2015•2016

FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN

*master in de biomedische wetenschappen*

# Masterproef

## Cardiac Resynchronization Therapy:  Search for parameters that influence Survival and Exercise capacity

Promotor :
dr. Lieven HERBOTS

Promotor :
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Chaima Fadlaoui


*Scriptie ingediend tot het behalen van de graad van master in de biomedische wetenschappen*

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universiteit hasselt | Maastricht University

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# Abbreviations

| | |
|---|---|
| AF | Atrial fibrillation |
| AO | Aortic valve |
| ATP | Antitachypacing |
| AV | Atrioventricular |
| BR | Breath rate |
| CCS | Cardiac conduction system |
| CPET | Cardiopulmonary exercise test |
| CRT | Cardiac resynchronization therapy |
| CS | Coronary sinus |
| CVD | Cardiovascular diseases |
| DCM | Dilated cardiomyopathy |
| ECG | Electrocardiogram |
| EDV | End diastolic volume |
| ESV | End systolic volume |
| FDA | Food and Drug Administration |
| HF | Heart failure |
| HR | Heart rate |
| ICM | Ischemic cardiomyopathy |
| LA | Left atrium |
| LBBB | Left bundle branch block |
| LV | Left ventricle |
| LVEF | Left ventricular ejection fraction |
| MV | Mitral valve |
| NIDDM | Non-Insulin-Dependent Diabetes Mellitus |
| NYHA | New York Health Association |
| OUES | Oxygen uptake efficiency slope |
| RA | Right atrium |
| RBBB | Right bundle branch block |
| RER | Respiratory gas exchange ratio |
| SA | Sinoatrial |
| SBP | Systolic blood pressure |
| SD | Standard deviation |

| | |
|---|---|
| VAT | Ventilatory anaerobic threshold |
| VE | Ventilation |
| WHO | World health organization |

# Acknowledgments

As a child, I always wanted to change the world and have an added value for the community. Although I did not reach that goal yet, I was honored to have the chance to work on such an interesting and useful study. Therefore I want to thank some people for their help during my internship and to bring this thesis to a successful end.

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For the ones who always believed in me,
my parents.

# Abstract

Cardiac resynchronization therapy (CRT) has proved to reduce the mortality rate, hospitalization frequency and quality of life in patients with heart failure and left bundle branch block (LBBB). Despite major advantages of CRT in the majority of patients, yet up to 30% of the CRT patients do not respond. The cause of this difference in response remains unknown. The aim of this study was to investigate the long-term survival of CRT in a real-live population of two major heart centers in Belgium and to gain insights into the parameters that determine outcome after CRT. Additionally, the effect of CRT on exercise capacity will be investigated.

Patients receiving a CRT implantation in a ten-year period (2006-2016) were included. The implantations were carried out in Jessa Hospital (Hasselt) and Imelda Hospital (Bonheiden). The influence of several parameters (pre-implantation, device type and device settings) on survival and echo-respond in both hospitals were investigated. Additionally, patients undertook an ergospirometry test to determine exercise capacity before implantation and after two and four months.

In this real-world CRT population, women and patients without ischemic cardiomyopathy or hypertension tend to have a higher survival rate. Device type and device settings proved to have an influence on CRT survival. Short AV sense intervals (>110 ms) were associated with a significant higher survival than long AV intervals. There was no significant difference in survival between both centers. Intriguingly the Jessa patients had a better recuperation of the left ventricular function by ultrasound echocardiography after CRT without effect on survival.

Differences in change of ejection fraction and number of echo-responders between both hospitals after CRT implantation may suggest that endocardial LV lead placement and AV optimization increases the LVEF much more than the epicardial LV lead placement and no AV optimization. These findings may raise the question whether endocardial or epicardial LV lead placement should be preferred.
New insights into which parameters can affect the survival and echo-response after CRT increases the knowledge about patients‘ chances to survive and will allow more tailored therapy in a patient group with poor outcomes.

Additionally, no significant increase of both OUES and $VO_2$ max were seen after two and four months. These results indicate that the exercise capacity did not improve after two and four months, but the sample size is likely too small to draw a real conclusion. However, for OUES a small increase was seen after two months and a bigger increase after four months. This trend could suggest that in a bigger study population some real differences in exercise capacity would be seen.

# Samenvatting

Cardiale resynchronisatie therapie (CRT) is een behandeling die de mortaliteit en het aantal hospitalisaties reduceert en de kwaliteit van leven verbetert voor patiënten met hartfalen en een volledige linker bundeltak blok. Ondanks de vele voordelen van CRT in de meerderheid van de patiënten, reageert ongeveer 30 % van de CRT patiënten niet op deze behandeling. De oorzaak van deze verschillen in reactie is onbekend. Het doel van deze studie is om de lange termijn overleving na CRT in een *real-world* populatie van twee grote hartcentra in België te onderzoeken. Daarnaast wilt men meer inzichten verwerven in welke parameters het resultaat na CRT bepalen. Vervolgens wordt ook het effect van CRT op de inspanningscapaciteit onderzocht.

Patiënten die een CRT implantatie ondergingen in het Jessa Ziekenhuis (Hasselt) en Imelda Ziekenhuis (Bonheiden) tussen 2006 en 2016 werden geïncludeerd. Het effect van verschillende parameters (pre-implantatie parameters, apparaat type en apparaat instellingen) op het overleven en de echo-respons in beide ziekenhuizen werd nagegaan. Ook vonden er ergospirometrie testen plaats om de inspanningscapaciteit voor - en twee en vier maanden na de CRT implantatie te bepalen.

Vrouwen en patiënten zonder ischemische cardiomyopathie of zonder hypertensie bleken een hogere kans op overleven te hebben. Ook het apparaat type en instellingen hadden een effect op het overleven van de patiënten na CRT. Korte AV sense intervallen (< 110 ms) werden geassocieerd met een hoger kans op overleven dan langere AV sense intervallen. Er was geen significant verschil in overleven tussen beide ziekenhuizen. Jessa patiënten hadden een betere verbetering van de linker ventrikel functie bij ultrasound echocardiografie na CRT zonder dat dit resulteerde in verschillen betreffend het overleven.

Het verschil in ejectie fractie en echo-responders voor en na de implantatie was significant hoger in het Jessa Ziekenhuis. Dit kan suggereren dat de endocardiale linker ventrikel lead plaatsing en de AV optimalisaties in het Jessa Ziekenhuis meer voordelen bieden ten opzichte van de epicardiale linker ventrikel plaatsing en het niet optimaliseren van de AV intervallen in Imelda. Deze bevindingen kunnen vragen oproepen of al dan niet een bepaalde insertie methode de voorkeur zou moeten krijgen. Nieuwe inzichten betreffend welke parameters het overleven en echo-respons na CRT beïnvloeden, verhogen de kennis over de kans op overleven van de patiënt en laten meer gepersonaliseerde therapieën toe in een patiëntengroep met een slechtere outcome.

Er werden geen significante verhogingen van zowel OUES als $VO_2$ max verkregen twee en vier maanden na de implantatie. Deze resultaten stellen dat de inspanningscapaciteit niet verbeterde na de implantatie, maar de studie populatie is te klein om hierover conclusie te trekken. OUES toonde echter wel een kleine toename na twee maanden en een grotere toename na vier maanden. Dit zou kunnen bijdragen tot significante verschillen van de inspanningscapaciteit in een grotere studie populatie.

# 1 Introduction

## 1.1 Structure and physiology of the human heart

The heart embodies four chambers: two upper named atria and two lower labeled ventricles within between the atrioventricular valves (AV-valves): tricuspid - (right) and mitral valve (left) .

The inter-atrial and inter-ventricular septa split the heart into a right and a left heart. The right heart receives oxygen-poor blood from the body via the caval veins and pumps the blood into the lung circulation for gas exchange via the capillary network around the alveoli of the lungs. Via the pulmonary veins, oxygen-rich blood enters the left heart that supplies the body organs and tissues of oxygen, hormones and metabolic substrates (1, 2). The coronary arteries deliver blood to the heart muscle (3).

