingly, of all biomarkers tested, relatively simple biomarkers remain to compose the CAVIAR score, which facilitates the clinical use of this score.

In contrast to most earlier studies, we analyzed reverse ventricular remodeling on a continuous scale to derive a reliable and easy-to-use response score. Over the entire patient cohort, 61% response was observed when assessing the usual cut off for response, reduction of ≥ 15% of $LVESV_i$. This percentage is consistent with earlier data [4]. Using the continuous scale, we found younger age, larger QRS_{AREA} derived from vectorcardiography and 2 echocardiographic dyssynchrony parameters (longer IVMD and presence of apical rocking) independently predicting response to CRT. Young age < 60 years was associated with a beneficial outcome whereas age > 75 years showed the opposite. The relevance of age for response is not well established but has been identified before [16,17].

A larger QRS_{AREA} was also independently associated with a larger benefit of CRT. This is in accordance with data of a smaller study in 81 CRT candidates where QRS_{AREA} was found to be a stronger predictor of CRT response (≥ 15% LVESV reduction) than QRS morphology or QRS duration [18]. The strong association of 3D vectorcardiographic derived QRS_{AREA} and CRT response may be explained by the fact that it shows the extent of unopposed electrical forces generated within the heart during ventricular depolarization, representing the direction as well as the delay of electrical activation. Figure 5 shows that QRS_{AREA} incorporates both QRS duration and core lab judged QRS morphology but the variability shows that there are unexplained other factors influencing this parameter.

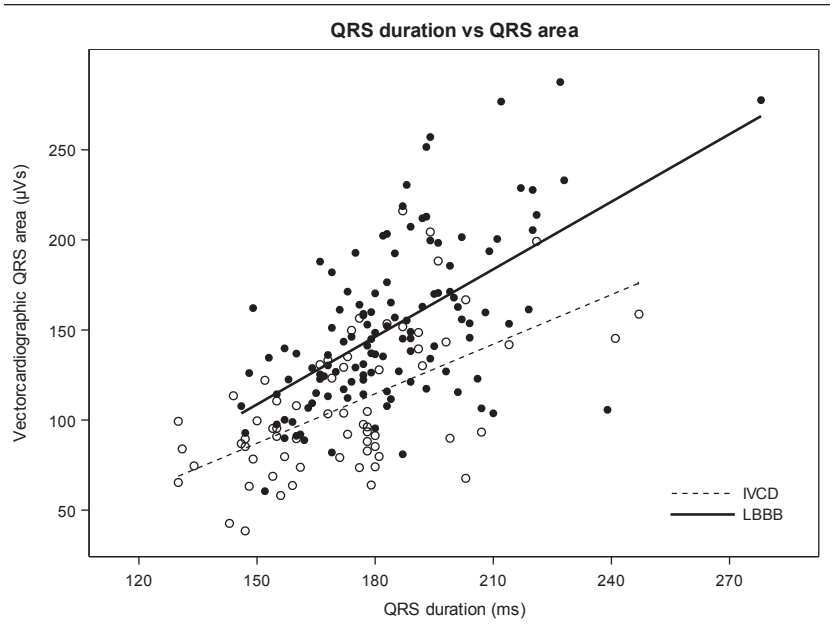

Figure 5. Relation between QRS_{AREA} derived from vectorcardiography and QRS duration on standard 12-lead ECG. Black dots are patients with core lab judged left bundle branch block (LBBB) and white dots patients with non-specific interventricular conduction delay (IVCD).

One of these parameters may be scar as QRS_{AREA} appears to be larger in non-ischemic heart failure patients [18]. QRS_{AREA} could therefore be a more comprehensive marker of the electrical substrate amendable to CRT than conventional ECG markers. This was supported by observations in an invasive electro-anatomic mapping study during CRT implantation in which patients with a large QRS_{AREA} had a significantly more delayed activation of the LV posterolateral wall [19]. The advantage of QRS_{AREA} compared to conventional ECG markers is that this parameter is observer-independent and represented in a quantitative manner, while as opposed to QRS-morphology indices (LBBB, IVCD) it is objectively determined and is a continuous variable. QRS_{AREA} predicts reduction of $LVESV_i$ independent of QRS morphology *(supplementary figure 3)*. Of importance for clinical use of the CAVIAR response score, the 3D vectorcardiogram can be constructed by commercially available ECG machines, and QRS_{AREA} calculation can be automated using the inverse Dower or Kors' regression transformation [20].

The strong association of two echocardiographic dyssynchrony parameters, IVMD as measure of *inter*ventricular dyssynchrony and apical rocking as marker of *intra*ventricular dyssynchrony, is not surprising. IVMD was one of the first parameters being associated with response to CRT but prospective studies were disappointing [5,13]. However, of all echocardiographic dyssynchrony markers, IVMD showed the lowest inter- and intraobserver variability [13]. Apical rocking is a less-investigated marker predicting CRT response [15]. Apical rocking was a stronger predictor than septal flash as the latter parameter is more easily underreported. Our study now identifies both an *inter*ventricular and an *intra*ventricular dyssynchrony parameter independently predicting reverse remodeling.

Non-ischemic cardiomyopathy, QRS duration and morphology and blood biomarkers did not significantly improve the predictive value of the CAVIAR response score. This may relate to the fact that these parameters are adequately reflected by age, vectorcardiography and echocardiography. Additionally, only few patients in our study had QRS duration < 150ms and the relation between QRS duration and CRT response flattens for higher QRS duration values [10]. The magnitude of remodeling predicted by the CAVIAR score in females exceeds that in males, as is demonstrated in Figure 2. The higher success rate in females has been described before [2]. The mechanism of better response in women is still unknown and will be investigated in the BioWomen study (NCT02344420).

LBBB was a significant predictor of CRT benefit in the univariate analysis, but it disappeared in the multivariate analysis due to the stronger predictive power of QRS_{AREA}, which is correlated with LBBB, as illustrated in figure 5 [18]. Another problem with LBBB is that it is subjectively assessed and that there are multiple definitions used, even between clinical trials [5]. This is also highlighted in our study cohort with 87% investigator-reported versus 57% core-lab reported study patients had LBBB (Table 1).

An advantage of our continuous response scale is that reverse remodeling in the individual patient can be compared to the predicted value, which could trigger additional efforts to

improve response [8]. This also holds for patients in whom super-response, defined as a decrease of $LVESV_i$ > 30%, is predicted by a CAVIAR score of 4 or more.
Clinical events such as all-cause mortality and heart failure hospitalizations have been correlated with reverse ventricular remodeling in earlier cohorts [9]. The CAVIAR score predicts the occurrence of these events with less than 2% adverse clinical events in the first year in super-responders with a CAVIAR score >4 and more than 20% events if CAVIAR is <2 (Figure 4).

Strength and limitations

The strength of our study is the homogenous group of patients included in only 6 centers and analyses of our data in core labs with specific expertise in respective areas. Another strength is the large number of biomarkers assessed to find the response score. This allows weighing the predictive value and statistically assessing the relationship between some of the biomarkers. Patients were included according to the most recent ESC guidelines [11] and were comparable to those included in other CRT trials. We excluded patients with a right bundle branch block because previous data showed a low response rate in these patients. Furthermore, we excluded patients with permanent AF and AF at baseline to avoid inadequate biventricular pacing. Follow up was excellent with paired echocardiographic studies available in 213 of 240 (89%) patients. Since AF often leads to inadequate biventricular stimulation, especially in patients without AV block, we designed strict inclusion criteria permitting inclusion only patients without recent AF. This precluded interference of AF during biventricular pacing in almost all patients. AHRE of more than one month were recorded in only 2 patients.

Limitations are the relatively small number of patients as compared to the landmark trials. Our response score has not yet been replicated in a different cohort. Furthermore, we did not systematically study the effects of scar burden on CRT response as cardiac magnetic resonance imaging was performed in only a subset of patients. Optimization of atrioventricular and interventricular delays was not uniform in all centers and we cannot exclude that this had an effect on the presented results. We included a majority of patients in functional class NYHA II. Therefore, our data may not apply for patients with severe heart failure.

Clinical implications:

Of importance for clinical use of the CAVIAR response score, the three parameters needed to calculate CAVIAR require relatively standard echocardiography and ECG. Apical rocking can be assessed from regular B-mode echo and IVMD from Doppler ultrasound measurements of pulmonary and aortic valve opening times, the 3D vectorcardiogram can be constructed by commercially available ECG machines, and QRS_{AREA} calculation can be

automated using the inverse Dower or Kors' regression transformation. Therefore, all tools required to determine a patients' CAVIAR score are clinically available.

Conclusion

In this prospective study, specifically designed to study markers of response to CRT from multiple domains, we identified lower age, larger QRS area, longer interventricular mechanical delay and presence of apical rocking as independent predictors of response, all represented in the CAVIAR response score. This score can be used both to identify candidates for CRT and predict the amount of ventricular reverse remodeling, as well as to validate the achieved reverse remodeling after CRT to recognize patients with suboptimally delivered CRT, who may benefit from additional optimization.

Funding

This research was performed within the framework of the Center for Translational Molecular Medicine (CTMM), project COHFAR (grant 01C-203), and additionally financially supported by Medtronic Inc., Minneapolis, MN, USA

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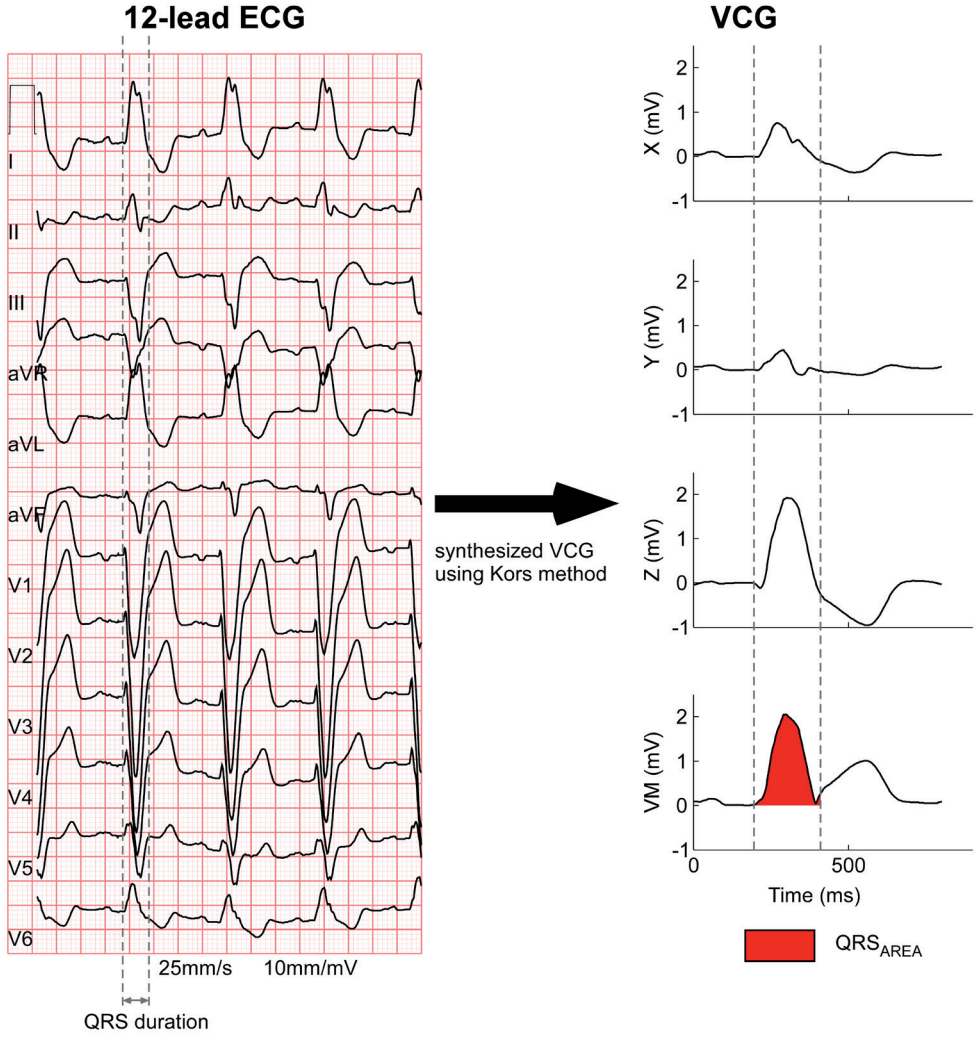
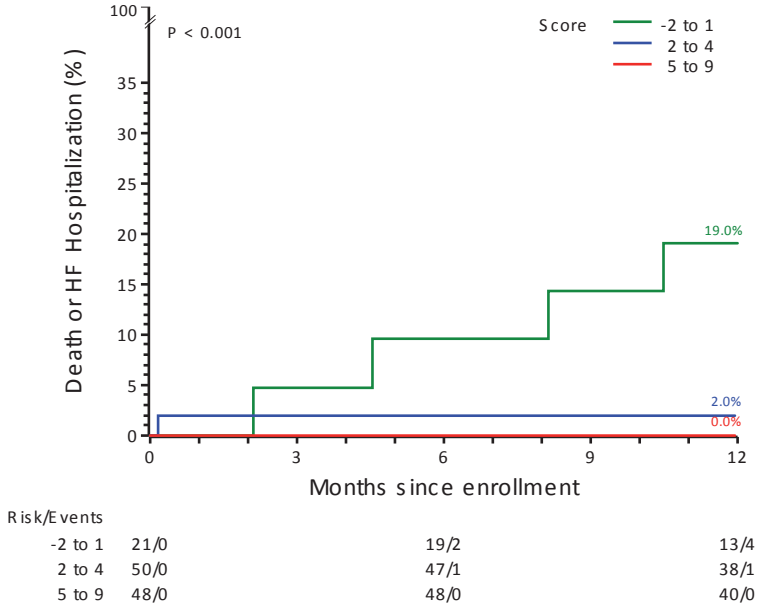
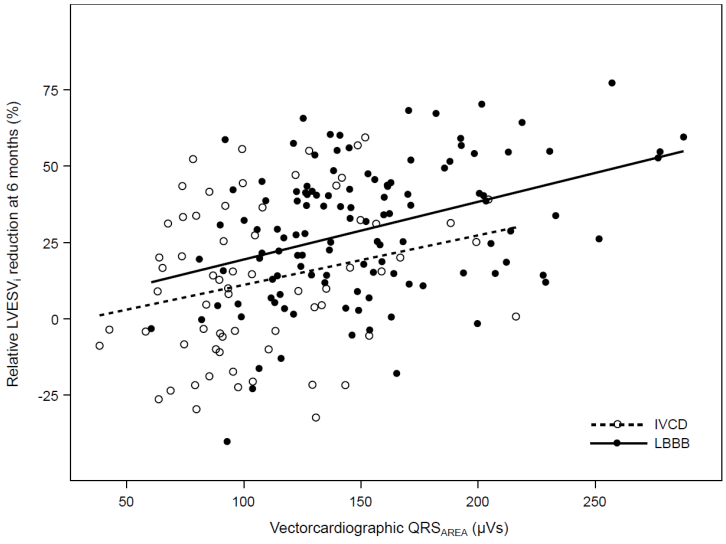
Supplementary figures



Supplementary figure 1: conversion of 12 lead ECG by the Kors method into a vectorcardiogram (VCG). QRS_{AREA} is automatically calculated as the area under the curve.