The heart muscle generates pressure to force out blood into the lung and systemic circulation in a pulsatile manner. Each cardiac cycle is made up of a systolic ejection and diastolic filling phase. By convention, the cardiac cycle begins at the end-diastolic time point. During isovolumetric contraction left ventricular (LV) pressure rises while mitral (MV) and aortic valve (AO) are closed, hence the LV volume does not change. As soon as LV pressure exceeds aortic pressure, the A0 opens and blood is ejected into the systemic circulation, causing a pressure fall in the LV. The moment LV pressure drops below aortic pressure, the AO closes and ejection is terminated. During isovolumetric relaxation both AO and MV are closed and LV pressure rapidly decreases. When LV pressure falls below left atrial (LA) pressure, the MV opens to induce rapid LV filling. After this rapid filling phase, the pressures in the LV and LA are almost equal (= diastasis). In the later part of diastole, LA pressure increases again by atrial contraction which results in late diastolic blood flow from the LA to the LV. When LA pressure drops below end-diastolic LV pressure the mitral valve closes. At this time point, systole resumes and the cycle that creates pulsatile flow will start all over (**Figure 1**)(4).

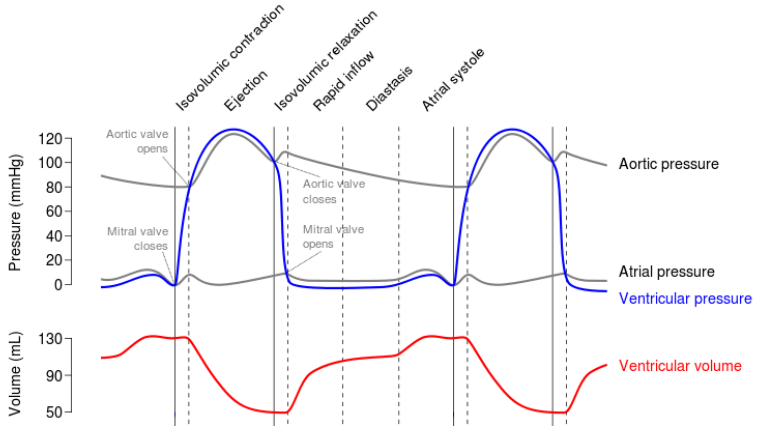


Figure 1 **Cardiac cycle.** ***Upper part****: Pressure curve containing the isovolumic contraction, ejection, Isovolumic relaxation, diastasis and atrial systole. The different pressures are distinguished: Aortic pressure (upper grey), atrial pressure (lower grey) and the ventricular pressure (bleu).* ***Lower part****: The corresponding ventricular volumes are given in red.*

To build up LV intracavitary pressures in an energy-efficient manner, a coordinated contraction of the cardiac walls and fibers is required. This coordinated contraction is provided by the electrical conduction system of the heart, which is called the cardiac conduction system (CCS). The main parts of the CCS are the sinoatrial node (heart pacemaker) (SA node), atrioventricular node (AV node), bundle of His, left- and right bundle branches and Purkinje fibers.

The SA node is the pacemaker of the heart and is located at the junction of the vena cava superior and the right atrium. It generates electrical impulses that are conducted throughout the right atrium and reach the LA via the Bachmann's Bundle. This will induce a synchronized contraction of the atria which corresponds to the P wave on the electrocardiogram (ECG) (**Figure 2.1**). The electrical impulse will reach the AV node via the intermodal tract. The AV node is in normal conditions the only pathway available to conduct the electrical impulse from the atria to the ventricles. It provides a conduction delay allowing the atria to completely depolarize and contract. This AV-delay is shown as the PQ interval on the ECG (**Figure 2.2**). Next, the depolarization wave enters the fast-conducting Bundle of His followed by the left- and right bundle branches to reach the Purkinje fibers. This results in a coordinated activation of both ventricles from apex to base shown as the QRS complex on the ECG (**Figure 2.3, 2.4**). At last, the ventricles will repolarize beginning from the apex to the base (**Figure 2.5, 2.6**) (5).

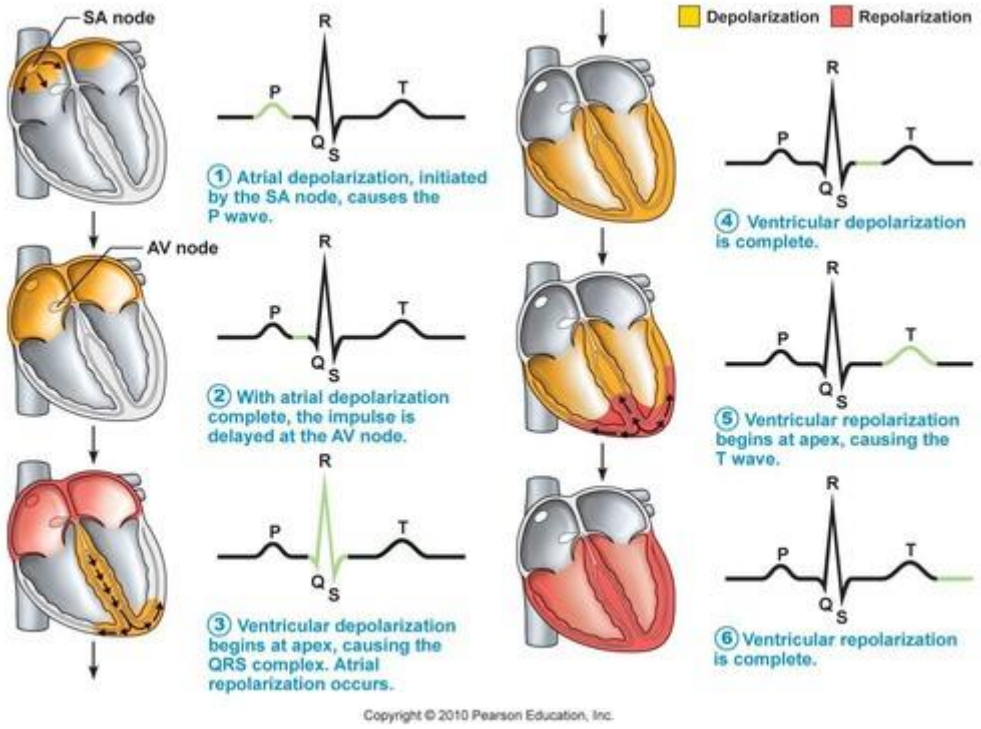


Figure 2 **Cardiac conduction system (CCS) in the heart and on the electrocardiogram (ECG).** *Different steps of the CCS and their corresponding with the ECG.*

## 1.2 Heart failure

Cardiovascular diseases (CVDs) are the leading cause of mortality. According to the World Health Organization 17.5 million people died worldwide from cardiovascular diseases in 2012, representing 31% of all global deaths. Most of these people died from ischemic heart disease (7,4 million) or stroke (6,7 million). Similar numbers are seen in Flanders where one out of three dies from CVDs (6).

Cardiac diseases are typically characterized by chest pain, fatigue, shortness of breath, exercise intolerance, arrhythmia's and syncope. These symptoms are often caused by ischemia, heart muscle dysfunction, heart rate disorders or valvular heart disease, all conditions that can lead to increased intracardiac pressures, congestion, decreased cardiac output and eventually overt heart failure (HF) (7).

HF is a major public health problem. An aging population and improvements in the treatment of acute cardiovascular diseases and of HF may contribute to the growing prevalence of HF (8). In the United States of America, 5.7 million persons of 20 years and older were living with HF between 2009 and 2011. It is thought that the prevalence will increase 46% from 2010 to 2030. Annually, there are 870,000 new cases of HF and more than one million hospitalizations. This contributes to an enormous medical cost, estimated around 30.7 billion US$ (9). In Belgium, the overall prevalence is 9.89 ‰ and about 180 people per 100 000 are yearly diagnosed with HF (6).