Supplementary figure 2: Kaplan-Meier estimates for the incidence of the combined endpoint of all-cause death and hospitalization for worsening heart failure, for patients with left bundle branch block grouped by response score tertile. A lower score is associated with a significantly increased event incidence (p<0.001 with score as a continuous variable)



Supplementary figure 3: relative reduction of left ventricular end-systolic volume index (LVESV$_i$) for patients with left bundle branch block (LBBB) or non-specific intraventricular conduction delay (IVCD) and relation to vectorcardiographic QRS$_{AREA}$. The corresponding linear regression model shows that overall LVESV$_i$ reduction is greater for LBBB patients (p=0.018; assessed at average QRS area of 136 µVs). The slope for LBBB patients is 0.1891 and is significantly different from 0 (p<0.0001). The slope for IVCD patients is 0.1624 and also significantly different from 0 (p=0.020). The two slopes are not significantly different (p=0.75).

Supplementary tables

Supplementary Table 1. Unadjusted prediction of $LVESV_i$ reduction.

Covariate or Biomarker		Univariable models		
Parameter	**Patients with paired $LVESV_i$ (N = 213)**	**Effect Estimate***	**95% Confidence Interval**	**P-value**
Patient baseline characteristic				
Female Gender	81 (38)	-12.2%	(-20.1%, -3.7%)	0.006
Age	66 ± 10	5.7%	(1.1%, 10.7%)	0.016
Ischemic Cardiomyopathy	90 (42)	25.8%	(15.3%, 37.3%)	< 0.0001
NYHA class (I/II)	134 (63)	-12.2%	(-20.0%, -3.5%)	0.007
History of Atrial Fibrillation	27 (13)	2.7%	(-10.5%, 17.9%)	0.70
Left Bundle Branch Block	129 (61)	-20.2%	(-27.1%, -12.7%)	< 0.0001
QRS duration (ms)	179 ± 23	-3.1%	(-7.8%, 1.7%)	0.20
Diabetes	56 (26)	6.5%	(-4.0%, 18.1%)	0.23
Prior heart failure hospitalization	35 (16)	-1.5%	(-12.9%, 11.4%)	0.81
Smoking History	105 (49)	-2.6%	(-11.2%, 6.8%)	0.57
Renal Dysfunction	10 (5)	5.4%	(-15.1%, 30.9%)	0.63
Blood markers				
Procollagen Type III N-terminal Peptide (P3NP) - ng/l	4 ± 2	4.5%	(-0.2%, 9.4%)	0.060
Blood Urea Nitrogen (BUN) - ng/ml	8 ± 4	5.6%	(0.9%, 10.5%)	0.019
Creatinine - ng/ml	93 ± 33	6.2%	(1.5%, 11.2%)	0.009
N-terminal Prohormone Brain Natriuretic Peptide (NT-proBNP) - ng/ml**	974 (440 - 1815)	2.0%	(-3.0%, 7.4%)	0.44
TIMP Metallopeptidase Inhibitor 1 (TIMP1) - ng/ml	202 ± 81	-3.5%	(-7.8%, 1.1%)	0.13
Galectin 3 - ng/ml	18 ± 6	5.6%	(0.8%, 10.5%)	0.021
C-terminal Propeptide of Type I Procollagen (PICP) - ng/ml	91 ± 48	-1.9%	(-6.3%, 2.7%)	0.42
Matrix Metallopeptidase 9 (MMP9) - ng/ml	263 ± 155	0.5%	(-4.0%, 5.2%)	0.84
C-terminal Telopeptide of Type I Collagen (ICTP) - ng/ml	7 ± 5	-0.3%	(-4.8%, 4.4%)	0.89
Aldosterone - ng/ml	111 ± 127	2.3%	(-2.3%, 7.2%)	0.33
High-sensitivity C-reactive Protein (hsCRP) - ng/ml	4 ± 6	-0.1%	(-4.6%, 4.7%)	0.98
High-sensitivity Troponin T - ng/ml	27 ± 26	4.4%	(-0.2%, 9.3%)	0.063
Interleukin 6 (IL6) - ng/ml	4 ± 5	-0.4%	(-5.0%, 4.3%)	0.85
ST2	28 ± 13	7.3%	(2.4%, 12.4%)	0.003
Growth differentiation factor 15 (GDF15)	1357 ± 871	4.4%	(-0.4%, 9.4%)	0.075
PICP/ICTP ratio	20 ± 18	-3.2%	(-7.5%, 1.3%)	0.16
Electrocardiographic markers				
Heart rate - bpm	68 ± 10	1.3%	(-3.3%, 6.1%)	0.58
PQ interval - ms	192 ± 37	6.1%	(1.3%, 11.1%)	0.012
QRS duration - ms	179 ± 23	-3.1%	(-7.8%, 1.7%)	0.20
QT interval - ms	518 ± 54	2.3%	(-2.3%, 7.1%)	0.34
QTc interval (Bazett) - ms	547 ± 50	3.4%	(-1.3%, 8.3%)	0.16
JT interval - ms	339 ± 46	4.1%	(-0.6%, 9.0%)	0.086
JTc interval - ms	368 ± 42	5.6%	(0.8%, 10.5%)	0.020
QT Short-Term Variability (STV QT) - ms	0.79 ± 0.35	5.2%	(0.3%, 10.3%)	0.038
RR Short-Term Variability (STV RR) - ms	13 ± 15	1.7%	(-3.1%, 6.7%)	0.49

Covariate or Biomarker		Univariable models		
Parameter	**Patients with paired $LVESV_i$ (N = 213)**	**Effect Estimate***	**95% Confidence Interval**	**P-value**
QRS_{AREA} - μVs	136 ± 47	-13.9%	(-17.7%, -9.8%)	< 0.0001
T wave area - μVs	93 ± 36	-11.2%	(-15.5%, -6.6%)	< 0.0001
Echocardiographic markers				
Inter-Ventricular Mechanical Delay - ms	47 ± 29	-12.1%	(-15.9%, -8.1%)	< 0.0001
Apical rocking	135 (63%)	-19.6%	(-26.5%, -12.0%)	< 0.0001
Mitral regurgitation***	120 (56%)	-3.0%	(-7.9%, 2.1%)	0.24
Septal flash	102 (48%)	-18.0%	(-25.3%, -10.0%)	< 0.0001

* Effect Estimate for continuous variables is for 1 standard deviation (s.d.) change. For example, 5.7% for age, with s.d. = 10 years, means that a patient who is 10 years older had on average 5.7% greater $LVESV_i$ change (less reverse remodeling).
** Median (quartiles).
*** Mitral regurgitation is classified in categories No, Trace, Little, Moderate, Severe. The percentage of patients in the latter 3 categories is reported. Effect estimate is for 1 category worsening.
Severe renal dysfunction: Glomerular Filtration Rate (GFR) < 30 mL/min/1.73m^2

Supplementary Table 2. Programmed atrioventricular (AV) and interventricular (VV) delays after optimization.

AV and VV optimization at 1 month	**Patients with paired LVESVi (N = 213)**
Echo based CRT optimization performed	209 (98.1%)
Atrial paced	19 (9.1%)
Heart rate (bpm)	
mean ± standard deviation	70.4 ± 12.2
median	70.0
25th percentile - 75th percentile	61 - 76
minimum - maximum	45 - 110
measure available (N,%)	209 (100.0%)
Ventricular pacing vector	
RV → LV	28 (13.4%)
LV → RV	181 (86.6%)
VV delay (ms)	
mean ± standard deviation	7.3 ± 14.4
median	0.0
25th percentile - 75th percentile	0 - 5
minimum - maximum	0 - 70
measure available (N,%)	208 (99.5%)
Sensed AV delay (ms)	
mean ± standard deviation	87.2 ± 27.1
median	90.0
25th percentile - 75th percentile	70 - 100
minimum - maximum	30 - 190
measure available (N,%)	208 (99.5%)
Paced AV delay (ms)	
mean ± standard deviation	135.0 ± 24.1
median	130.0
25th percentile - 75th percentile	130 - 150
minimum - maximum	50 - 220
measure available (N,%)	202 (96.7%)

CHAPTER 11

QRS vector amplitude in the transversal plane for quantification of leftward conduction delay - an objective alternative for selecting patients for cardiac resynchronization therapy.

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Submitted

Abstract

Introduction: Cardiac resynchronization therapy (CRT) is proven to be a successful therapy for patients with heart failure and conduction delay. The presence of left bundle branch block (LBBB) determines whether patients have a class I indication following the guidelines. However, it is questionable how this translates into clinical practice since several LBBB definitions exist, constructed of criteria that are open for multiple interpretations. Our aim was to quantify this and to find an objective alternative derived from the vectorcardiogram (VCG) that identifies the electrical substrate favorable to CRT response.

Methods: In the prospective observational multicenter study 'Markers And Response to CRT (MARC)' 240 patients underwent CRT implantation. All criteria of seven different LBBB definitions and intra/inter rater agreement were scored. The VCG was derived from the 12-lead ECG. Regression analysis was performed (n=213) to relate the definitions, criteria and vectorcardiographic measurements to response defined as relative reduction in indexed left ventricular end systolic volume index (LVESVi). C-statistics were calculated to compare diagnostic performance.

Results: 29-88% of the patients had a LBBB depending on definition used. Most definitions had a statistical significant relation with response except the definition according to Strauss. The guideline (LBBB ESC 2013) definition and the individual criteria R-peak time in I of ≥ 60ms and broad/notched R-wave in lead I, aVL, V5 or V6 were most associated with response. QRS vector amplitude in the transversal plane ≥ 1,56mV ($QRS_{VA\text{-}Tpl}$) performed at least as good as the LBBB ESC 2013 definition in predicting CRT response (sensitivity 72% vs 77% and specificity 67% and 49% respectively, odds ratio 5.3 vs 3.2).

Conclusion: Adherence to the guideline for CRT implantation depends greatly on which LBBB definition is used and how it is applied. $QRS_{VA\text{-}Tpl}$ is an easy and objective alternative that quantifies leftward ventricular conduction delay.

Introduction

With the advent of cardiac resynchronization therapy (CRT) the definition of left bundle branch block (LBBB) has regained new interest. Aside from QRS prolongation, LBBB is a prerequisite for a class I indication for CRT implantation in most recent guidelines [1-3]. This is mainly based on large registries and subanalyses of large clinical trials that investigated the benefit of CRT [4-7]. Although an exact definition is provided in the supplement of the European Society of Cardiology (ESC) 2013 guidelines, clinicians are often unaware which of the many definitions they apply [1,4,5,8-10]. Furthermore, evidence regarding the relationship between LBBB and CRT response is clouded by the different and/or often not reported definitions used. The goal of this study is not to advocate strict adherence to the ESC guideline definition of LBBB but to show the poor agreement between and within definitions constructed of descriptive criteria that are open for multiple interpretations. For the selection of patients eligible for CRT implantation we need a more objective measurement of leftward ventricular conduction delay. We therefore focused on finding an alternative that can quantify the electrical substrate favorable for CRT response by investigating the vectorcardiogram (VCG) derived from the 12-lead ECG.

In short, the aims of this study were to 1) assess how the different definitions and criteria of LBBB are represented in the patient population eligible for CRT, 2) identify those definitions and criteria that are most related to CRT response. 3) Finding a more objective vectorcardiographic alternative that quantifies leftward conduction delay and identifies a substrate favorable to CRT response.

Methods

Patient population

The prospective Markers and Response to CRT (MARC) study included 240 patients that were implanted with a CRT device with defibrillator (CRT-D). In this multicenter study, clinical, electrical, structural and blood markers were collected to identify (a combination of) parameters that can optimize the response rate of CRT. Patients were enrolled between February 2012 en November 2013. Total follow-up was 12 months. The study was initiated and coordinated by the 6 centers within the framework of the Center for Translational Molecular Medicine (CTMM), project COHFAR (grant 01C-203). Inclusion criteria were an indication for CRT according to the guidelines at the time of inclusion [1,11]. Exclusion criteria included severe renal insufficiency with a glomerular filtration rate (GFR) <30ml/min/1.73m^2, an upgrade from a bradycardia pacemaker or CRT-P to CRT-D, permanent atrial fibrillation (AF) or flutter or tachycardia, right bundle branch block, and permanent 2nd or 3rd degree atrioventricular block. Patients were seen at the outpatient department at baseline, 1, 6 and 12 months after CRT-D implantation. The institutional review boards of

all participating centers approved the study protocol. All patients provided written informed consent. (A more extensive description of methods is provided in the main paper of the MARC study, chapter 10).
In this substudy all 240 patients included in the main analysis were taken into account. As in the main analysis, regression analysis was performed with patients that had both pre-CRT and post-CRT (6 months) echocardiogram available (n=213).

ECG recording and analysis

The 12-lead digital ECG's (Cardio Perfect, Welch Allyn, sampling frequency 1200Hz, filter setting 0.05-300Hz) were recorded at baseline (pre-CRT). The raw data was imported in the Intraval software (Ritsema van Eck, Rotterdam) and analyzed offline with the fiducial segment averaging method [12] (chapter 7). After analysis, conventional intervals (RR, PQ, QRS, QT) and vectorcardiographic parameters were extracted. The VCG was synthesized from the 12-lead ECG's using the Kors regression method [13,14]. A VCG consists of three orthogonal leads X, Y and Z, which together form a 3D vector loop. The axes and angles were defined as stated by the American Heart Association (AHA) recommendations for vectorcardiography 1967 [15]. A positive azimuth was defined as backwards rotation from left in the transversal plane. Elevation was defined as the angle between the transversal plane with an upward angle defined as positive. QRS and T amplitude were taken at maximum. QRS and T wave area were calculated as the integral of the X, Y,Z by the formula area = $\int \sqrt{(X^2 + Y^2 + Z^2)}$.

Next to the in the MARC main study prespecified vectorcardiographic parameters (QRS_{AREA}, QRS vector amplitude (QRS_{VA}), T_{AREA}, T vector amplitude (T_{VA}), QRS_{VA} in the transversal plane ($QRS_{VA\text{-}Tpl}$) and QRST-angle we constructed 2 parameters by combining QRS and T azimuth and elevation based on expected direction of QRS and T-wave when leftward conduction delay is present. QRS vector for leftward conduction delay (QRS_{LWCD}) was defined as a QRS vector with an azimuth between 0 and +90 degrees and elevation between 0 and +90 degrees. T vector for leftward conduction delay (T_{LWCD}) was defined as a T vector with an azimuth between -90 and -180 degrees and elevation between 0 and + 90 degrees.