Heart failure is characterized by a decreased pump function of the heart. This results in right sided congestion and a lower cardiac output and the inability to cover the oxygen need of the body. Multiple organs and tissue will receive insufficient blood and metabolic substrate (2). Several pharmacologic therapies have been carried out with major improved outcomes. Angiotensin-converting enzyme inhibitors, beta-blockers, Ivabradine and spironolactone have proved to reduce the mortality and frequency of hospitalizations in HF patients (10-13). However, recent years a new device-based therapy has emerged. Cardiac resynchronization therapy (CRT) has proved to reduce the mortality rate, hospitalization frequency and quality of life in patients with heart failure and left bundle branch block (LBBB) (14).

## 1.1 Cardiac resynchronization therapy

CRT devices were introduced at the end of the 1990s. The first clinical studies started in 1998 and the first devices have been on the market after the Food and Drug Administration (FDA) approval in 2001. Ever since, the FDA has approved many different models from different manufactures (15). CRT targets dyssynchronous ventricular contraction caused by heart failure and LBBB. Asynchronous LV activation and contraction declines the efficient building up of intracavitairy pressures during systole leading to

energy loss and left and right sided congestion (16). It reduces the heart's pumping function and worsens valvular regurgitation (17).

### 1.1.1 Dyssynchrony markers

CRT is used to restore mechanical synchrony by electrically activating the heart in a synchronized manner. The most accessible ventricular dyssynchrony marker is the duration of the QRS-complex which represents ventricular depolarization (18, 19)**.** A wide QRS-complex corresponds to prolonged ventricular conduction time. These electrical abnormalities cause mechanical dyssynchrony, resulting in a prolonged isovolumic contraction and relaxation intervals and a decreased left ventricle filling time (18, 19). Mechanical dyssynchrony can be subdivided in three groups: Intraventricular -, Interventricular – and atrioventricular dyssynchrony whereby every form can prolong the isovolumic contraction and relaxation (20).

### 1.1.2 Selection criteria

A direct correlation exists between the width of QRS complex and the left ventricular ejection fraction (LVEF). A prolonged QRS complex contributes to a decreased LVEF. Both QRS-width and LVEF are used as inclusion criteria for selection of CRT candidates (QRS > 120 ms, LVEF < 30%). New York Heart Association (NYHA) class (II)-III-IV and a sinus rhythm were selection parameters in several clinical trials (CARE-HF, COMPANION,..). NYHA classification is used to define the extent of symptoms of heart failure (**Table 1**).

*Table 1* **New York Heart Association classification.**

| CLASS | SYMPTOMS |
|---|---|
| **I** | Patients with cardiac disease without any symptoms or physical limitations. The patient does not experience fatigue, dyspnea or angina pain after physical activities. |
| **II** | Patients with cardiac disease resulting in mild symptoms and slight limitations of physical activity. The patient experiences fatigue, dyspnea or angina pain after physical activities. |
| **III** | Patients with cardiac disease resulting in physical limitations and symptoms even in less than ordinary physical activities. The patient does not experience any discomfort in rest. |
| **IV** | Patients with cardiac disease who suffer from discomfort even in rest. This discomfort increases when any physical activity is performed. |

### 1.1.3 Procedure

Standard pacemakers or defibrillators have two leads: one targeting the right auriculum and one the apex of the right ventricle (21). In CRT, a third left ventricular pacing lead is added to the standard pacemaker or defibrillator. These device can be either a CRT-P or CRT-D. Via the right atrium and cannulation of the coronary sinus (CS), the left ventricular lead is generally placed into the lateral, posterolateral or anterolateral branches of the coronary venous system (22). Optimal lead placement is important and is obtained by searching optimal thresholds without phrenic nerve or diaphragm stimulation (23). However, sometimes this approach cannot be carried out successfully due to difficult access to the CS (eg. CS anatomy variability, right heart remodeling and tricuspid regurgitation) (14). In these cases, epicardial LV lead placement via minithoracotomy might be necessary (24). Although placing the LV lead endocardially is the standard, some hospitals prefer the epicardial way.

Despite major advantages of CRT in the majority of patients with improved survival and restoration of the heart function , yet up to 30% of the CRT patients do not respond (25). The cause of this difference in response remains unknown.

Killu *et al.* investigated the effect of age on survival and compared overall survival between young (< 80 y) and older patients (> 80 y). They concluded that despite similar improvements in ejection fraction, overall survival was worse in the older patient group (26). Another study, which investigated the cause of implantation, showed that patients with mild-heart failure, left ventricular dysfunction and left bundle branch block had a significant long-term survival benefit after an early treatment with CRT-D(27). Lastly, Gorcsan *et al.* studied the relationship between echocardiographic dyssynchrony markers of long-term survival after CRT. They suggested that lacking radial dyssynchrony leads to less favorable outcomes (28).

## 1.3 Exercise capacity after CRT

CRT has positive effects on the mortality, morbidity and reduces hospitalizations (29). Besides survival, the improvement of exercise capacity is an important goal. Exercise capacity is mostly tested with the cardiopulmonary exercise test (CPET) – using breath-by-breath - or the six-minute walk test (30).

To determine the exercise performance, the peak oxygen uptake ($VO_2$) is a commonly used parameter. However, this index requires maximal effort which can be a problem for HF patients (31). HF patients suffer from heart diseases that can lead to limitations of their maximal effort. Parameters based on submaximal efforts are therefore preferred over $VO_2$. Ventilatory anaerobic threshold (VAT) is such a parameter, but it relies on the protocol and evaluator (32).

In 1996, Baba *et al.* introduced the oxygen uptake efficiency slope (OUES). OUES incorporates respiratory, cardiovascular and muscular function in one index ($VO_2 = a.\log_{10} V_E + b$; where a is the OUES) . It is a validated parameter obtained from the CPET test and has the major advantage that it leads to reliable results even if the patient did not achieve his fullest potential (33). Multiple studies investigated the reliability of OUES in different patient groups, such as healthy children, obese children and cardiac patients (33-36).

Some studies investigated the improvement of the exercise capacity after CRT (with or without extra rehabilitation program) and exercise capacity is taken into account in several studies that investigated outcome.

De Marco *et al.* did not find a significant improvement of exercise capacity after 6 months ($VO_2$ peak as endpoint) before and after CRT compared optimal medical therapy only (37). Another study with CRT-D patients showed a significant increase in the ventilator efficiency. However, there was no significant improvement in oxygen uptake ($VO_2$ peak) (38).

On the contrary, Parthenakis *et al.* did find a significant improvement of the $VO_2$ peak after 6 months and Illiou *et al.* a $VO_2$ peak increase of 38% (30, 39).

## 1.4 Hypothesis and objectives

The aim of this study was to investigate the long term survival of CRT in a real-live population of two major heart centers in Belgium and to gain insights into the parameters that determine outcome after CRT.

We hypothesize that heart status at the time of implantation, device settings and the insertion method affect the survival after CRT. To investigate this hypothesis, two main objectives are formulated.

First, parameters that have an impact on survival of the patients will be determined. Subsequently, the differences in parameters between the two major contributing Heart Centers to this study will be focused.

New insights into which parameters can affect the survival after CRT will be developed. This increases the knowledge about patients‘ chances to survive and will allow more tailored therapy in a patient group with poor outcomes. The results of this study might have an impact on hospitals and on medical costs.

Additionally, the effect of CRT on the exercise capacity will be investigated. For this purpose, all patients that are eligible to a CRT will undertake an ergospirometry test before the implantation, two months – and four months after.

# 2 Materials and methods

## 2.1 PART I: Parameters that affect survival after CRT

### 2.1.1 Study population

In this retrospective study, patients receiving a CRT implantation were included. The CRT implantations were carried out in two hospitals: Jessa Hospital (Hasselt, Belgium) and Imelda Hospital (Bonheiden, Belgium) in a ten-year period (2006-2016). CRT patients were identified from the electronical medical reports of both hospitals and all the needed data were transferred to a clinical database using Filemaker Pro 14 (Windows version)**.** All patients of the Jessa Hospital underwent a optimization protocol after CRT implantation: the device settings were optimized using echocardiography after the implantation and this was repeated each new follow-up visit. CRT optimizations were not performed at the Imelda Hospital. Their CRT devices remained in the out of the box settings.

This study was conducted in accordance with the Declaration of Helsinki. The author had full access to the electronical medical reports of all patients and privacy of patients was maintained at all times.

### 2.1.2 Patient characteristics and device information

Baseline patient characteristics were obtained from the electronical medical reports of the patients in both hospitals. Demographic, clinical and therapy data pertain to the baseline characteristics. Device characteristics (company, pacemaker and LV lead placement,..) and device settings at baseline were included from operative reports.

To achieve a follow-up view, all the CRT and echocardiography consultations were included in the database. LVEF, end diastolic - and systolic volume (EDV, ESV), valvular parameters,.. described the hemodynamical state of the heart. CRT consultations were defined by brady-therapy, percentage biventricular pacing, AV sense and AV pace intervals, shocks and/or antitachypacings (ATPs),…

All hospitalizations for heart failure and survival status of the patients were registered.

### 2.1.3 Statistics

Statistical analyses were performed using IBM SPSS (Version 22.0) statistical software for Windows and MedCalc. Kaplan-Meier Estimates were performed to determine the survival rate. Paired and independent t-test were performed to compare ejection fraction data before and after implantation and between hospitals, respectively.

Categorical variables are shown as absolute numbers and percentages and continues variables were given as mean ± standard deviations (SD). A P-value $<0.05$ was considered as significant.

## 2.2 PART II: Exercise capacity after CRT

### 2.2.1 Study design and participants

This study was conducted in the Jessa Hospital, department Cardiology (Hasselt, Belgium) between February 2016 and June 2016. The ethical committee (*Ethisch Toetsingscommissie, vzw Jessa)* approved the study protocol. Prior to the study, signed informed consents were obtained from all participating patients. This study was conducted in accordance with the Declaration of Helsinki.

In this prospective study, all patients who had a CRT implantation in the Jessa Hospital were eligible for inclusion. On fixed time points after implantation, maximal exercise tests were performed: Baseline (before CRT implantation) and, two and four month after CRT implantation (**Figure 3**). There will be no randomization since this study consists only one group and comparison will be made with the exercise data before and after CRT implantation.

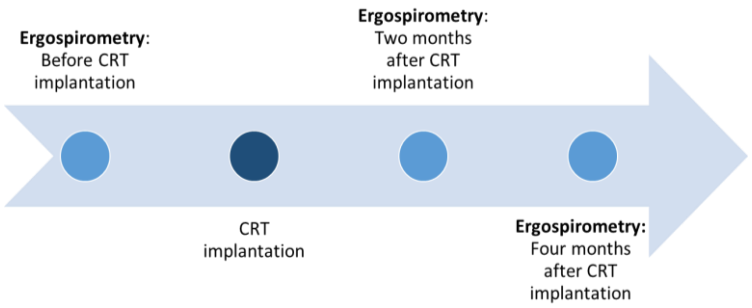


Figure 3 **Timeline of the study.** *Before, two months and four months after CRT implantation the ergospirometry test wil be performed.*

### 2.2.2 Investigation: Ergospirometry test

Exercise tests were performed on a cycle ergometer (eBike 1.8, GE Healthcare) in non-fasting conditions. The room temperature was held on 20°C and the ergospirometer was calibrated automatically before every test. Heart rate, blood pressure, a 12-lead electrocardiogram, cycling power output and respiratory parameters through breath-by-breath analysis were measured continuously. First, a lung function test was performed to have the exact respiratory values. After a two-minute warming-up, the initial load was increased every minute until exhaustion by a load calculated using following formula: [($VO_2$ max - $VO_2$ in rest) / 100], with $VO_2$ in rest = 6 x weight + 150 and $VO_2$ max = length (in cm) – age x 20 (men) or x 14 (women).

The initial load was set at the double of the increasing workload. The tests were continued until physical exhaustion. Maximal exercise was reached if:

- Respiratory gas exchange ratio (RER) > 1.1.
- Heart rate (HR) (220 – age) > 85 %
- Breath rate (BR) > 30 breaths/min

If the RER was between 1.0 and 1.1, a submaximal test was reached. After evident exhaustion, a cooling-down period of 2 minutes was followed.

Minute ventilation (VE), oxygen uptake ($VO_2$), carbon dioxide output ($VCO_2$), minimal breathing equivalent of $CO_2$ and $O_2$ ($eqCO_2$, $eqO_2$) and the breath rate (BR) were averaged every 10 seconds. VO2 peak and RER were obtained using the highest value in the last minute. OUES was determined using: $VO_2 = a \log_{10} V_E + b$, where a is the OUES and b the intercept (40).

### 2.2.3 Study endpoints

The pre-specified primary endpoint of this study was the change in exercise capacity, measured by the OUES. Other parameters collected were $VO_2$ peak and workload.

### 2.2.4 Statistics

Statistical analysis was performed using SPSS 22.0 statistic software (Windows Version). A paired sample t-test was used to compare two time points (before implantation vs after two months; before implantation vs after four months; after two months vs after four months).

# 3 Results

## 3.1 PART I: Parameters that affect survival after CRT

### 3.1.1 Study population

A total of 511 patients were included in the study. The mean follow-up of the study population was 3.8 ± 2.75 years since device implantation. Patient baseline characteristics are summarized in **Table 2**.

Patients were aged 29-91 years (mean age was 69.2 ± 10.26 years) and 68.7 % were male. From the study population, 70.3 % were patients in the Jessa Hospital, Hasselt while 29,7 % were patients in the Imelda Hospital, Bonheiden.

Cause of LV dysfunction at baseline was an idiopathic dilated cardiomyopathy (DCM) in 57.5% whereas 42.5% had an ischemic cardiomyopathy (ICM). Mean QRS width was 163.97 ± 27.32 ms with an average LVEF of 28.32 ± 8.6 % and LVEDV 225.6 ± 72 ml. Most patients were in sinus rhythm at the time of device implantation. Only 19.4% of the patients were in atrial fibrillation (AF).

The implanted devices were a CRT-D in 72.2% and a CRT-P in 27.8%. The LV lead was inserted endocardially in 71.6% and 28.4 % epicardially. Most patients (31.2%) had no risk factor, followed by one (24.9%), two (22.5%) and three (14.3%) risk factors. Hypercholesterolemia, hypertension and Non-Insulin-Dependent Diabetes Mellitus (NIDDM) were the most common risk factors.

Table 2 **Baseline characteristics.**

| | Total population (n = 511) |
|---|---|
| Age (years) | 69.2 ± 10.26 |
| **Male Gender** | 68.7 % (351) |
| **Center** | |
| Jessa | 70.3 % (355) |
| Imelda | 29.7 % (150) |
| **Risk factors** | |
| Hypercholesterolemia | 40.6% (207) |
| Hypertension | 40.1% (204) |
| NIDDM | 20.0% (102) |
| Obesity | 15.3% (78) |
| Smoking | 14.9 % (76) |
| Familial | 11.6% (59) |
| IDDM | 0.2% (1) |
| **ICM** | 42.5% (218) |
| **AF** | 19.4% (99) |
| **QRS width (ms)** | 163.97 ± 27.32 |
| **LVEF (%)** | 28.32 ± 8.6 |
| **LVEDV (ml)** | 225.6 ± 72 |
| **Creatine** | 133.9 ± 72 |
| **eGFR (mL/min/1.73m²)** | 48.62 ± 13.9 |
| **Conduction delays** | |
| LBBB | 61.8 % (316) |
| RBBB | 3.9% (20) |
| None | 34.2 % (175) |
| **Device** | |
| CRT-P | 27.8 % (140) |
| CRT-D | 72.2 % (364) |
| **LV lead location** | |
| Epicardial | 28.4 % (134) |
| Endocardial | 71.6% |
| *Lateral* | 42.4 % (200) |
| *Posterolateral* | 20.8 % (98) |
| *Anterlatoral* | 7.6 % (36) |
| *Great cardiac vein* | 0.8 % (4) |

AF: Atrial fibrillation, CRT-D: Cardiac resynchronization therapy with defibrillator, CRT-P: Cardiac resynchronization therapy with pacemaker only, GFR: glomerular filtration rate, ICM: ischemic cardiomyopathy, LBBB: Left bundle branch block, LEDV: Left end diastolic volume, LVEF: left ventricle ejection fraction, (N)IDDM: (Non)-Insulin-Dependent Diabetes Mellitus

### 3.1.2 Overall Survival

The primary end-point – death from any cause - occurred in 127 patients (25.15%) (**Figure 4A)**. 40 patients died as a result of heart failure, whereas 59 had another known cause of death (e.g. kidney failure, pneumonia,…). For 28 patients the cause of death was not clear. Mean survival since device implantation was 8.7 years and 42.1 % survived after 10 years. Some indicators were added to the figure to get a hint how this relates to the survival of a general heart failure population (without device implantation) and the survival rates of the general population (41, 42).