Assessment of QRS morphology

For the analysis of QRS morphology all ECG's were reviewed twice by two investigators (S.W and I.H). Discrepancies between the first and second analysis were reviewed one final time before the results between investigators was compared. Disagreements between reviewers were discussed and resolved by consensus. When consensus could not be reached a third investigator (cardiologist) was consulted.
The ECG's were scored for all different criteria of the LBBB definitions studied. We chose to score all criteria separately outside the context of fulfillment of other criteria to appreciate

the separate value of the criteria. To assess inter and intra observer variability Cohen's kappa's were calculated for all definitions [16,17].
Table 1 provides an overview of all definitions and criteria scored in this study. We included the following definitions; LBBB ESC old [8] (Refers to Willems et al, JACC 1985 [18]), LBBB ESC 2013 [1] (Refers to Surawicz et al JACC 2009 [9] and Zareba et al, Circ 2011 [4]), LBBB AHA [9], LBBB Strauss [10], LBBB Large Trials [4,5] (Refer to Willems et al JACC 1985 [18]) and Surawicz et al, JACC 2009 [9]), LBBB MARC (chapter 10) (Prespecified criteria determined by ECG core lab of the MARC study) and LBBB conventional (Prespecified criteria based on common clinical practice). Because some criteria are open for multiple interpretations we further specified them in advance. The leads in which the broad notched/slurred R-wave had to be present slightly differed between the different definitions; for the LBBB AHA definition it had to be present in I, aVL, V5 and V6, in the LBBB ESC 2013 and the LBBB large trials in I, aVL, V5 or V6 (# Table 1) and in the MARC study I, aVL and V6 (## Table 1). In the analysis we scored these criteria separately. Slurred R-wave was defined as a R-peak of > 60ms. R-peak time was determined as described by Willems et al [18]. Mid in the definition of mid-QRS notching or slurring is defined as start of notch >40ms after QRS onset and ≤ 50% of total QRS duration (correspondence with Strauss). Notching was defined as a sudden change in the slope of a waveform of ≥ 90 degrees and slurring as a sudden change in the slope of a waveform of < 90 degrees. We scored QRS notching and slurring with (F) and without (UF) the muscle filter (35Hz) on. For the criteria absent q in aVL we defined q as >40ms and/or > 1/4 of R amplitude.

Statistics - Relation with response

Separate univariate and multivariate analysis were performed with the 1) LBBB definitions (n=7) 2) individual LBBB criteria (n=20) and 3) vectorcardiographic parameters (n=8). The parameters included in the univariate analysis were tested for multicollinearity and excluded when correlation was higher than or equal to 0.85, marker of choice was based on beta coefficient and clinical applicability. Subsequently only parameters that showed a significant relation ($p<0.05$) with response (% relative change in indexed left ventricular end-systolic volume (LVESVi)) in the univariate analysis were included in the multivariate analysis. Linear regression was performed using backwards elimination. Acceptability of the regression model was checked by looking at the normality of the residuals by the Shapiro test and by looking at the linearity. The multivariate regression analyses were adjusted for age, gender and etiology of heart disease.

To compare diagnostic performance of best vectorcardiographic marker of leftward conduction delay to the best performing definition of LBBB, concordance-statistics (C-statistic) were calculated by univariate and multivariate (addition of age, gender and etiology of heart disease to the test) regression analysis with relative reduction of LVESVi

≥ 15% as outcome. Cut-off values of the continuous vectorcardiographic variable was determined by A) sensitivity comparable to the LBBB definition, B) specificity comparable to the LBBB definition C) Cut off determined based on the Youden index (= maximum (sensitivity + specificity -1) [19].

Results

Baseline - Clinical characteristics

All 240 patients included in the MARC main study were included in this subanalysis. Mean age of the patients was 67 ± 10 years, 37% was female and 46% had an ischemic etiology of heart disease. Mean left ventricular ejection fraction (LVEF) was 26 ± 8% and LVESVi was 74±30ml/m2 at baseline. In 213 patients paired pre-CRT and 6 months LVESVi measurements were available. No significant differences were found between the total population (n=240) and the 213 patients included in the regression analysis (an overview of baseline characteristics is provided in *supplemental Table 1*).

Baseline – Left bundle branch block definitions and criteria

QRS morphology could be scored in 229 patients (Table 1). Only 16 patients (7%) fulfilled none of the LBBB definitions. When using Strauss definition of LBBB most patients fulfilled the criteria for LBBB (88%), followed by the clinically used definition (LBBB conventional 79%). 60% of patients fulfilled the criteria for LBBB used in the MARC study and only 33% fulfilled the criteria following the old ESC definition. There was a complete overlap of patients fulfilling the conventional definition (79%) and the ESC 2013 definition (63%), whereas only 34% of patients fulfilling the LBBB ESC 2013 definition also fulfilled the Strauss definition.

Inter-and intra-rater agreement is presented in Table 1. Intra-rater agreement (repeatability) was as expected better than inter-rater agreement (reproducibility). Almost all kappa's for inter-rater agreement had a value around 0.7 except for the conventional definition that showed a higher reproducibility of 0.89 and for the Strauss definition that showed a lower reproducibility of 0.42.

Almost all patients (91-100%) fulfilled the criteria positive T in V1, QS or rS in V1, R-peak time of V1-V3 <60ms, and absent q in V5 and V6. The number of patients that had a notched/slurred R-wave in I, aVL, V5 and V6 was 96 (42%) while a notched/slurred R-wave in I, aVL, V5 or V6 was present in 149 patients (64%). 90% of patients had mid QRS notching/slurring in ≥ 2 leads of I, aVL, V1, V2, V5 or V6.

Baseline – Electrocardiographic parameters

Table 2 provides baseline values of electrocardiographic parameters including the vectorcardiographic measurements derived from the 12-lead ECG. In Figure 1 vectorcardiographic characteristics of the patients included in the MARC study before CRT

Table 1. Overview of definitions and criteria scored.

	ESC old 1	ESC 2013 2	AHA 3	STRAUSS 4	MADIT/ REVERSE 5	MARC main 6	Conventional 7	*MARC patients (%)*	*MARC patients (number)*
QRS duration ≥ 120ms	+	+	+	-	+	+	+	**100**	228
QRS duration ≥ 130ms	-	-	-	-	+	-	-	**99**	227
QRS duration ≥ 130ms (women), ≥ 140ms (men)	-	-	-	+	-	-	-	**99**	227
Positive T-wave in V1	+	-	-	-	-	-	-	**99**	226
QS or rS in V1	+	+	-	+	+	-	+	**99**	227
R-peak time V1-V3 <60ms	-	-	+	-	-	+	-	**98**	224
R-peak time I > 60ms	+	-	-	-	-	-	-	**87**	198
R-peak time V5 >60ms	-	-	+	-	-	-	-	**49**	112
R-peak time V6 >60ms	+	-	+	-	-	+	-	**75**	172
Notched/slurred R-wave in I, aVL, V5, V6	-	+[#]	+	-	+[#]	+[##]	-	**42/64[#]/64[##]**	95/147[#]/146[##]
Mid QRS notch/slurring in ≥ 2 leads of V1-2, V5-6, I,aVL	-	-	-	+	-	-	-	**90/76[F]**	205/174[F]
No rS pattern in V6	+	-	-	-	-	-	-	**85**	196
Absent q in I	+	-	+	-	-	+	+	**83**	189
Absent q in aVL	-	-	+	-	-	-	-	**89**	202
Absent q in V5	-	+	+	-	+	+	-	**92**	210
Absent q in V6	+	+	+	-	+	+	+	**91**	206
QS with positive T-wave in aVR	+	-	-	-	-	-	-	**44**	100
Usually discordant T-wave	+	-	+	-	-	-	-	**84**	193
MARC patients (%)	**33**	**63**	**29**	**88**	**62**	**60**	**79**		
MARC patients (number)	**75**	**144**	**66**	**202**	**143**	**137**	**180**		
inter rater agreement (Kappa)	**0.69**	**0.69**	**0.67**	**0.42**	**0.69**	**0.70**	**0.89**		
intra rater agreement (Kappa)	**0.78**	**0.91**	**0.86**	**0.77**	**0.91**	**0.92**	**0.86**		

LBBB ESC old[5]= European Society of Cardiology textbook definition by Luna et al. LBBB ESC 2013[1] = definition following ESC guidelines. LBBB AHA[6] = definition following American Heart Association (AHA) guidelines. LBBB Strauss[7] = definition as described by Strauss et al 2011. LBBB Large Trials[2,3] = definition as described by Zareba and Gold et al. LBBB MARC = definition used in the Markers and Response to CRT (MARC) study. LBBB conventional = Prespecified criteria based on common clinical practice. [#] = Present in I, aVL, V5 or V6. [##] = Present in I, aVL and V6. [F]= with muscle filter of 35Hz.

implantation are shown. Main QRS vector pointed backwards and to the left (azimuth 68±10 degrees) almost equal to the transversal plane (elevation 1.6±17 degrees) with a $QRS_{VA\text{-}Tpl}$ of 1.6±0.5. The mean QRS duration was 178±23ms and mean QRS_{AREA} was 131±47μVs. T vector pointed forward, to the right (azimuth -101±20 degrees) and also almost equal to the transversal plane (elevation -3.7±15).

Table 2. Baseline values of electrocardiographic and vectorcardiographic parameters in all patients included in the Markers and Response to Cardiac Resynchronization therapy (MARC) study (n=240) and in those included in the regression analysis (n=213). Values are provided as mean (±standard deviation) or number (proportion in %). VA = vector amplitude.

Electrocardiographic parameters	**N=240**	**N=213**
PQ-interval - ms	195 (±41)	192 (±37)
QRS duration - ms	178 (±23)	179 (±23)
QT-interval - ms	519 (±56)	518 (±54)
Vectorcardiographic parameters		
QRS_{VA} - mV	1.70 (±0.46)	1.74 (±0.46)
QRS_{AREA} - μVs	131 (±47)	136 (±47)
QRS azimuth - 0 until 180°	68 (±19)	67 (±18)
QRS elevation - +90 until -90°	1.6 (±17)	0.8 (±17)
QRS_{LWCD}	82 (39.6%)	70 (37.8%)
T_{VA} - mV	0.55 (±0.22)	0.57 (±0.22)
T_{AREA} - μVs	90 (±36)	93 (±36)
T azimuth - 0 until -180°	-101 (±20)	-101 (±20)
T elevation - +90 until -90°	-3.7 (±15)	-3.3 (±15)
T_{LWCD}	64 (33.7%)	60 (35.3%)
$QRS_{VA\text{-}Tpl}$ - mV	1.6 (±0.5)	1.7 (±0.5)
QRST angle - between 0 and 180°	160 (±12)	160 (±12)

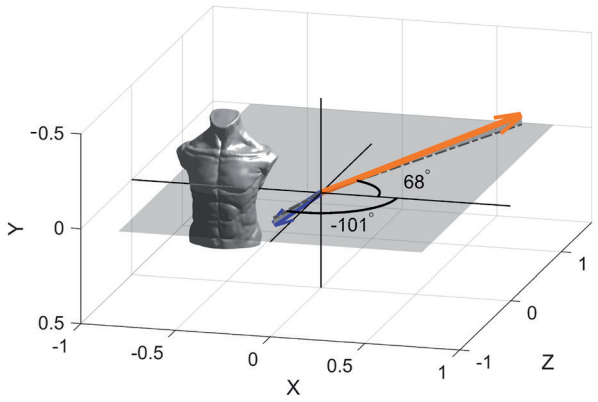

Figure 1. Mean vector of QRS and T-wave before cardiac resynchronization therapy (CRT) device implantation of patients included in the Markers and Response to CRT (MARC) study. Figure courtesy of R. van Es.

Relation with response – left bundle branch block definitions and criteria

We performed an univariate regression analysis for the seven different LBBB definitions to determine the relationship with CRT response (Table 3, upper panel). All definitions except the one from Strauss had a statistical significant relation with response quantified as relative reduction in LVESVi. Multivariate analysis showed the LBBB ESC 2013 definition to have the highest correlation with CRT response (Table 3, lower panel).

Table 3. Univariate (upper panel) and multivariate (lower panel) analysis of the different definitions of left bundle branch block (LBBB) definitions in relation to relative change in indexed left ventricular end systolic volume (LVESVi).

Univariate analysis LBBB definitions	Relative LVESVi change (%) per unit	p-value
ESC old	12.28	<0.001
ESC 2013	16.82	<0.001
AHA	12.94	<0.001
Strauss	-	0.071
Large trials	16.02	<0.001
MARC	16.49	<0.001
Conventional	13.36	0.001

Multivariate analysis LBBB definitions	Relative LVESVi change (%) per unit	p-value
ESC 2013	14.12	<0.001

Note that beta coefficient for the LBBB definitions are provided per unit, which results in a relative but not absolute higher beta coefficient compared to continuous variables.
LBBB ESC old[5]= European Society of Cardiology textbook definition by Luna et al. LBBB ESC 2013[1] = definition following ESC guidelines. LBBB AHA[6] = definition following American Heart Association (AHA) guidelines. LBBB Strauss[7] = definition as described by Strauss et al 2011. LBBB Large Trials[2,3] = definition as described by Zareba and Gold et al. LBBB MARC = definition used in the Markers and Response to CRT (MARC) study. LBBB conventional = Prespecified criteria based on common clinical practice.

In Table 4 (upper panel) univariate relationship between every criterion used in the various LBBB definitions with CRT response are depicted. Based on multicollinearity with notched/slurred R-wave in I, aVL, V5 or V6 we excluded notched/slurred R wave in I, aVL, V5 and V6 and notched/slurred R-wave in I, aVL and V6. Multivariate analysis of the significant criteria (Table 4, lower panel) showed R-peak time >60ms in lead I and a notched/slurred R-wave in I, aVL, V5 or V6 as most relevant to CRT response.

Table 4. Univariate (upper panel) and multivariate (lower panel) analysis of the different definitions of left bundle branch block (LBBB) criteria in relation to relative change in indexed left ventricular end systolic volume (LVESVi).

Univariate analysis LBBB criteria	Relative LVESVi change (%) per unit	p-value
QRS duration ≥ 120ms	-	0.809
QRS duration ≥ 130ms	-	0.279
QRS duration ≥ 130ms (women), ≥ 140ms (men)	-	0.279
Positive T-wave in V1	-	0.488
QS or rS in V1	-	0.390
R-peak time V1-V3 <60ms	-	0.947
R-peak time I > 60ms	18.55	<0.001
R-peak time V5 >60ms	8.88	0.009
R-peak time V6 >60ms	15.08	<0.001
Notched/slurred R-wave in I, aVL, V5 and V6	13.92	<0.001
Notched/slurred R-wave in I, aVL, and V6	16.34	<0.001
Notched/slurred R-wave in I, aVL, V5 or V6	16.67	<0.001
Mid QRS notch/slurring in ≥ 2 leads of V1-2, V5-6, I, aVL	11.73	0.050
No rS pattern in V6	13.24	0.010
Absent q in I	14.42	0.002
Absent q in aVL	-	0.069
Absent q in V5	-	0.058
Absent q in V6	-	0.290
QS with positive T-wave in aVR	12.19	<0.001
Usually discordant T-wave	-	0.332

Multivariate analysis LBBB criteria	Relative LVESVi change (%) per unit	p-value
R-peak time I > 60ms	10.26	<0.001
Notched/slurred R-wave in I, aVL, V5 or V6	11.91	<0.001

Note that beta coefficient for the LBBB criteria are provided per unit, which results in a relative but not absolute higher beta coefficient compared to continuous variables.

Relation to response – Vectorcardiographic parameters

In Table 5 (upper panel) the univariate relation to response of the tested vectorcardiographic parameters is depicted. Based on multicollinearity with QRS_{AREA} we excluded QRS_{VA}, T_{AREA} and T_{VA}. Multivariate analysis of these parameters showed that $QRS_{VA\text{-}Tpl}$ has greatest relation with response (Table 5 middle panel). In Table 5 (lower panel) the multivariate analysis is shown including both LBBB criteria and vectorcardiographic measurements. A notched/slurred R-wave in I, aVL, V5 or V6 and $QRS_{VA\text{-}Tpl}$ remained significant in this analysis. Note that beta coefficient for vectorcardiographic parameters are provided per standard deviation because these are continuous variables. This is in contrast to the LBBB definitions and criteria that are dichotomous variables, which results in a relative but not absolute higher beta coefficient.

Table 5. Univariate (upper panel) and multivariate (middle panel) regression analysis of the vectorcardiographic (VCG) parameters. In the lower panel the multivariate of VCG parameters and left bundle branch (LBBB) criteria are shown.

Univariate analysis VCG parameters	Relative LVESVi change (%) per standard deviation	p-value
QRS_{VA}	10.54	<0.001
QRS_{AREA}	10.46	<0.001
QRS_{LWCD}	-	0.118
QRS_{VA-Tpl}	10.70	<0.001
T_{VA}	7.01	<0.001
T_{AREA}	7.79	<0.001
T_{LWCD}	10.58	0.005
QRST-angle	-	0.210

Multivariate analysis VCG parameters	Relative LVESVi change (%) per standard deviation	p-value
QRS_{VA-Tpl}	9.47	<0.001

Multivariate analysis VCG parameters + LBBB criteria	Relative LVESVi change (%)	p-value
Notched/slurred R-wave in I, aVL, V5 or V6	8.98 **	0.02
QRS_{VA-Tpl}	7.78 *	<0.001

* Note that beta coefficient for VCG parameters are provided per standard deviation because these are continuous variables. ** For dichotomous variables such as the LBBB criteria beta coefficients are provided per unit, this results in a relative but not absolute higher value. LWCD = left ward conduction delay; Tpl = transversal plane VA=vector amplitude.

Performance to predict CRT response

We compared the diagnostic performance of the best LBBB definition (LBBB ESC 2013) to QRS_{VA-Tpl}, the most significant vectorcardiographic measurement resembling leftward conduction delay. In Figure 2 ROC curve of QRS_{VA-Tpl} is plotted to compare sensitivity and specificity to LBBB ESC 2013. The c-statistics for QRS_{VA-Tpl} (0.63) and LBBB ESC 2013 (0.69) were not significantly different. By adding adjustment variables (gender, age and etiology of heart disease) to the model c-statistic improved to 0.69 and 0.71 respectively ($p>0.05$). LBBB ESC 2013 as marker for response to CRT had a sensitivity of 77% and a specificity of 49% in our study with an odds ratio of 3.2. As shown in Figure 2 sensitivity and specificity of QRS_{VA-Tpl} were dependent of cut-off value. We showed three different cut-off values A) $QRS_{VA-Tpl} \geq 1.48$ that resulted in a comparable sensitivity to LBBB ESC 2013, B) $QRS_{VA-Tpl} \geq 1.40$ that resulted in a comparable specificity to LBBB ESC 2013, C) $QRS_{VA-Tpl} \geq 1.56$ that was determined based on Youden index resulted in a sensitivity of 72% and a specificity of 67% with an odds ratio of 5.3.

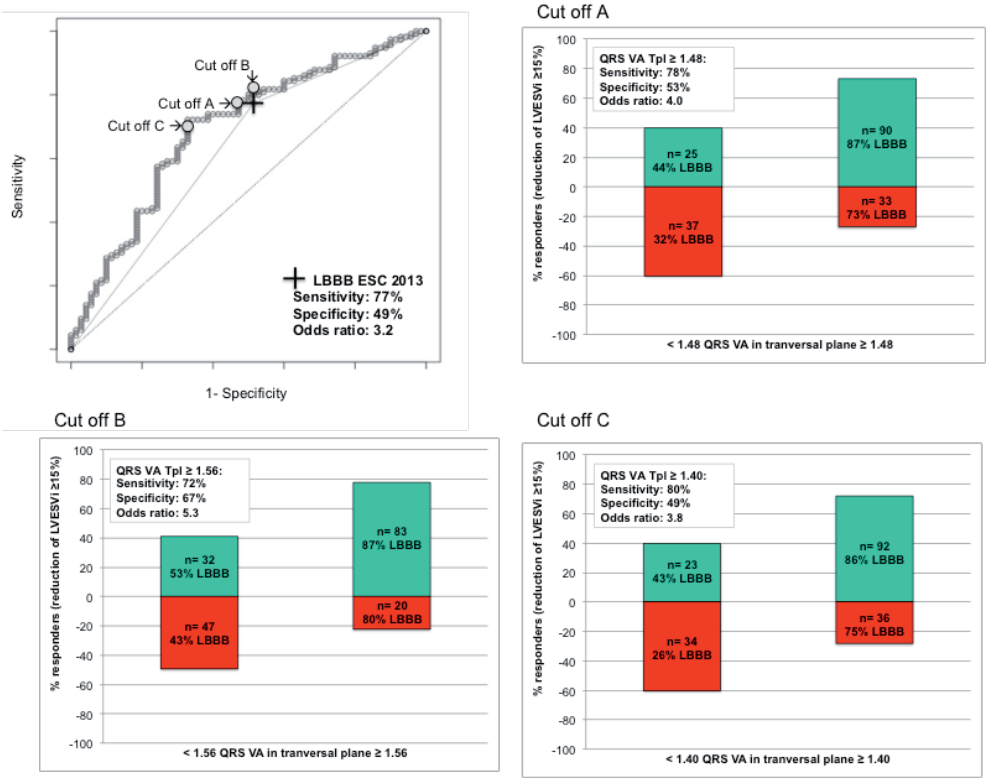

Figure 2. Performance of QRS vector amplitude in the transversal plane (QRS VA TpI) compared to the European Society of Cardiology guideline definition (LBBB ESC 2013). In the first panel the ROC curve of QRS VA TpI is plotted, the black cross depicts the sensitivity and specificity of LBBB ESC 2013. The other 3 panels show rates of responders (quantified as a reduction of left ventricular end systolic volume index (LVESVi) of ≥ 15%) for three different cut off values of QRS VA TpI; A) sensitivity comparable to LBBB ESC 2013, B) specificity comparable to LBBB ESC 2013 and C) optimal cut off value based on Youden index. The proportion and absolute number of responders is depicted in green, non-responders in red. For every group, percentages of patients with a LBBB following ESC 2013 definition are also provided. Sensitivity, specificity and odds ratio are given for every cut off value.

Relationship of $QRS_{VA\text{-}TpI}$ with QRS duration and LBBB is depicted in Figure 3. It shows that patients with LBBB had a larger $QRS_{VA\text{-}TpI}$ (black dots and triangles). Furthermore, you can appreciate a higher proportion of white and black dots, representing the CRT responders, above the cut off of $QRS_{VA\text{-}TpI}$ > 1.56. Interestingly, it also shows that most of the few patients without a LBBB and a QRS < 150ms and therefore should not have been included in this study.

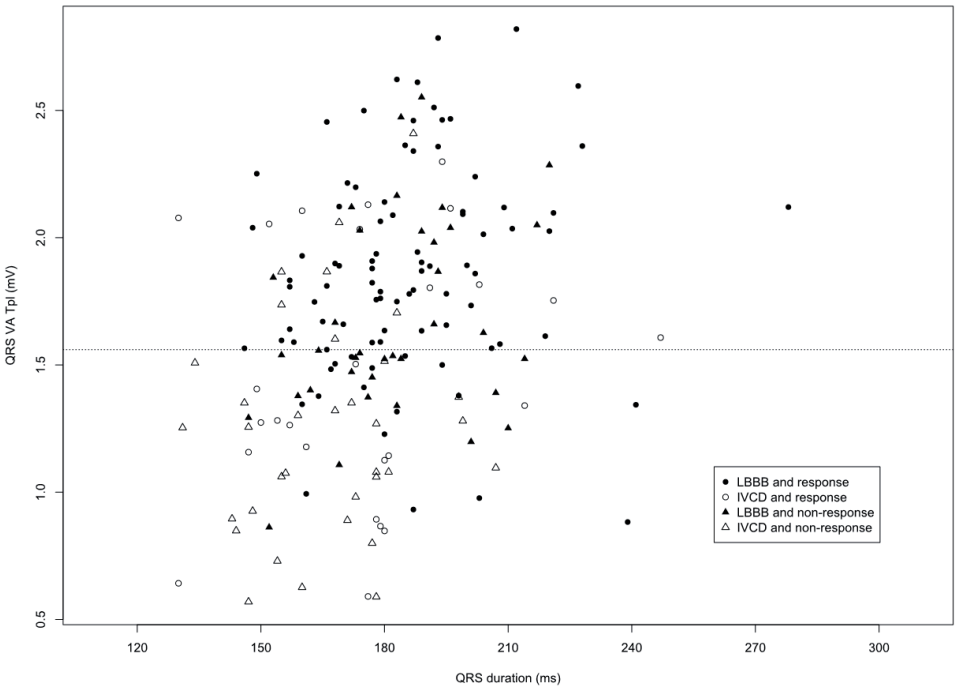

Figure 3. QRS duration plotted against QRS vector amplitude in the transversal plane ($QRS_{VA\text{-}Tpl}$). Dots are patients with left bundle branch block (LBBB) defined by the LBBB ESC 2013 definition (QRS≥120ms, QS or rS in V1, notched/slurred R in I, aVL, V5, V6 and absent q in V5 and V6). Triangles are patients with intraventricular conduction delay (IVCD). Black filling of the dots and triangles represents responders defined as reverse structural remodeling with a reduction in left ventricular end systolic volume index (LVESVi) of ≥ 15%. The dotted horizontal line represents the cut-off value of $QRS_{VA\text{-}Tpl}$ of 1.56mV.

Discussion

Although the most recent class I indication for CRT requires the presence of a LBBB, adherence of the guidelines is hampered by the existence of multiple LBBB definitions, constructed of criteria that are open for multiple interpretations. We showed in our cohort of patients eligible for CRT that the proportion of patients having a LBBB depends greatly on the definition used and the various definitions have different relations with CRT response. $QRS_{VA\text{-}Tpl}$, an objective vectorcardiographic marker derived from the ECG that quantifies leftward conduction delay, performed at least as good as the best LBBB definition in predicting response to CRT.

LBBB and CRT response

The class I indication for CRT implantation in patients with LBBB is based on several large registries and substudies of the large clinical trials on CRT [4-7]. It is important to note that these trials included patients based on QRS width as stated by previous guidelines and not

QRS morphology. None of these studies were powered for subgroup analyses. Therefore, it is debated in the latest ESC guideline on heart failure whether QRS duration or QRS morphology is the main predictor of a beneficial response to CRT [3]. This discussion is complicated by the fact that the majority of the randomized controlled trials included in the both meta-analyses do not report which definition of LBBB was used [20,21].

Definition of LBBB –which one is best?

The definition of LBBB is not unambiguous as shown in Table 1. Interestingly, the criteria used by the various definitions in different combinations are almost all based on two statements with recommendations made on expert opinions authored by Willems et al in 1985 [18] and Surawicz et al in 2009 [9]. Willems et al subsequently refers to a previous statement of experts of the New York Association and an interesting review of Scott et al 1965 that relate the New York Association recommendations of electrocardiographic criteria to evidence of ventricular activation at that time [22,23]. Several endocardial mapping and also vectorcardiographic studies over time had influence on these statements. However, because of the heterogeneous and complicated activation patterns, indisputable evidence of the true LBBB activation pattern and subsequent electrocardiographic characteristics was not, and is still not available [24-28].

Nevertheless, finding the patients with a most favorable response to CRT will probably not depend on defining the true LBBB but on defining dominant leftward conduction delay. Patients eligible for CRT often have progressed heart failure with enlarged hearts which makes it likely that the conduction delay present is not only caused by abnormal initial activation but is at least accompanied by some intraventricular conduction delay. Scars in patients with ischemic cardiomyopathies will further complicate the sum of activation that is visible on the surface ECG. However, it is important that the same definition is used in a similar manner, in research as well as clinical setting. At the moment the exact LBBB definition used is not described in a large proportion of the scientific publications on CRT. This is a major problem since we show that the proportion of patients having a LBBB depends greatly on the definition used and the various definitions have different relations with CRT response. Even cardiologists that have to determine indication for CRT implantation are not always aware of this problem, this is reflected in the fact that even in our study patients were erroneous included based on non LBBB QRS morphology and a QRS duration < 150ms (Figure 3).