A combined end-point, all-cause death and hospitalization, occurred in 224 patients. In the first year, already 20 % had an event, mostly rehospitalization. Mean event-free was 6.3 years and only 27.1 % of the patients had no events during the entire follow-up period (**Figure 4B**).

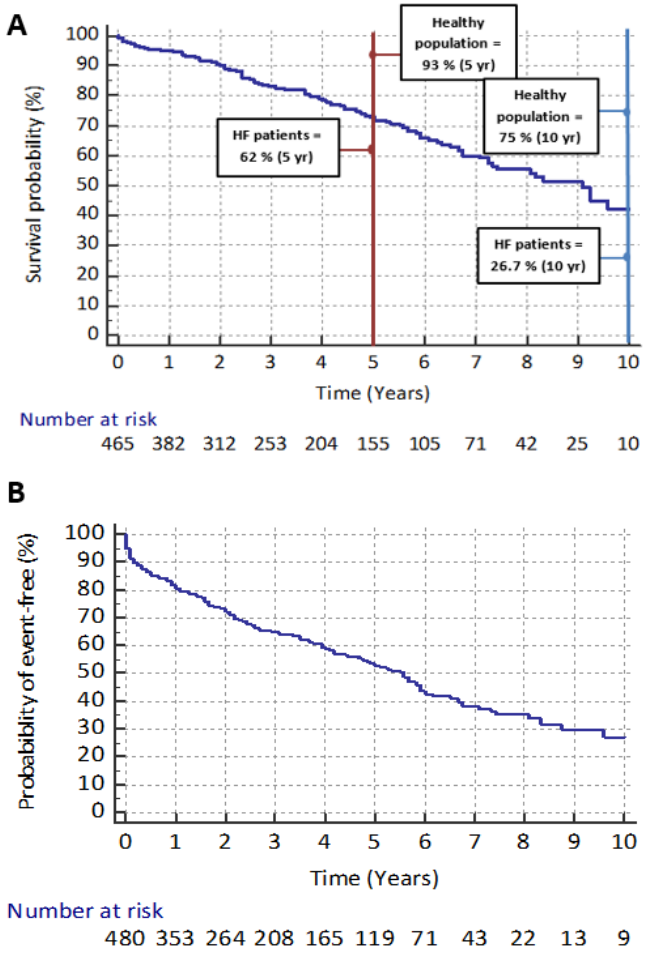


Figure 4 **Kaplan-Meier Estimates of the probability of event-free.** *(A) Overall survival after ten years follow-up. Red line: ECHOES-study 5-year follow-up. Blue line: ECHOE-study 10-year follow-up (41, 42) (B) Combined end-point: All-cause death and hospitalization during follow-up.*

The survival rate did not differ between  both Jessa and Imelda Hospital (**Figure 5**). Mean survival was 7.43 ± 0.24 and 8.37 years ± 0.7 for Jessa and Imelda respectively. Survival after ten years was 43.6 % for Jessa and 42.1% for Imelda (Log Rank Test: P = 0.307).

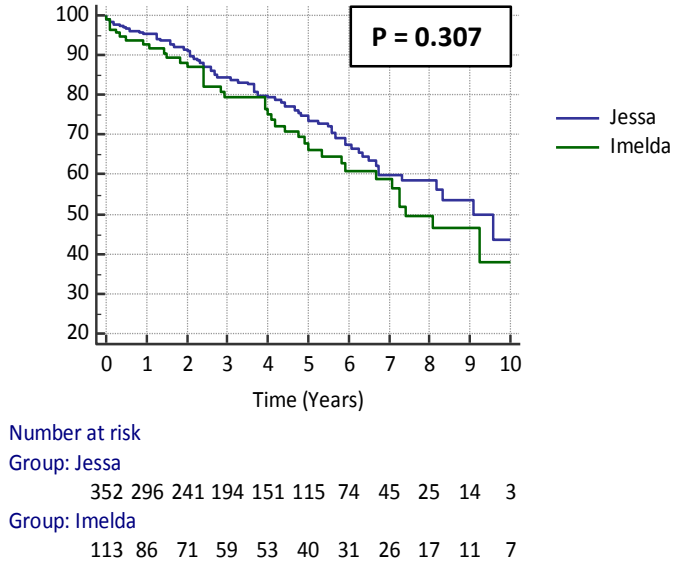


Figure 5 **Kaplan-Meier Estimates of survival probability in both hospitals.** *No significant differences obtained between Jessa and Imelda Hospital.*

### 3.1.3 Effect of pre-implantation characteristics of the patient on survival

Women had a higher survival rate compared to men after ten years (65.1% vs 32.2  %). Mean survival was significantly different (Log Rank test: p-value = 0.0051) with 8.03 years ± 0.5 for men and 8.88 years ± 0.47 for women (**Figure 6A**).

Patients with ICM (mean survival 7.6 years ± 0.37) died earlier than patients with DCM (9.2 years ± 0.53) (Log Rank test: P-value <0.0001). After ten years 59.7 % of DCM survive. This was significantly more than patients with ICM (32.2%) (**Figure 6B**)**.**

Hypertension is the only risk factor that affected survival (mean survival: 9.24 years ± 0.54 vs 7.95 years ± 0.48) early and later in the follow-up (Breslow test: P-value= 0.018; Tarone-Ware test: P-value = 0.026). Remarkably after 8 years, a cross-over occurs where patients with hypertension tend to have a better survival rate (**Figure 6C**). Presence of diabetes did not seem to affect the survival rate of these CRT patients (Log Rank test: P-value =0.500) (**Figure 6D**).