According to the most recent guideline definition 63% of the patients in our study had a LBBB. This LBBB ESC 2013 definition (QRS≥120ms, QS or rS in V1, notched/slurred R in I, aVL, V5, V6 and absent q in V5 and V6) showed the strongest correlation with response. 88% of patients had an LBBB following the Strauss definition and although there was overlap with the LBBB ESC 2013 definition, 29% of the patient population falsely fitted the QRS morphology criteria of a class I indication. This is of importance since the

Strauss LBBB definition did not show a significant relation with response. Various studies advocated 'strict' LBBB criteria as provided by Strauss et al [29-31] to be superior in predicting CRT response. That is not confirmed in our study, which can be explained by the fact that in previous studies the LBBB definition according to Strauss was only compared to the conventional LBBB definition and not to the AHA or ESC definitions that also include slurring and/or notching, although differently defined. In two of those studies [29,30] the conventional LBBB definition was only defined as QRS ≥120ms and QS or rS in V1. Furthermore, Strauss et al stated that the definition of complete LBBB should include their criteria, not that they should be used as a separate definition. This stresses the problem of unambiguous interpretation of the definitions and individual criteria and the fact that the criteria are also (incorrectly) used in various combinations [2,4,5,7,32].
The subjective, non-reproducible assessment of the descriptive criteria is reflected in the relatively low inter-rater agreement (Table 1), even though many criteria were prespecified. It is for example unclear how broad the R-wave has to be to fulfill the criteria 'broad/notched R-wave in the lateral leads' already described by Willems et al and in which lateral leads this broad/notched R-wave has to be present. Furthermore, we experienced difficulty in consequently assess the mid-QRS slurring/notching in the definition of Strauss, even though additional specifications were provided by the authors, which resulted in a low inter-and intra-rater agreement (Table 1). R-peak time in I of ≥ 60ms and broad/notched R-wave in the lateral leads were the criteria most associated with CRT response - interestingly, none of the definitions use both of these criteria (Table 4). There were also several criteria that almost all patients (99-100%) fulfilled and therefore were redundant for making the distinction between intra ventricular conduction delay and LBBB.

Finding an alternative - The renewed interest in the vectorcardiogram

Several studies have suggested alternatives for assessing leftward conduction delay but often have the disadvantage to be invasive, complicated and/or only possible during of after implantation procedure [33-36]. Computerized determination of fiducial points and dominant vector on the 12-lead ECG could aid in defining a more objective 'description' of QRS morphology that represents a favorable substrate for CRT response. An example is the VCG derived from the 12-lead ECG. This is an easy applicable non-invasive tool that is specifically suitable for description of conduction delay since this is dominantly present in the transversal plane (elevation around 0 degrees)[22]. Vectorcardiography makes this plane more visible than the standard ECG and can quantify vectors of depolarization and repolarization that are parallel to this plane (Figure 1).
In the MARC main analysis QRS_{AREA} was found to be superior to QRS duration and morphology in predicting CRT response (chapter 10). In this study we looked for a vectorcardiographic parameter that specifically represents leftward conduction delay and found a larger QRS vector amplitude in the transversal plane ($QRS_{VA\text{-}TpI}$) to be most related with CRT response (Table 5). QRS_{VA} contains information about the amount of conduction

delay and is highly correlated to QRS_{AREA}. $QRS_{VA\text{-}TpI}$ also takes the direction of conduction delay into account because the amplitude of the vector is measured in the transversal plane. Therefore $QRS_{VA\text{-}TpI}$ performed slightly better than QRS_{AREA} and overall better than LBBB ESC 2013 in predicting CRT response. The additional strength of $QRS_{VA\text{-}TpI}$ compared to LBBB could be explained by taking also right ventricular activation into account. Less electrical forces opposing the leftward activation when right ventricular activation is preserved, resulting in a larger amplitude of the QRS vector in the transversal plane. Preserved right ventricular function and activation appear to be important for CRT response [34,37].
The advantage of a continuous variable is that cut off value can be adapted to achieve a desired relationship between sensitivity and specificity (Figure 2). For this analysis we compared three different cut-off values. The optimal $QRS_{VA\text{-}TpI}$ cut-off in this population based on the Youden index was ≥1.56 mV and resulted in a substantial higher specificity (67% versus 49% for LBBB ESC 2013) with only a slight difference in not identified responders (32 versus 26 non-identified responders with LBBB ESC 2013).

Limitations

First of all, results of this study have to be validated in another cohort of patients.
Although LBBB was not a determinant in the guidelines for CRT implantation at the start of the inclusion period in February 2012 it was included in the AHA guidelines that appeared later that year and the ESC guidelines in 2013. This resulted in a pre-specified population with relatively few patients with non-LBBB morphology. Furthermore, it would have been interesting to determine $QRS_{VA\text{-}TpI}$ and QRS_{AREA} in patients with a right bundle branch block.
For clinical applicability the VCG was derived from the 12-lead ECG with Kors' regression method, this is an estimation of the gold standard Frank-VCG. However, Kors' method resembles the Frank-VCG most [14,38]. Although recommended by Strauss, the high quality (high-resolution) of the ECG's in this study could have influenced the scoring of R-wave slurring and notching. The vector values will not be influenced much by ECG resolution or method of ECG analysis.

Future directions

First step to validate results could be the retrospective analysis of patients included in the large clinical trials that demonstrated the importance of leftward conduction delay for CRT response. The VCG can be constructed from the raw data but also PDF file of a 12-lead ECG acquired by any commercially available ECG machine [13,39]. This would also be a cost-effective manner to be able to determine an optimal cut off value of $QRS_{VA\text{-}TpI}$.

Conclusion

In a patient population eligible for CRT implantation, the proportion of patients having a LBBB depends greatly on definition used and the various definitions have different relations to reverse structural remodeling. This is not only a major problem for solid research on the importance of QRS morphology in relation to beneficial response to CRT, but also adherence to the current guidelines for CRT implantation is hampered. $QRS_{VA\text{-}TpI}$ is a simple and objective determinant of leftward ventricular conduction delay that can be automatically derived from the 12-lead ECG and predicts CRT response at least as good as the best performing LBBB definition as defined in the ESC 2013 guidelines.

Funding

This research was performed within the framework of the Center for Translational Molecular Medicine (CTMM), project COHFAR (grant 01C-203), and additionally financially supported by Medtronic Inc., Minneapolis, MN, USA

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Supplementary tables

Supplementary Table 1. Overview of baseline characteristics of patients included in the Markers and Response to Cardiac Resynchronization Therapy (CRT) (MARC) study. Data are provided for all patients (n=240) and patients with paired indexed left ventricular end systolic volume measurements before and 6 months after CRT implantation (n=213). Values are provided as mean (± standard deviation); number (proportion in %); value (interquartile range). ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker, NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association.

Clinical characteristics	N=240	N=213
Age - years	67 (±10)	66 (±10)
Female sex	89 (37%)	81 (38%)
Ischemic etiology of heart disease	111 (46%)	90 (42%)
History of atrial fibrillation	32 (13%)	27 (13%)
Diabetes	65 (27%)	56 (26%)
Renal dysfunction	15 (6%)	10 (5%)
NYHA functional class		
Class I	1 (0.4%)	1 (0.5%)
Class II	150 (63%)	133 (62%)
Class III	89 (37%)	79 (37%)
Class IV	0 (0%)	0 (0%)
Laboratory values		
NT-proBNP - ng/l	966 (437-1839)	974 (443-1803)
Creatinine - umol/l	87 (72-111)	85 (71-109)
Echocardiographic parameters		
Left ventricular ejection fraction - %	26 (±8)	26 (±7)
Left ventricular end systolic volume index - mL/m2	74 (±30)	75 (±31)
Baseline medication		
ACE inhibitor or ARB	225 (94%)	200(945)
Aldosterone antagonist	116 (48%)	105 (49%)
Beta-blocker	201 (84%)	181 (85%)
Diuretic	170 (71%)	152 (71%)
Statin	142 (59%)	120 (56%)

CHAPTER 12

General discussion and future perspectives

General discussion and future perspectives

In this thesis an effort was made to translate basic research into clinical practice to improve cardiac device therapy. We showed the electrocardiogram (ECG) is everything but obsolete or outdated and is of great value as a simple non-invasive tool in identifying individuals that can benefit from implantable cardioverter-defibrillator (ICD) and/or cardiac resynchronization therapy (CRT) implantation. Furthermore, in-device monitoring via the electrogram (EGM) can further tune cardiac device therapy.

Part 1. Patient selection for ICD therapy

Based on multiple large clinical trials conducted over the last decades, guidelines for ICD implantation have been evolving [1,2]. The increase in primary prophylactic ICD implantations challenges us to be critical towards the evidence as concerns rise about cost-effectiveness and the benefit/complication ratio. In chapter 2, we show that the benefit of ICD implantation in clinical practice is similar to the large clinical trials and in patients with non-ischemic cardiomyopathy implanted for primary prophylaxis a low number of appropriate shocks occur. The benefit of ICD implantation in non-ischemic cardiomyopathy has been a subject of debate because large trials failed to reach significance for the benefit of primary prophylactic ICD implantation in this subgroup [1,3]. Because of the low number of event in the patient population with non-ischemic cardiomyopathy, studies were often underpowered. However, recently the 'Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality' (DANISH) trial was published. This study only included patients with non-ischemic etiology of heart failure and was especially powered to investigate benefit of ICD implantation in this population. They randomized between ICD implantation and standard clinical care and showed a significant difference in death from arrhythmic causes but not overall mortality [4]. The authors emphasize better risk stratification in this group to identify those subjects at risk for life-threatening arrhythmias but not death from other causes, they state risk scores could be of advantage. Another subgroup that shows a lower benefit of ICD implantation according to our findings is women (chapter 2) [5]. Our results were combined in a European registry for primary prophylactic patients from 11 countries that demonstrated similar results [6].
These observations imply that better risk stratification will be lucrative and will allow a more patient-tailored approach. Electrophysiological parameters are the most obvious candidates to improve risk stratification since we must identify patients specifically at risk for sudden cardiac death (SCD) and exclude those that are more likely to die from non-arrhythmic causes. Several efforts have been made to develop such electrophysiological proarrhythmic markers but these often turn out to have disappointing hazard ratios. To embrace the complexity of the various cardiac substrates underlying SCD, combining different methods of risk stratification could be the solution. This is performed in the

prospective observational EUTrigTreat clinical trial in which multiple electrophysiological markers were tested and combined in a large multicenter patient population (chapter 5 and 6). Interestingly, microvolt T-wave alternans and programmed electrophysiological stimulation combined were predictive of appropriate shock but not mortality. Unfortunately, both tests comprise a significant burden for the patient and clinical applicability is limited (chapter 4) both are therefore less ideal candidates for risk stratification.

We proposed a non-invasive alternative called short-term variability (STV) of the QT interval (STV_{QT}) that can be derived from a digital 2-minute 12 lead resting ECG. STV measures temporal dispersion by quantifying beat-to-beat changes in repolarization. In the canine chronic atrioventricular block (CAVB) model STV of the left monophasic action potential (STV_{LVMAP}) was found to be able to identify subjects at risk for drug-induced Torsade de Pointes arrhythmias (TdP) (chapter 3) [7]. In several small patient studies, STV_{QT} showed to be superior to QT interval prolongation not only in identifying long QT syndrome patients at risk for drug-induced TdP but also heart failure patients at risk for arrhythmic death (chapters 3 and 7)[8-12]. In chapter 6 we investigated the predictive value of STV_{QT} for the first time in a larger patient cohort at risk for ventricular arrhythmias included in the EUTrigTreat trial. We found that also STV_{QT} is associated with appropriate ICD shock and not with mortality. Unfortunately, we could only show a trend in the multivariate analysis because an insufficient number of patients were available for analysis. Aside from the relatively low event rate, this was mainly due to logistical reasons or low-quality ECG's. Another reason was the exclusion of patients with atrial fibrillation and patients with a CRT device. We demonstrated that these patient groups had different distributions of STV_{QT} compared to patients in sinus rhythm.

Beat-to-beat variability of repolarization derived from the ECG; STV_{QT}

To be able to accurately measure beat-to-beat changes in repolarization we think high-quality ECG's are necessary to prevent interference with our measurement. Therefore, we used a high-resolution ECG (1000-1200Hz) and analyzed this in a semi-automatic matter with the fiducial segment averaging method. This method allows us to align all waveforms neatly around every fiducial point separately and is described in more detail in chapter 7. One of the great advantages is that the end of the T-wave, that can be difficult to determine, only has to be determined once for all beats in the recording, which diminishes measurement error. A disadvantage of STV is that the absolute value can depend on method of analysis. Sample frequency has an influence on the precision of alignment. A lower sample frequency causes a higher baseline value as no cancellation of measurement error occurs. This does not hamper the value of STV as proarrhythmic marker but it does make it difficult to compare studies performed and complicates the determination of a cut-off value based on literature.

Future perspectives

As mentioned in the introduction, long follow-up is a prerequisite for trials investigating risk markers for ventricular arrhythmias. Therefore longer follow-up of the EUTrigTreat is currently achieved. This will enable us to reach a higher number of events and confirm the value of STV_{QT} in predicting appropriate ICD shocks. Aside from that, we take part in another large European consortium that is conducting a multicenter clinical study including around 2400 patients with a primary prophylactic indication for ICD implantation. Next to digital 12 lead ECG's, high-resolution holter recordings will be collected that enable a more elaborate analysis of various non-invasive electrophysiological markers including STV_{QT}. To be able to process so much ECG and holter data it will be lucrative to automate further and subsequently validate the software used in the EUTrigTreat study. This would also be beneficial for reproducibility.

To improve risk stratification we have to gain better insights into the subpopulations that experience less benefit. Since the underlying mechanism of arrhythmias can differ between men and women, it could be that proarrhythmic markers perform better or worse depending on gender. Due to the extension of follow-up of the EUTrigTreat trial and in the EU CERT ICD study this interesting topic will be investigated and predictive value of different electrophysiological tests between gender can be compared.

Part 2. Monitoring of arrhythmic risk

Finding a curative or preventive therapy for ventricular arrhythmias became less imperative by the widening of indications for ICD therapy. Nevertheless, patients with repetitive ventricular arrhythmias will have benefit from preventive pharmacological agents and/or strategies such as ablation or pacing at higher rates. To learn how temporary accelerated pacing (TAP) is effective in averting TdP and how to integrate this into clinical practice, the canine CAVB model was deployed. In this model not only inducibility but also reproducibility of ectopy and subsequent TdP arrhythmias is high [13]. We showed that TAP is not only effective in preventing TdP but also ectopy, which is accompanied by a decrease in temporal and spatial dispersion. The antiarrhythmic effect of pacing at higher rates can be explained by multiple mechanisms; reverse rate dependency, suppressive effect on early after depolarizations (EADs) by augmentation of I_{Kr} and hastening of calcium-induced inactivation of L-type calcium current and a decrease in spatial dispersion. Spatial dispersion is supposed to at least facilitate EADs to propagate and to become an ectopic beat. In Figure 1 a schematic overview is given of the cascade leading to TdP.