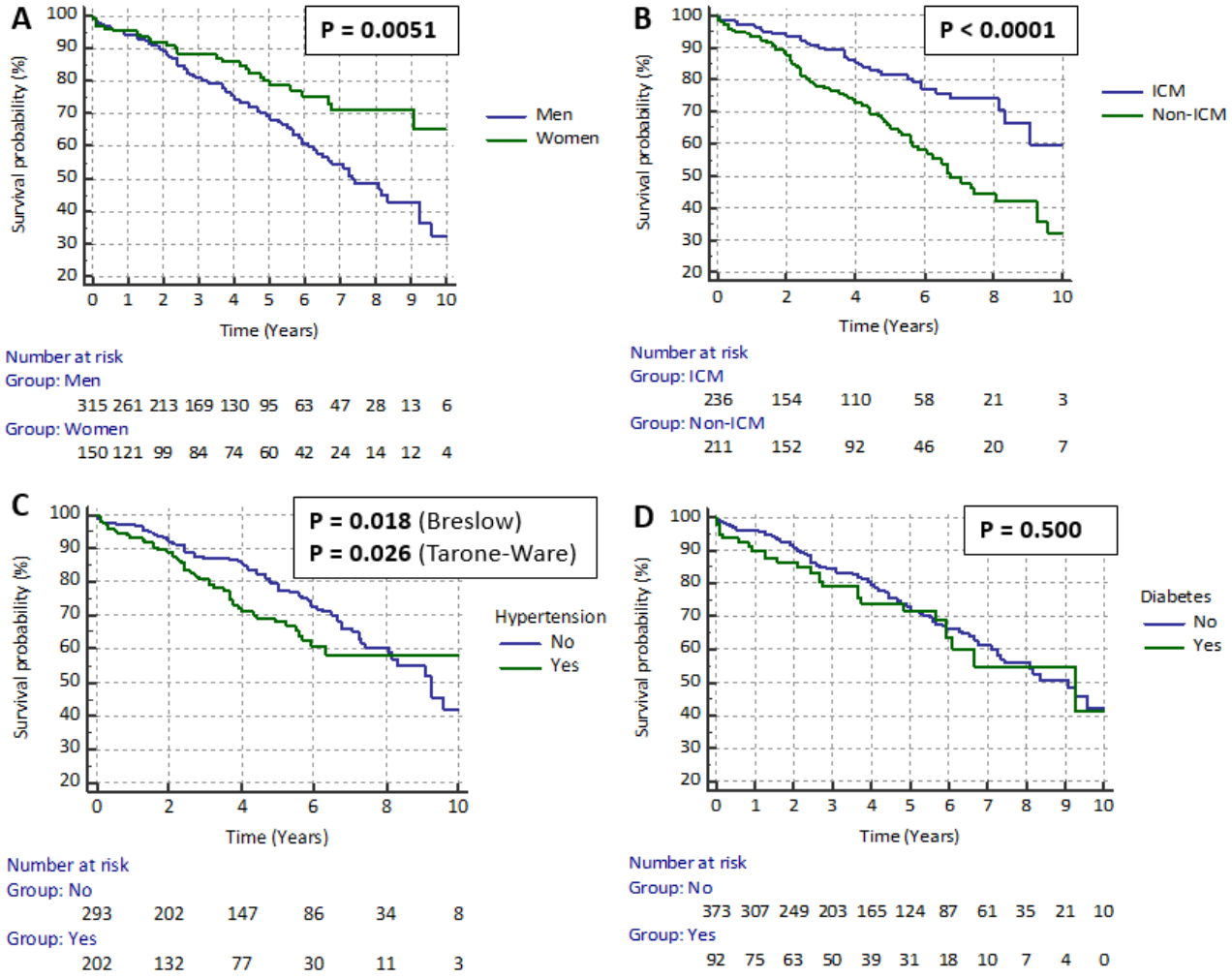


Figure 6 **Kaplan-Meier Estimates of the survival probability.** *(A) Men vs women (Log Rank test: P = 0.0051), (B) ICM vs non-ICM (Log Rank Test: P < 0.0001, (C) Hypertension vs no hypertension (Breslow Test: P = 0.018; Tarone-Ware Test: P = 0.026), (D) Diabetes vs no diabetes (Log Rank Test: P = 0.500). ICM: Ischemic cardiomyopathy*

Both for heart rhythm and heart rate no significant differences were shown. Sinus rhythm and atrial fibrillation had similar survival rates. (Log Rank test: P-value = 0.2) (**Figure 7A**). Patients with lower baseline heart rates (< 60 bpm at rest) tended to have a better outcome, but these findings were not significant during ten year follow-up (**Figure 7B)**.

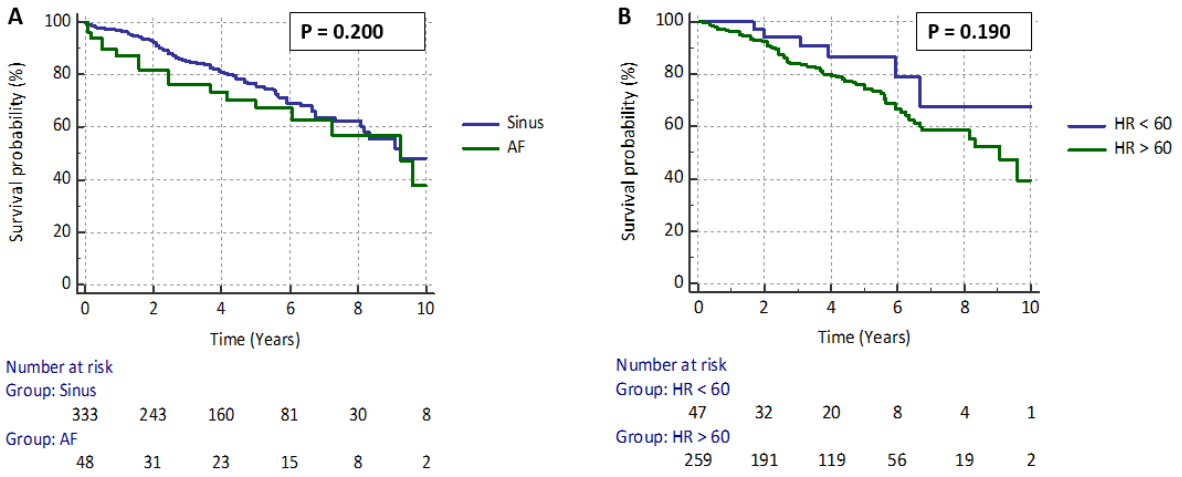


Figure 7 **Kaplan-Meier Estimates of the survival probability.** *(A) Heart rhythm: Sinus vs AF (Log Rank Test: P=0.200) (B) Heart rate < 60 bpm vs heart rate > 60 bpm (Log Rank Test: P= 0.190).*

### 3.1.4 Effect of device type and insertion method on survival of the patients

Next, the influence of device characteristics and settings was investigated on the survival of the patients after CRT implantation.

Kaplan-Meier survival analysis was performed to compare the two different types of CRT: CRT-P and CRT-D. Patients with CRT-P had a significant lower mean survival (6.6 years ± 0.41) than CRT-D implanted patients (8.95 years ± 0.52) (Log Rank test: P-value = 0.0088). The differences in survival probability are the highest after around six years follow-up and decrease substantially after 7.5 years of follow-up. At the end of the study, both survival curves come together and the differences in survival disappear (**Figure 8**).

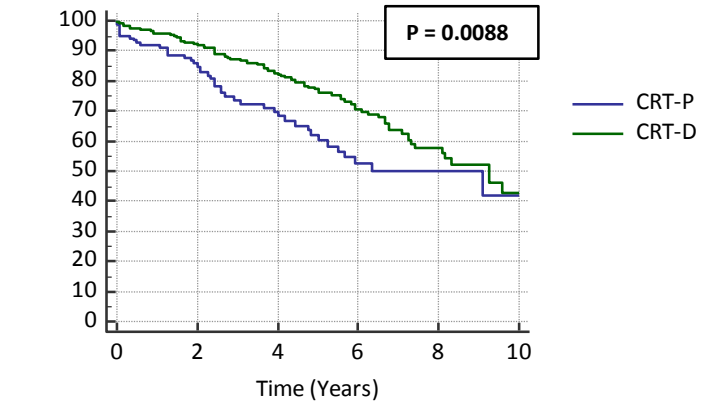


*Figure 8* **Kaplan-Meier Estimates of the survival probability.** *CRT-P vs CRT-D (P-value = 0.088). CRT-D: Cardiac resynchronization therapy with defibrillator; CRT-P: Cardiac resynchronization therapy with only pacemaker.*

The major difference between the two centers was the insertion method. Jessa Hospital mainly implants the LV lead endocardially, whereas Imelda prefers the epicardial route. Both survival curves were very similar and no significance was seen (Log Rank test: P-value = 0.855) (**Figure 9**). After ten-year follow-up the survival were 36.5% and 39.8% for the endocardial - and epicardial LV lead placement, respectively.

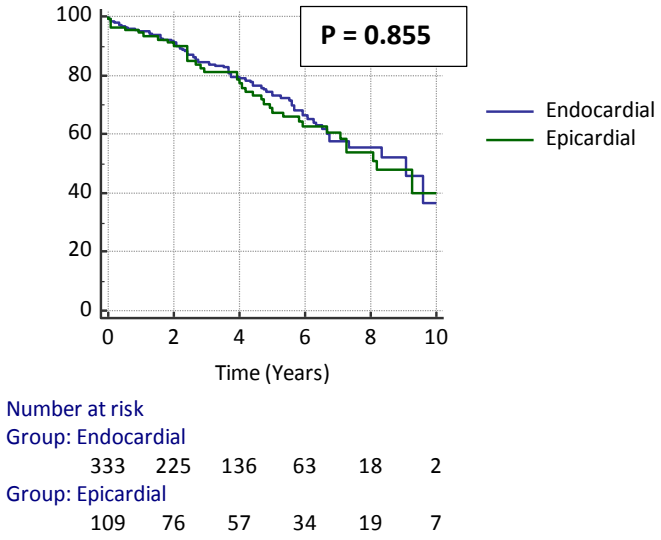


*Figure 9* **Kaplan-Meier Estimates of the survival probability *of the LV lead position.*** *Endocardial vs epicardial (P-value = 0.855).*

### 3.1.5 Influence of device settings on survival

The percentage of biventricular pacing (> 95% or < 95%) did not significantly affect (P-value = 0.17) ten-year survival in this study. Mean survival time were 9.92 years ± 0.94 and 9.86 years ± 0.63 for patients with percentages under and above 95 %, respectively (**Figure 10**).