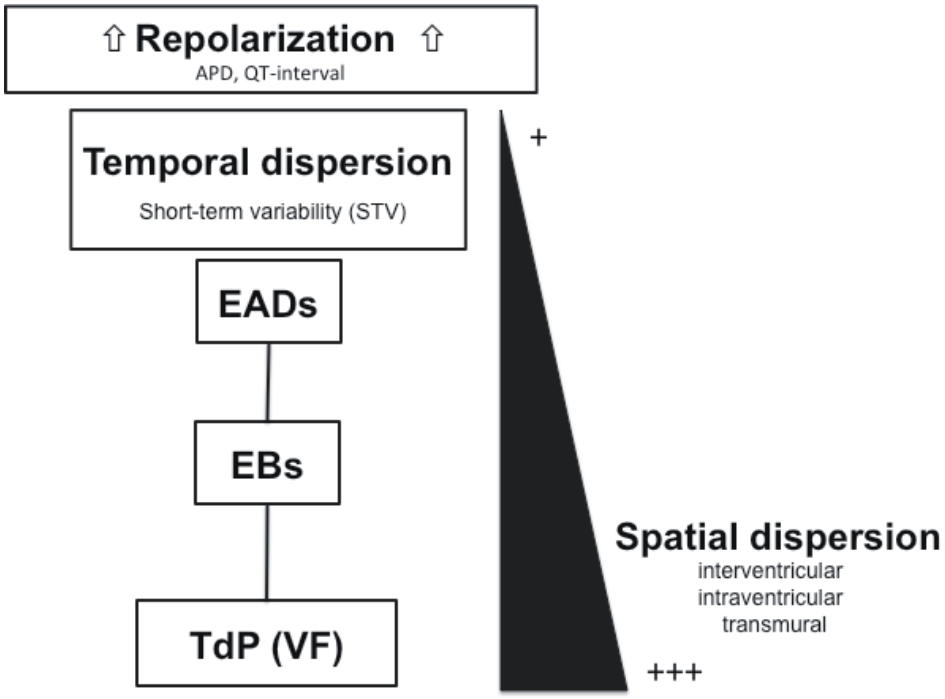

Figure 1. Cascade leading to torsade de pointes arrhythmia (TdP). APD = action potential duration; EAD = early after depolarization; EB = ectopic beat; VF = ventricular fibrillation.

As you can appreciate repolarization prolongation is followed by an increase in temporal dispersion (STV) and the occurrence of early after depolarizations, subsequent ectopic beats and eventually TdP. This is facilitated by an increase in spatial dispersion, creating a substrate in which TdP is more likely to occur. In our study we measured interventricular dispersion by determining the difference between LV and RV MAPD. Intraventricular dispersion was assessed by the assessment of vertical dispersion with the duo-decapolar catheter as described by Dunnink et al (chapter 7, thesis Dunnink). Even though the resolution reached with this catheter is limited (compared to the more invasive and complicated needle mapping), we demonstrated an initial increase of intraventricular spatial dispersion upon challenge with the I_{Kr} blocker dofetilide and a subsequent decrease upon antiarrhythmic TAP.

Various studies showed that sudden rate changes (pauses but also premature stimuli) can exaggerate the substrate by a steep increase in dispersion[14-16]. Therefore, we gradually increased pacing rate from 60 to 100bpm. Preventing 'pauses', with for example a rate-smoothing algorithm as suggested by Viskin et al. [17,18], can be very effective but will not prevent TdP if the substrate is severe enough. Furthermore, the algorithm is

initiated based on ectopy; this is quite late in the cascade leading to TdP. In the studies described in chapters 8 and 9, it is concluded that TAP could be guided by an increase in temporal dispersion (STV). This increase occurs early in the cascade leading to TdP and allows us to interfere on time, before the occurrence of ectopic beats that in their turn can increase spatial dispersion and exaggerate the substrate (Figure 1). To demonstrate clinical feasibility of this marker we showed that the right ventricular (RV) EGM could be used to measure STV of the RV activation recovery interval (STV_{RVARI}). STV_{RVARI} increases upon challenge with proarrhythmic drugs in anesthetized and awake conditions.

Future perspectives

Assessment of in depth (transmural) spatial dispersion with needle mapping before and during TAP could provide further insides in the role of spatial dispersion and the antiarrhythmic effect of TAP. Nevertheless, needle mapping does also have several disadvantages. Aside from being an extensive procedure, it is invasive, which can lead to alterations in the substrate (less susceptible) and it prevents us from being able to do serial experiments (since it is a terminal experiment).

STV_{RVARI} derived from the RV EGM can be integrated in devices to monitor arrhythmic risk 24/7. The measured increase in STV_{RVARI} can subsequently initiate preventive therapies, such as TAP, when necessary. To realize 24/7 monitoring, fully automatic analysis of the EGM will have to be enabled by further optimization of the software that was developed in cooperation with Medtronic. To confirm these experimental results in patients, analysis of STV from (pre arrhythmia) intracardiac EGMs exported from patients' ICD and/or pacemaker has to be performed.

Part 3. The electrical substrate in patients eligible for CRT.

In the multicenter prospective Markers and Response to CRT (MARC) study the goal was to find (a combination of) clinical, electrical, structural and blood markers that can optimize the response rate of CRT. As ECG core lab, we not only included conventional ECG markers but also enabled our software to derive the vectorcardiogram (VCG) from the 12 lead ECG. As already proposed by Van Deursen et al. [19], a larger QRS_{AREA} is an important predictor of CRT response. QRS_{AREA} showed to be a stronger predictor than QRS duration and morphology. This may be explained by the fact that it shows the extent of unopposed electrical forces generated within the heart during ventricular depolarization representing the direction as well as the amount of delay of electrical activation. Together with the other independent predictors of response, young age, longer interventricular mechanical delay and presence of apical rocking, the CAVIAR score was constructed. This clinically applicable score can result in a score from -2 to 9 and provides an individual prediction of response. The main strength of this study is the fact that the outcome (structural remodeling based on a reduction in indexed left ventricular end systolic volume (LVEVSi)) was analyzed

on a continuous scale. Other strengths are the many markers assessed to construct the score and the high quality of data handling (expert core labs, professional data management (Medtronic)) that resulted in an excellent follow up with paired echocardiographic data in 89% of the patients.

Left bundle branch block (LBBB) was a significant predictor of CRT benefit in the univariate analysis but disappeared in the multivariate analysis. This can be explained by the addition of the correlated but superior vectorcardiographic QRS_{AREA}. LBBB is required to have a class I indication for CRT [20-25] but adherence to the guidelines is hampered by the existence of multiple LBBB definitions, constructed of criteria that are open for multiple interpretations [20,22,23,26-28]. We show that more objective, vectorcardiographic markers could be equal or superior to LBBB in reflecting leftward ventricular conduction delay and therefore, identifying a favorable substrate for response to CRT. This was further elucidated in a subanalysis of the MARC study.

It was shown that the proportion of patients having an LBBB depends greatly on the definition used and that the various definitions have different relations with CRT response. Several studies have suggested alternatives for assessing leftward conduction delay but often have the disadvantage to be, invasive, complicated and/or only possible during or after implantation procedure. We show that a larger QRS vector amplitude in the transversal plane ($QRS_{VA\text{-}Tpl}$), an objective marker of leftward conduction delay derived from the VCG, predicts CRT response at least as good as the best performing LBBB definition (as described in the European Society Guidelines 2013). $QRS_{VA\text{-}Tpl}$ performs slightly better than QRS_{AREA}, which is probably explained by the fact it also takes unopposed conduction in the right ventricle into account. Conduction delay in the right ventricle, related to non-response, results in a smaller $QRS_{VA\text{-}Tpl}$.

Future perspectives

The markers that construct the CAVIAR score are all easily clinically assessed. Although not yet commonly available in clinical practice, the VCG can be derived from commercially available ECG machines. Allowing markers such as QRS_{AREA} and $QRS_{VA\text{-}Tpl}$ to be provided without additional recordings and/or leads. Like every risk prediction score, the CAVIAR score has to be validated in another cohort of patients eligible for CRT implantation. To confirm that $QRS_{VA\text{-}Tpl}$ can be used as an objective alternative for LBBB and to determine the optimal cut-off value, retrospective analysis of the large trials that demonstrated the importance of leftward conduction delay could be performed. The hypothesis that the additional value of $QRS_{VA\text{-}Tpl}$ compared to QRS_{AREA} in predicting CRT response is explained by unopposed conduction in the RV has to be further investigated. This could be done in an experimental setting but also with information from the CRT device implanted in the patients. For example, Q-RV sense can be derived to quantify amount of RV conduction delay.

Conclusion

Although cardiac implantable electronic devices have caused improvement not only in survival but also in quality of life in patients with heart failure, we have to remain critical towards the evidence. Effort should be made to improve risk stratification to identify those patients that do benefit. This way, guidelines could provide more patient-tailored recommendations. In this thesis, we show that the ECG is an easily applicable and non-invasive tool that can be used for this purpose. Beat-to-beat variability of repolarization is a promising parameter that can be used to improve risk stratification for ventricular arrhythmias and therefore the benefit of ICDs. The vectorcardiogram derived from the ECG gives a more objective and accurate impression of the electrical substrate favorable to CRT response. Furthermore, technological advancements will enable in-device monitoring of these electrocardiographic markers to extend the benefit of cardiac implantable electronic devices.

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APPENDIX

ENGLISH SUMMARY
NEDERLANDSE SAMENVATTING
DANKWOORD/ACKNOWLEDGEMENTS
CURRICULUM VITAE
LIST OF PUBLICATIONS

ENGLISH SUMMARY

Summary

Heart failure is a prevalent and severe disease in which progressive decrease of pump function of the heart occurs. The lifetime risk for developing heart failure has been reported to range from 20-33%. It renders a poor prognosis; only half of the patients are still alive 5 years after first symptoms occur. Heart failure can be due to myocardial infarction but also has non-ischemic causes, genetic or acquired. A substantial number of heart failure patients die suddenly from ventricular arrhythmias. In the last decades, new, more invasive, treatment modalities for patients with heart failure have been developed.

Part 1. Patient selection for ICD therapy

The implantable cardioverter defibrillator (ICD) is a device that can monitor the rhythm of the heart. When a life-threatening ventricular arrhythmia occurs (chaotic or very fast rhythm that causes failure of the heart to circulate blood) an ICD can interfere by providing an electric shock that terminates the arrhythmia and restores normal sinus rhythm. The first ICD in the Netherlands was implanted at the University Medical Center Utrecht in 1984. At first only patients that survived a life-threatening arrhythmia received an ICD (secondary indication). Because the number of patients that survives a cardiac arrest is limited, efforts were made to identify patients that were at risk for ventricular arrhythmias (but did not experience them yet) and could therefore benefit of ICD implantation (primary indication). Several large clinical trials were constructed to demonstrate benefit of ICD implantation in this population. They chose to select patients at higher risk for ventricular arrhythmias based on a decreased systolic pump function of the heart (left ventricular ejection fraction (LVEF) < 35%) i.e patients with systolic heart failure. By this approach, the number of patients destined to receive an ICD is high, but with an acceptable number needed to treat. Nevertheless analyses within this patient population show that benefit can differ greatly between subgroups. Patients with non-ischemic etiology of heart failure and women show less benefit and doubts are rising if ICD therapy should be indicated for these patients. Aside from the cost/effectiveness ratio ICD implantation is an invasive therapy with a substantial complication risk. Furthermore inappropriate shocks can lead to discomfort, anxiety and even depression.

On the other hand we need to be aware that selection based on decreased LVEF does not identify all patients at risk for ventricular arrhythmias. In fact, the absolute number of sudden cardiac deaths is higher in the general population compared to the relatively small group of patients with decreased LVEF. Often these are people with undiagnosed coronary atherosclerosis.

Taken abovementioned in to account, improving risk stratification and early identification of patients at risk for ventricular arrhythmias is necessary to improve patient selection for ICD therapy.

In chapter 1, the introduction of this thesis, the need for improvement of risk stratification is further elaborated. Chapter 2 shows implementation of the ICD guidelines, based on the large trials, in clinical practice and addresses the fact that certain subpopulations, such as patients with non-ischemic etiology of heart failure and women, benefit less than others. In chapters 3, 4, 5 and 6 electrocardiographic parameters are discussed that can be used to improve risk stratification in these subgroups. Beat-to-beat variability of repolarization (repolarization reflects the relaxation phase of the heart cycle) is a promising parameter that reflects a higher risk for ventricular arrhythmias. Quantified as short-term variability (STV)) it already showed its value in extensive experimental research in the canine chronic atrioventricular block (CAVB) model (chapter 3). This animal model is made sensitive for Torsade de Pointes (TdP) arrhythmias (a repolarization dependent ventricular arrhythmia) by creating an atrioventricular block, which leads to bradycardia (slow heart rhythm) and eventually, compensated hypertrophy (thickened heart muscle). Contractile, structural and electrical remodeling (adaptations of the heart tissue) creates a substrate sensitive for TdP arrhythmias. When challenged with a repolarization prolonging drug under anesthesia, 70% of the subjects show multiple ectopic beats followed by repetitive TdP arrhythmias. STV increases upon the challenge with a repolarization prolonging drug, especially in the subjects that show subsequent TdP arrhythmias. In the large European multicenter EUTrigTreat clinical study (chapter 5) various electrocardiographic (microvolt T-wave alternans and programmed electrophysiological stimulation) and clinical parameters (kidney function. LVEF and secondary indication) combined were predictive of appropriate shock but not mortality. This is an important property of a risk stratifier because it can select patients specifically at risk for ventricular arrhythmias that will therefore benefit from ICD implantation and will not die from other causes in the foreseeable future. In a substudy of this trial (chapter 6) we investigated short-term variability of the QT-interval (a measure for repolarization duration) for the first time in a large patient cohort. A larger variability was associated with a higher risk of appropriate ICD shock in this population. To accurately measure this parameter we made use of a high-quality digital electrocardiogram and used a special method (fiducial segment averaging) to determine the beat-to-beat changes in QT-interval (chapter 7).

Part 2. Monitoring of arrhythmic risk.

Having an ICD is meant as a safety net to prevent sudden cardiac death. Patients that experience inappropriate but also appropriate ICD shocks can experience much discomfort from this. Therefore additional pharmacological and electrophysiological therapies to prevent ventricular arrhythmias are still important. With the evolving technological possibilities in-device automated analysis of the electrogram derived from the right ventricular lead of the ICD and/or pacemaker could aid in monitoring of for example arrhythmic risk. This could be used to interfere with anti-arrhythmic therapies before ventricular arrhythmias

actually occur and will prevent the need for an ICD shock. In **chapter 8** we show in the canine CAVB model that we can avert the occurrence of torsade de pointes arrhythmias by initiating pacing at higher rates (temporary accelerated pacing (TAP)) based on an increase in beat-to-beat variability of repolarization. In **chapter 9** we demonstrate that the increase in beat-to-beat variations of repolarization (reflecting an increased risk for ventricular arrhythmias) can be detected and monitored on the intracardiac electrogram derived from the right ventricular lead in anesthetized and awake conditions.

Part 3. The electrical substrate in patients eligible for CRT.