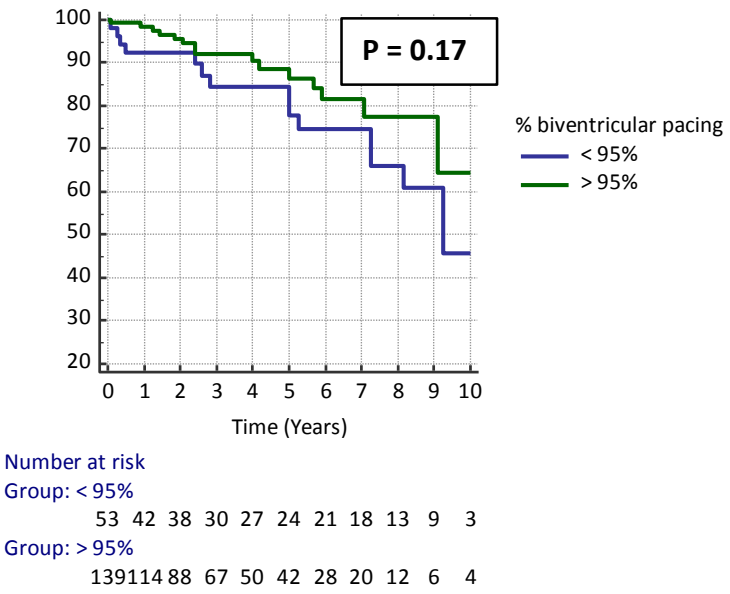


Figure 10 **Kaplan-Meier Estimates of the survival probability for biventricular pacing.** *No significant effect of biventricular pacing (P=0.17)*

AV pacing intervals can be optimized with the use of Echo Doppler. The influence of differences in AV sense, AV pace and VV pacing settings on survival was explored.

Short AV sense intervals (<110 ms) were associated with a significant higher survival than long AV sense intervals (>110 ms) (mean survival: 9.6 years ± 0.31 (<110 ms) vs 7.42 years ± 0.6 (> 110 ms)) (Log Rank test: P-value = 0.0315) (**Figure 11**).

AV sense intervals ranged from 30 ms to 300 ms. The distribution of AV sense intervals is shown in **Figure 12**.

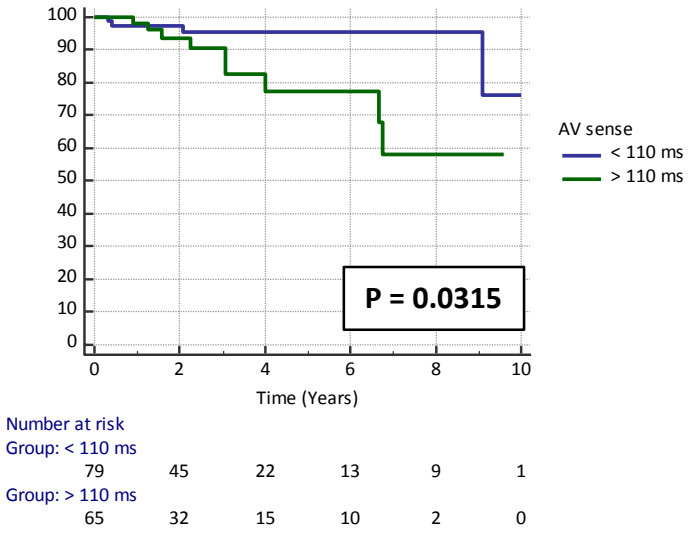


Figure 11 **Kaplan-Meier Estimates of survival probability for AV sense intervals.** *AV sense < 110 ms has a significant higher survival compared to > 110 ms (Log Rank Test: P = 0.0315)*

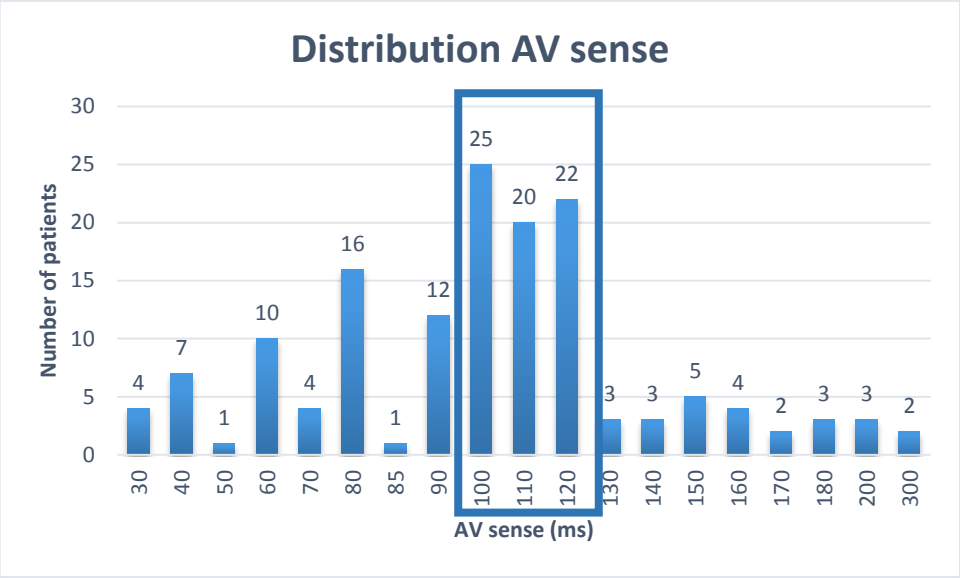


Figure 12 **Distribution of AV sense (ms).** Most used AV sense were 100, 110 and 120 ms (Blue square).

Long AV pace time intervals did not result in significant differences in survival (Log Rank test: P-value = 0.222). Mean survival were 8.83 years ± 0.22 for AV pace intervals below 150 ms and 8.11 years ± 0.5 for intervals above 150 ms (**Figure 13**).

AV pace intervals range from 70 ms to 350 ms. The dispersion of the AV pace settings are mainly between 120 and 170 ms (**Figure 14**).

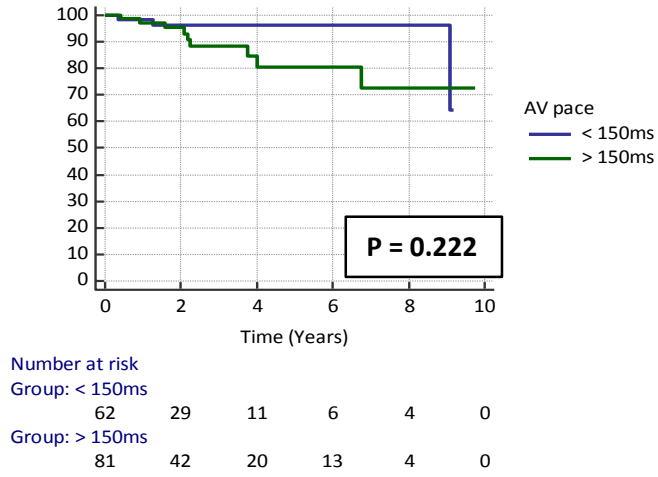


Figure 13 **Kaplan-Meier Estimates of survival probability of AV pace.** No significant differences between AV pace intervals < 150 ms and >150 ms (Log Rank Test: P = 0.222)