Another promising therapy for patients with heart failure is cardiac resynchronization therapy (CRT). In patients with heart failure disturbances in the conduction pattern are frequently observed which leads to a slowed and often dyssynchronous activation of the left en right ventricle that causes a suboptimal proportion of blood that can be ejected by the heart. By placing not only a lead in the right ventricle (as with a normal pacemaker or ICD implantation) but also a lead around the heart on the left ventricle, the activation pattern can be synchronized by stimulating the heart from both sides. This improves pump function and induces reverse structural remodeling observed by echocardiography (decrease of left ventricular end diastolic volumes (LVEDV). The United States Food and Drug Administration (FDA) approved the first device in August 2001. Since then various studies have been performed showing benefit of CRT on mortality, hospital admission and structural reverse remodeling in 40-60 % of the patients. But also for this therapy we have to be critical towards the evidence since a significant number of patients do not respond to CRT. In the Dutch multicenter Markers And Response to CRT (MARC) study (**chapter 10**) we prospectively investigated the predictive value of various clinical, electrical, structural and blood biomarkers to predict reverse remodeling upon CRT implantation. As ECG core lab we did not only measure conventional ECG parameters but also derived vectorcardiographic markers from the ECG. The vectorcardiogram gives a more 3D impression of the (altered) electrical activation of the heart. The vectorcardiographic QRS area showed to have the highest predictive value for response. In combination with clinical (age) and structural (intraventricular mechanical delay and apical rocking) biomarkers a clinical response score was developed; the CAVIAR score. This score can be used for individual risk prediction. Its use will have to be validated in another cohort of CRT recipients.
In the landmark trials on CRT selection of patients was mainly based on the severity of conduction delay (measured by QRS duration, duration of ventricular depolarization on the ECG). Subanalysis of these trials showed that success was different among QRS morphology (pattern of conduction delay); a higher benefit was seen in patients with conduction disturbances in the left ventricle as defined by a left bundle branch block (LBBB) on the ECG. In our study this was not confirmed (LBBB was significant in the univariate regression analysis, but not in the multivariate). This can be explained by the addition of

vectorcardiographic parameters that can quantify the electrical substrate more accurately and objectively. In a subanalysis of the MARC study (**chapter 11**) we therefore propose to use a vectorcardiographic alternative for patient selection for CRT implantation; the QRS vector amplitude in the transversal plane. This is a simple and more objective measure of dominant left ventricular conduction delay than LBBB. Moreover, our analysis shows that having a LBBB depends greatly on which definition of LBBB is used, the criteria used to make up the definitions are open for multiple interpretations and the various definitions have different relations with response. This is an important issue since having a LBBB is a prerequisite for a class I indication for CRT implantation.

Conclusion

Cardiac implantable electronic devices can improve prognosis and quality of life of patients with heart failure. Nevertheless patient selection for both ICD as CRT implantation remains a challenge. The ECG is an easy non-invasive tool that can aid patient selection and thereby enhance the benefit/complication ratio. Furthermore electrocardiographic parameters can contribute to innovative concepts for in-device monitoring.

NEDERLANDSE SAMENVATTING

Nederlandse samenvatting

Hartfalen is een veelvoorkomende en ernstige ziekte waarbij geleidelijke afname van de pompfunctie van het hart optreedt. Het levenslange risico voor het ontwikkelen van hartfalen varieert van 20-33%. Het heeft een slechte prognose; slechts de helft van de patiënten is nog in leven 5 jaar nadat de eerste symptomen optreden. Hartfalen kan worden veroorzaakt door myocardinfarct, maar heeft ook niet-ischemische oorzaken, genetische of verworven. Een aanzienlijk aantal patiënten met hartfalen sterft plotseling door een ritmestoornis van de kamers van het hart. In de afgelopen decennia zijn er nieuwe, meer invasieve, behandelingsmogelijkheden voor patiënten met hartfalen ontwikkeld.

Deel 1. Patiëntselectie voor ICD-therapie

De implanteerbare cardioverter defibrillator (ICD) is een apparaat dat het ritme van het hart kan monitoren. Wanneer een levensbedreigende kamerritmestoornis optreedt (chaotische of zeer snel ritme dat het onmogelijk maakt voor het hart om het bloed rond te pompen) kan een ICD dit detecteren en ingrijpen door middel van een elektrische schok die de aritmie stopt en het normale ritme hersteld. De eerste ICD in Nederland werd geïmplanteerd in het Universitair Medisch Centrum Utrecht in 1984. In eerste instantie kregen alleen patiënten die een levensbedreigende kamerritmestoornis overleefden een ICD (secundaire indicatie). Omdat het aantal patiënten dat een levensbedreigende kamerritmestoornis (ook wel hartstilstand genoemd) overleeft beperkt is, werden er al snel pogingen gedaan om patiënten die een verhoogd risico daarop hebben te identificeren om zo preventief een ICD te kunnen implanteren (primaire indicatie). Verschillende grote klinische studies werden opgezet om het profijt van ICD implantatie in deze patiëntengroep aan te tonen. Er werd gekozen patiënten met een hoger risico op kamerritmestoornissen te selecteren op basis van een verminderde systolische pompfunctie van het hart (linker ventrikel ejectiefractie (LVEF) <35%). Door deze benadering komt een groot aantal patiënten in aanmerking voor een ICD, met een aanvaardbaar aantal patiënten dat behandeld moet worden om 1 leven te redden (number needed to treat). Niettemin laten analyses zien dat binnen deze patiëntengroep het profijt van ICD implantatie sterk kan verschillen. Patiënten met niet-ischemische etiologie van het hartfalen en vrouwen lijken minder profijt van ICD implantatie te hebben en de discussie neemt daarom toe over de indicatie van ICD-therapie voor deze patiënten. Afgezien van de kosten/baten verhouding is ICD implantatie een invasieve therapie met een aanzienlijk complicatie risico. Bovendien kunnen (ongewenste) ICD schokken leiden tot ongemak, angst en zelfs depressie. Aan de andere kant moeten we ervan bewust zijn dat selectie op basis van verminderde LVEF niet alle patiënten identificeert met een verhoogd risico op kamerritmestoornissen. In feite is het absolute aantal plotselinge hartdood in de totale populatie hoger dan in de relatief kleinere

groep patiënten met hartfalen. Vaak zijn dit mensen met nog niet gediagnosticeerde vaatverkalking in de kransslagaderen die het hart van bloed voorzien.
Concluderend; het is noodzakelijk de patiëntselectie voor ICD implantatie te verbeteren door betere risicostratificatie en daarnaast vroegtijdige identificatie van patiënten met een verhoogd risico op kamerritmestoornissen.

In **hoofdstuk 1**, de introductie van dit proefschrift, wordt de behoefte aan verbetering van risicostratificatie verder uitgewerkt. **Hoofdstuk 2** toont de uitvoering van de richtlijnen voor ICD implantatie in de klinische praktijk en richt zich op het feit dat bepaalde subpopulaties, zoals patiënten met niet-ischemische etiologie van het hartfalen en vrouwen minder profiteren van ICD therapie. In de **hoofdstukken 3, 4, 5 en 6** worden electrocardiografische parameters (parameters af te leiden van het hartfilmpje) besproken die gebruikt kunnen worden om de risicostratificatie in deze subgroepen te verbeteren. Slag op slag variatie van de repolarisatieduur (repolarisatie reflecteert de ontspannings fase van de hartcyclus) is een veelbelovende parameter dat een verhoogd risico op kamerritmestoornissen reflecteert. Gekwantificeerd als short-term variabiliteit (STV) is de waarde van deze parameter al uitgebreid aangetoond in experimenteel onderzoek in het chronische atrioventriculair blok (CAVB) hond model (**hoofdstuk 3**). Dit diermodel is gevoelig gemaakt Torsade de Pointes (TdP) aritmieën (een repolarisatie afhankelijke kammerritmestoornis) door het maken van een atrioventriculair blok, dit leidt tot bradycardie (langzame hartslag) en uiteindelijk gecompenseerde hypertrofie (verdikte hartspier). De contractiele, structurele en elektrische remodeling (aanpassingen in het hart) die daardoor optreden creëren een substraat gevoelig voor TdP artimieen. Bij provocatie met een repolarisatie verlengend middel onder narcose vertoont 70% van de honden meervoudige ectopische slagen gevolgd door herhaaldelijke TdP artimieen. STV neemt toe na provocatie met een repolarisatie verlengend geneesmiddel, met name in de honden die de herhaaldelijke TdP artimieen vertonen. In de grote Europese multicenter klinische studie, EUTrigTreat (**hoofdstuk 5**), zijn verschillende elektrocardiografische (microvolt T-wave alternans en geprogrammeerde elektrofysiologische stimulatie) en klinische parameters (nierfunctie, LVEF en secundaire indicatie) gecombineerd. Samen waren ze voorspellend voor het optreden van een ICD shock en niet voor het optreden van de dood in het algemeen. Dit is een belangrijke eigenschap voor een risicostratificator omdat dit specifiek patiënten selecteert met een hoog risico op kamerritmestoornissen die daarom baat zullen hebben van ICD implantatie maar (voorlopig) niet dood gaan door een andere oorzaak. In een substudie van deze EUTrigTreat studie (**hoofdstuk 6**) onderzochten we de waarde van STV van het QT-interval (maat voor repolarisatieduur) voor de eerste keer in een groot patiënten cohort. Een grotere variabiliteit (hoge STV) werd geassocieerd met een hoger risico op een ICD schok in deze populatie. Om deze parameter nauwkeurig te kunnen meten hebben we gebruik gemaakt van een hoge kwaliteit digitaal elektrocardiogram en een speciale methode

om de variatie van slag op slag goed te kunnen meten. Deze methode, fiducial segment averaging, is beschreven in **hoofdstuk 7**.

Deel 2. Monitoring van pro-aritmische risico

Het hebben van een ICD is bedoeld als vangnet om plotselinge hartdood te voorkomen. Patiënten die ICD schokken ervaren, terecht en onterecht, kunnen hiervan veel hinder ondervinden. Daarom zijn aanvullende farmacologische en elektrofysiologische therapieën om kamerritmestoornissen te voorkomen nog steeds erg belangrijk. Met de veranderende technologische mogelijkheden kan in-device monitoring door geautomatiseerde analyse van het elektrogram, afgeleid van de draad van het device (ICD en / of pacemaker) die zich in de rechter kamer van het hart bevindt, helpen bij het monitoren van bijvoorbeeld het pro-aritmische risico. Dit kan gebruikt worden om in te grijpen met antiaritmische therapie voordat de kamerritmestoornis daadwerkelijk optreedt. Zo zal een noodzakelijke ICD schok voorkomen kunnen worden. In **hoofdstuk 8** laten we zien dat het optreden van Torsade de Pointes aritmieen in het CAVB hond model voorkomen kan worden door tijdelijk te pacen op een hogere hartfrequentie (temporary accelerated pacing (TAP)) geïnitieerd op basis van een toename in slag op slag variatie van de repolarisatie (STV). In **hoofdstuk 9** tonen we in het CAVB hond model aan dat deze toename van slag op slag variatie van repolarisatie (dat een verhoogd risico op kamerritmestoornissen reflecteert) kan worden gedetecteerd en continue gemonitord door de elektrode van de draad van een ICD of pacemaker in de rechter kamer van het hart, onder narcose maar ook wakker.

Deel 3. Het elektrische substraat in patienten die in aanmerking komen voor CRT

Een andere veelbelovende therapie voor patiënten met hartfalen is cardiale resynchronisatie therapie (CRT). Bij patiënten met hartfalen worden er vaak ook stoornissen in de elektrische geleiding geconstateerd wat leidt tot een vertraagde en vaak niet gelijktijdige activatie van de linker en rechter hartkamer waardoor er een niet optimale hoeveelheid bloed door het hart uitgepompt kan worden. Door niet alleen een draad met electrode in het rechterventrikel te plaatsen (zoals bij een normale pacemaker of ICD) maar ook een draad met electrode rond de linker hartkamer te implanteren kan het activeringspatroon gesynchroniseerd door het stimuleren van het hart van beide kanten. Dit verbetert de pompfunctie en induceert gunstige aanpassingen van het hartweefsel (omgekeerde structurele remodeling) geobserveerd door echocardiografie (afname van de linker ventrikel eind diastolische volumes (LVEDV)). De Amerikaanse Food and Drug Administration (FDA) keurde het eerste CRT apparaat goed in augustus 2001. Sindsdien zijn diverse onderzoeken uitgevoerd die het profijt bewijzen van CRT op mortaliteit, ziekenhuisopname en omgekeerde structurele remodelering in 40-60% van de patiënten. Maar ook voor deze therapie geldt dat wij kritisch moeten blijven tegenover het bewijs omdat er ook een aanzienlijk aantal patiënten is dat niet reageert

op CRT. In de Nederlandse multicenter Markers and Response to CRT (MARC) studie (**hoofdstuk 10**) hebben we prospectief onderzoek gedaan naar de voorspellende waarde van verschillende klinische, elektrische, structurele en bloed biomarkers voor omgekeerde structurele remodelering na CRT implantatie. Als electrocardiogram core-lab hebben we niet alleen conventionele ECG parameters gemeten, maar ook vectorcardiografische markers afgeleid van het ECG. Het vectorcardiogram geeft een meer 3D beeld van de (gewijzigde) elektrische activering van het hart. De vectorcardiografische marker QRSarea bleek de hoogste voorspellende waarde voor CRT respons te hebben. In combinatie met de klinische (leeftijd) en structurele (intraventriculaire mechanische vertraging en apicale rocking) biomarkers werd een klinische respons score ontwikkeld; de CAVIAR score. Deze score kan een patiënt specifieke inschatting maken van de kans op respons. Het gebruik van deze score zal nog moet worden gevalideerd in een ander cohort van patiënten die CRT implantatie hebben ondergaan.
De grote trials die onderzoek hebben gedaan naar selectie van patiënten voor CRT therapie hebben zich vooral gebaseerd op de ernst van de geleidingsvertraging (QRS-duur, duur van activatie van de hartkamers op het ECG). Uit subanalyses van deze trials is gebleken dat het succes van CRT therapie ook afhangt van de QRS morfologie (patroon van geleiding vertraging); patiënten met geleidingsstoornissen in de linker ventrikel zoals gedefinieerd door een linker bundeltakblok (LBTB) op het ECG leken meer profijt te hebben van CRT therapie in deze analyses. In onze studie werd dit echter niet bevestigd (LBTB was significant in de univariate regressie analyse, maar niet in het multivariate). Dit kan verklaard worden door de toevoeging van vectorcardiografische parameters aan de regressie analyse die het elektrische substraat nauwkeuriger en objectiever kwantificeren. In een subanalyse van de MARC studie (**hoofdstuk 11**) stellen we daarom een vectorcardiografische parameter voor om te gebruiken voor patiëntselectie voor CRT; QRS vector amplitude in het transversale vlak. Dit is bovendien een simpelere en meer objectievere maat van dominant naar links gerichte geleidingsvertraging dan het LBTB. Uit onze analyse blijkt dat het hebben van een LBTB sterk afhangt van de definitie die gebruikt wordt, bovendien zijn de criteria voor verschillende interpretaties vatbaar en zijn er verschillen in relatie met CRT response. Dit is een belangrijk probleem voor patiëntselectie voor CRT implantatie omdat het LBTB een onderdeel van de indicatie is volgens de richtlijnen.

Conclusie

Cardiale implanteerbare elektronische apparaten kunnen de prognose en de kwaliteit van leven van patiënten met hartfalen verbeteren. De selectie van patiënten voor zowel ICD als CRT implantatie blijft echter een uitdaging. Het ECG is een eenvoudig niet-invasief instrument dat kan helpen de juiste patiënten te selecteren en daarmee de kosten/baten verhouding te verbeteren. Bovendien kunnen de onderzochte elektrocardiografische parameters bijdragen aan innovatieve concepten voor in-device monitoring.

DANKWOORD/ACKNOWLEDGEMENTS

Dankwoord/acknowledgements

Tot slot, wil ik graag iedereen bedanken die heeft bijgedragen tot het tot stand komen van dit proefschrift. Bedanken voor het advies, de hulp, de steun, het vertrouwen en al wat niet meer. Hieronder een aantal personen in het bijzonder.

Allereerst wil ik graag **alle patiënten** die hebben bijgedragen aan dit onderzoek hartelijk bedanken voor hun medewerking. Ik vind het bewonderenswaardig dat je dat voor een ander doet. Bedankt!

Ik wil graag mijn promotor **Marc** Vos bedanken. Voor het vertrouwen in mij, je dagelijkse begeleiding maar vooral ook de eigen verantwoordelijkheid die je me hebt gegeven. Je hebt me niet alleen begeleid in het maken van dit proefschrift maar hebt me ook kennis laten maken met echt alle facetten van het wetenschappelijk onderzoek. Geheel op jouw manier, waarbij af en toe bier en bratwurst niet mochten ontbreken.

Mijn andere promotor, **Pieter** Doevendans, wil ik graag bedanken voor de mogelijkheid van het uitvoeren van de klinische studies bij de cardiologie in het UMCU, de scherpe aanvullingen in de voortgangsgesprekken en beknopt doch altijd bruikbaar advies. Daarnaast hebben we afgelopen jaren ook op sportief vlak samengewerkt. De tochten naar de verschillende ESC congressen waren pittig, maar prachtig! Ik hoop dat er nog velen volgen.

Beste **Mathias** Meine, bedankt voor je begeleiding, met het onderzoek maar ook met de eerste stappen in de kliniek. Ik heb erg veel gehad aan je kennis en kunde op het gebied van ICD en CRT. Naast de vaste bespreking op donderdag ochtend kon ik altijd langslopen voor vragen, je ben een soort wandelende richtlijn die altijd up to date is. Dit was je ook altijd over het reilen en zeilen binnen de arts onderzoekers groep, een waardevolle informatiebron. Je bent een voorbeeld en hoop dat ik in de kliniek nog veel van je mag leren. Je sportieve prestaties zijn moeilijk te overtreffen, maar ook daarvoor blijf ik m'n best doen.

Dear **Markus** Zabel, it was a great opportunity to be able to participate in the large ICD trials that you coordinated. You always gave me the opportunity to discuss issues with you personally and I enjoyed the visits to Gottingen. It was a pleasure working with you.

Beste **Anton** Tuinenburg, hartelijk dank voor je ontzettend harde werk voor de EU TrigTreat studie. Die maandagochtenden 7.00uur waren wel vroeg hè.. Daarnaast wil ik je ook bedanken voor je kennis, je hartelijkheid en steun tijdens de rest van mijn promotie en eerste periode in de kliniek. Ik hoop nog veel van je te kunnen leren de komende jaren. En ik hoop je over een aantal jaar te kunnen raadplegen bij de aanschaf van mijn nieuwe auto..

Beste **Henk** Ritsema van Eck, met enige regelmaat en met veel plezier heb ik tijdens mijn promotietijd de treinreizen naar Rotterdam ondernomen om een dag lang met jou te verdiepen in de wondere wereld van de computerized electrocardiology, de T-top en de U golf. Al heb ik het programma bij vlagen vervloekt, zonder deze precieze methode met alle extra aanpassingen door jou, waren de klinische ECG analyses niet mogelijk geweest. Dank daarvoor en hartelijk dank voor je begeleiding en bijzondere verhalen.

Harold van Rijen, je enthousiasme (voor de elektrofysiologie, onderwijs, voorliefde voor Apple, etc) is aanstekelijk. Het was een hele eer om het ECG college van je te mogen overnemen, de eerste stap naar het voltooien van mijn BKO. Bedankt voor het voorzitten van de beoordelingscommissie van dit proefschrift, ik waardeer je betrokkenheid enorm. Ik hoop dat onze wegen in de toekomst nog vaker zullen kruisen.

Beste **Jet**, bedankt voor je buitengewone inzet en deskundigheid voor de dierexperimenten, je analyses en je gezelligheid al die dagen op de OK. Ik heb ontzettend veel bewondering voor de manier waarop je met de honden omgaat. Ik hoop dat je nog lang plezier in je werk hebt en wens je veel geluk.

Beste **Albert**, het was prettig om af en toe te sparren met iemand die hetzelfde onderwerp bestudeerd. Naast de uitgebreide gesprekken over dispersie of de methodiek van STV meten, heb ik ook genoten van de meer diepzinnige gesprekken over hele andere thema's, meestal onder het genot van een biertje op de Duitse uitstapjes. Wat goed dat je aangenomen bent voor de opleiding, succes!

Ik wil ook graag alle anderen van de medische fysiologie bedanken. Wat heerst daar toch een fijne sfeer! Bedankt voor de altijd beschikbare hulp, leerzame praatjes, de nieuwjaarslunches, de enerverende labstapdagen en ga zo maar door. Allereerst de (oud) stafleden; **Toon** (dank voor je interesse en steun, in het bijzonder in de laatste 2 jaren), **Marcel** (je hebt het fouten detecteren in artikelen tot een (leuke) sport verheven), **Marti**, **Martin**, **Maria**, en **Teun**.
En bedankt al mijn gezellige collega's; **Alex**, I know your dutch is good enough to read my thanks to you so; dank je Alex voor al je hulp bij de experimenten, analyses en (uiteindelijk maar 1) fietstochtje(s).. Beste **Thom**, bedankt voor je hulp, in het bijzonder je precisie en kritische blik. We vlogen het probleem niet altijd op dezelfde manier aan, maar dat maakte de oplossing vaak alleen maar beter. **Peter**, dank voor je adviezen en al het werk waarop ik door kon borduren. **David**, je hebt het stokje overgenomen en bent al goed op weg. Heel veel succes en bedankt. **Iris** (ja, onder de categorie medische fysiologie) heel erg bedankt voor het voortzetten van de analyses, het is fijn om er op te kunnen vertrouwen dat het vele gedane werk een mooi vervolg krijgt. Ik ben erg benieuwd naar het artikel en natuurlijk de rest van je proefschrift. Ik bewonder je keuze om je eigen weg

te volgen en wens je veel succes in de toekomst. **Sanne** en **Rianne** bedankt voor jullie hulp en adviezen voor onderwijstaken en jullie altijd luisterende oor. **Rosanne**, bedankt voor je adviezen, je verhalen over de paarden en altijd goede boekentips. En ook heel veel dank aan alle andere collega's die op verschillende wijze hebben bijgedragen tot dit proefschrift (SPSS opsturen, interessante discussies, wijntje drinken, pipetteren uitleggen, bloodsamples analyseren en vooral de ontzettend prettige werksfeer); **Vincent**, **Bastiaan**, **Magda**, **Elise**, **Bart**, **Helen**, **Leonie**, **Marien**, **Hanneke** en **Yuan**.

Lieve **Tonny**, door jou voelt het als thuiskomen bij de afdeling medische fysiologie. Je bent echt een ontzettend lief en bijzonder mens en ik wil je ontzettend bedanken voor al je hulp en steun die je me afgelopen jaren geboden hebt. Ik hoop dat er nog velen na mij mogen ervaren wat voor een top mens je bent!

Al is onze afdeling fysiek gescheiden door een (eindeloos afgelegde) loopafstand (in duur afhankelijk van de route en weersomstandigheden) heb ik mogen ervaren dat er een goede en nog steeds door ontwikkelende samenwerking is met de kliniek. Een belangrijke voorwaarde voor dit translationele proefschrift, waarvoor ik dankbaar ben aan alle personen die daaraan hebben bijgedragen.

Voor het uitvoeren van de klinische studies wil ik naast eerder genoemden ook graag alle andere stafleden en ondersteuning van de afdeling Cardiologie bedanken. In het bijzonder **Peter** Loh voor de adviezen voor het invasieve EU TrigTreat protocol en de steun op weg naar de kliniek. **Jeroen** van der Heijden voor het aandragen van patiënten voor de EU TrigTreat studie (en de uitleg van de basisprincipes van het ECG, de eerste dagen van mijn semi arts stage). **Maarten-Jan** Cramer voor je enthousiasme en betrokkenheid bij de MARC studie (en escorte naar het benzine station toen ik midden in de nacht met een lege tank stond) en **Hans** Kirkels, voor de mogelijkheid tussen mijn promotie door klinische ervaring op te doen en dit nu te mogen voorzetten in de opleiding.

Jetske, mijn MARC studiegenoot van het eerste uur, wat was het fijn om af en toe met je te spuien en gewoon gezellig te kletsen onder het genot van een kopje koffie, bier of wijntje. Wij waren natuurlijk niet compleet zonder **Han** de (kale) man..spitsvondig, doch niet maligne. Ik mis de mailwisselingen. Ook **Manon** kan natuurlijk niet ontbreken, dank, wat een werk heb je aan die EUTrigTreat gehad, maar uiteindelijk wel alles mooi op orde! **Will,** dank voor de hulp met het Prucka systeem. En **Tanja**, bedankt voor je inzet al die vroeg maandagochtenden.

Mijn collega's van de cardiologie wil ik graag bedanken voor al die leuke congressen, borrels, feestjes, ski uitjes en alle andere gezelligheid; **Manon**, **Willemien**, **Anneline**, **Judith**, **Geert** , **Ing Han**, **René**, **Frebus**, **Stefan**, **Jan Willem**, **Remco**, **Henneke**, **Mirjam**,

Thomas, **Gijs**, **Stefan**, **Freek**, **Marloes**, **Mariam**, **Mieke**, **Cas**, **Peter-Paul, Jelte** en **Cheyenne**. **Wouter**, **Geert** en in het bijzonder de dames, **Roos** (bedankt voor je heerlijk enthousiaste aanwezigheid, blijf jezelf, komt het helemaal goed!), **Anneke**, **Annemiek** en **Christel**; dank voor de sportieve afleiding, letterlijk door diepe dalen maar ook prachtige hoge bergen.

Lieve **Sabine**, dank voor je (werk, last minute aanpassingen en advies voor de) mooie cover (waar het dankwoord meest gelezen wordt is dit onderdeel toch het meest bekeken;)), ik ben er erg blij mee!

Mijn paranimf **Dien**, lieve swes, fijn dat ik altijd op je kan rekenen en voor al je hulp bij dit boekwerk, wat betreft psychische ondersteuning maar ook praktisch, zelfs vanaf de andere kant van de wereld! Vind het zo knap dat je gekozen hebt iets anders te gaan doen. Heb er volste vertrouwen in dat het goed gaat komen met jullie. Ik mag jou ook niet vergeten **Ralph**, bedankt voor je hulp, met name de inwijding in de regelgeving rondom komma's. **Eem** en **BJ**, ook jullie hulp ben ik niet vergeten (als er spelfouten zitten in hoofdstuk .. dan moet je bij hun zijn ;)). **Chiel** en **Es**, ook aan jullie dank, in het bijzonder voor die heerlijke borden nasi welke ik af en toe bij jullie mocht komen nuttigen als ik in de avond verplichtingen in Utrecht had (ja Ralph, dat was voor jou (nasi)tijd).
Paps en **mams**, allereerst natuurlijk dank dat ik (nog net) op de wereld gezet ben, voor de vrijheid en zelfstandigheid die jullie mij hebben gegeven en al het andere dat jullie me hebben bijgebracht. Vooral het 'niet tevreden zijn met een 6-je (of een 7.5) mentaliteit' en het 'je kan niet beter dan je best doen' hebben mij bij dit proces heel erg geholpen! En mams, ook nog dank voor alle knipsels, dankzij jou heb ik geen krantenknipsel over ICD's gemist.

Mijn paranimf, **Lies**. Dank voor je eindeloze interesse en steun voor dit project. Je kon echt met me meedenken, wist namen van mijn promotoren, co-promotoren en verschillende studies te reproduceren en wanneer nodig luisterde je geduldig naar mijn frustraties (en stond altijd aan mijn kant).

Lieve andere KoneJin's (inclusief import), **Saar**, **Fiek**, **Lisette**, **Val**, **Tess**, **Miens**, **Louk** en **Lous**; gewoon omdat jullie het leven zoveel leuker maken en omdat je af en toe wat goed gemeende kritiek nodig hebt. Bedankt voor jullie interesse.

Lieve **Suutje**, je zit nu helemaal aan de andere kant van de wereld, m'n studiemaatje. We hadden elkaar al snel gevonden in een gedeelde hobby en ook al zijn we daar nu gelukkig vanaf, ik ben blij dat ik nog steeds je vriendinnetje mag zijn. Studie mag er inmiddels wel vanaf hè.

Lieve **Pita**, ik had je dit nog graag willen laten zien.

En tot slot, Lieve **Lo**, je hebt lange tijd getolereerd dat de eettafel als mijn bureau fungeerde. Al is het totaal je vakgebied niet, je hebt me ontzettend gesteund en je pogingen om er wel iets van te begrijpen heb ik enorm gewaardeerd (synapsknoop haha). Hoe dan ook, je begrijpt mij.

CURRICULUM VITAE

Curriculum Vitae

Sofieke Christina Wijers was born on the 25th of august, 1985 in Deventer, The Netherlands.

She completed her secondary education at the Geert Groote College in Deventer in 2003. After a gap year traveling and learning Spanish she studied Medicine at the Utrecht University. During her studies she performed a scientific internship at the Department of Medical Physiology of the University Medical Center Utrecht, which has awaken her interest for (translational) research and the fascinating world of electrophysiology. After obtaining her medical degree in 2010 she started a PhD trajectory at the departments of Medical Physiology and Cardiology of the University Medical Center Utrecht under supervision of Prof. dr. M.A. Vos, Prof. dr. P.A. Doevendans and dr. M. Meine, of which the results are presented in this thesis. Within that period she took half a year to explore the clinical aspects of cardiology as a resident at the department of Cardiology at the University Medical Center Utrecht. As of May 1st 2015 she is in training to be a cardiologist under supervision of Dr. J.H. Kirkels at the University Medical Center, Utrecht.

LIST OF PUBLICATIONS

List of publications

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