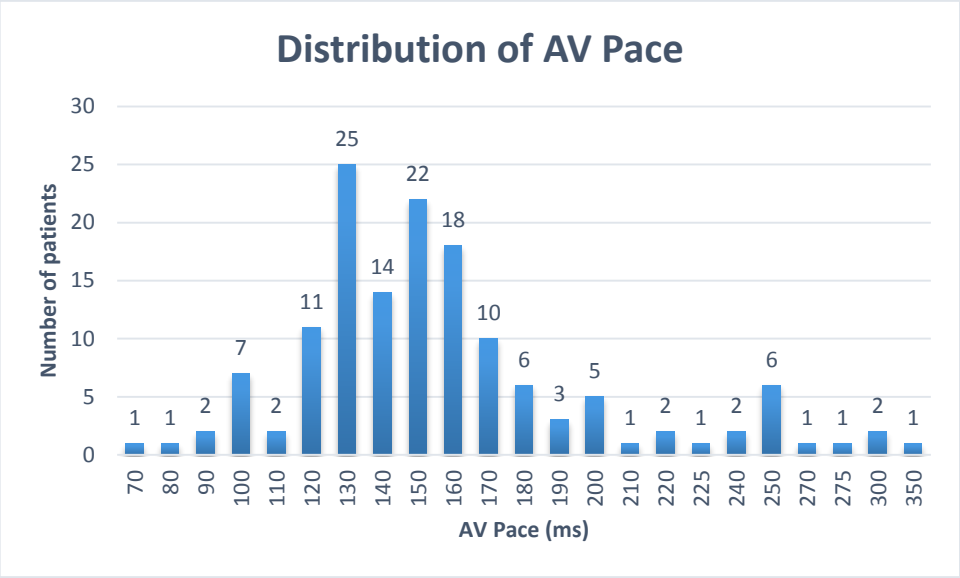


Figure 14 **Distribution of AV pace intervals (ms)**

### 3.1.6 Echo-responders after CRT in Jessa and Imelda Hospital

The major effects of resynchronization therapy should be measured in terms of survival. However, classically response to CRT is also measured looking at differences in clinical improvement (e.g. dyspnea at exercise) or in ultrasound ejection fraction (echo-responders). Echo-responders were defined as an increase of 15% of the LVEF estimated by ultrasound (43).

Baseline LVEF's were similar in both hospitals: 28.04 % for Jessa and 29.02% for Imelda (P-value = 0.42)(**Figure 15**). LVEF increased significantly in patients in Jessa (P-value <0.001) (**Figure 16A**). This increase was not seen with patients in the Imelda Hospital (before: 29.02 % vs after: 31.76 %) (P-value = 0.157)(**Figure 16B**).

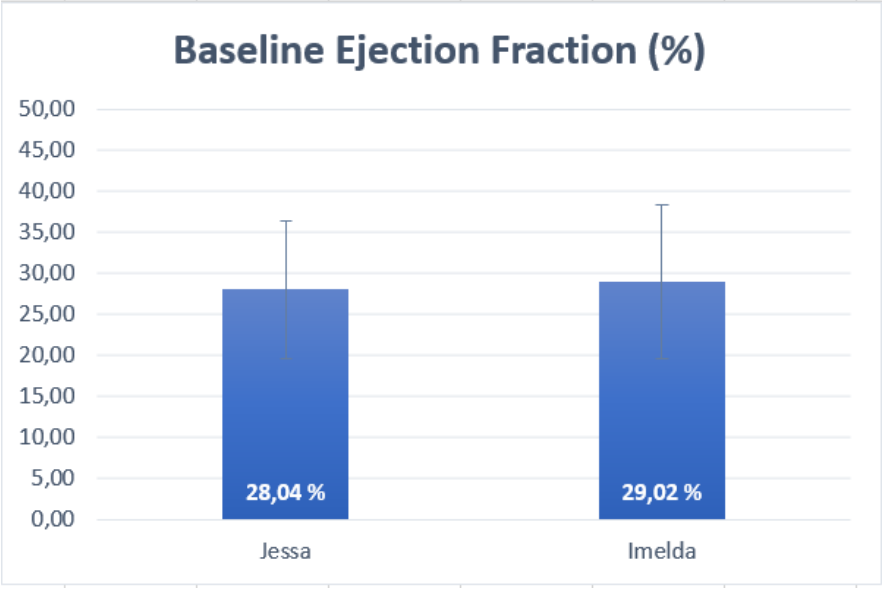


Figure 15 **Baseline ejection fraction (%) for both centers.** *No significant difference between baseline ejection fraction of Jessa and Imelda (P=0.42). Data bars represent mean ± SD.*

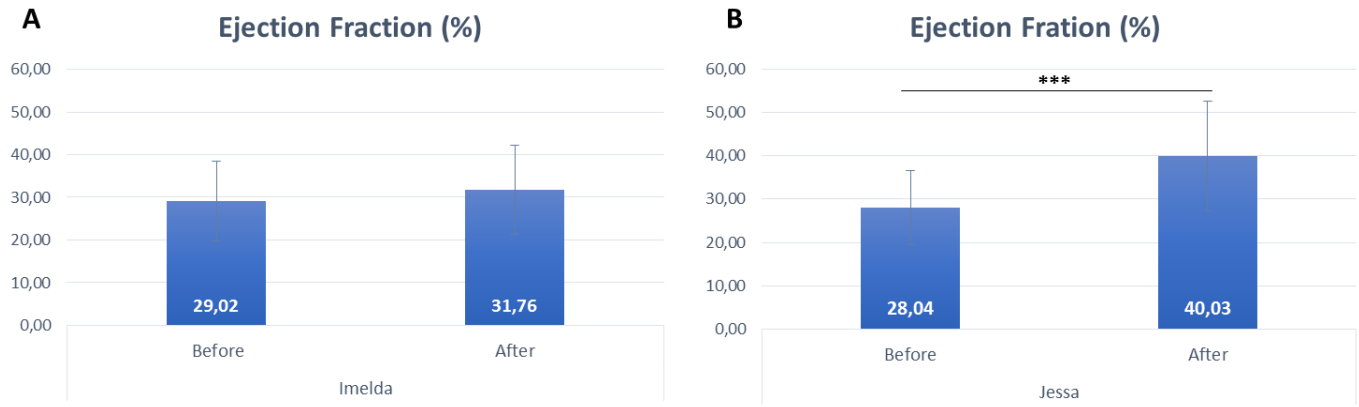


Figure 16 **Ejection fraction before and after CRT implantation.** *(A) Jessa hospital: LVEF before and after implantation. P < 0.0001. (B) Imelda Hospital: LVEF before and after implantation. P* = 0.157. Data bars represent mean ± SD

Change in ejection fraction (LVEF after – LVEF before) was significant higher in Jessa (12.33%) than in Imelda (2.22%) (P-value <0.0001) (**Figure 17**). This results in much less echo-responders in Imelda Hospital (10 of 71 patients) compared to Jessa Hospital (137 of 303) (**Figure 18**). A multi-variate analyses was performed where only insertion method was significant (P-value < 0.0001) which may demonstrate the effect of insertion method on change in ejection fraction. Optimization was significant in a univariate analysis.

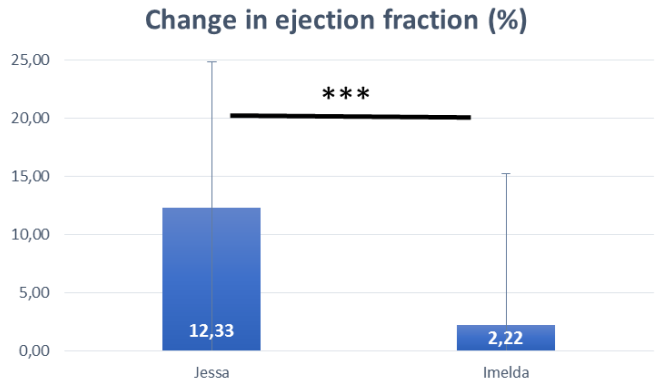


Figure 17 **Change in Ejection fraction per hospital**. *Change in ejection fraction was significant higher in Jessa Hospital (P < 0.0001). Data bars represent mean ± SD*

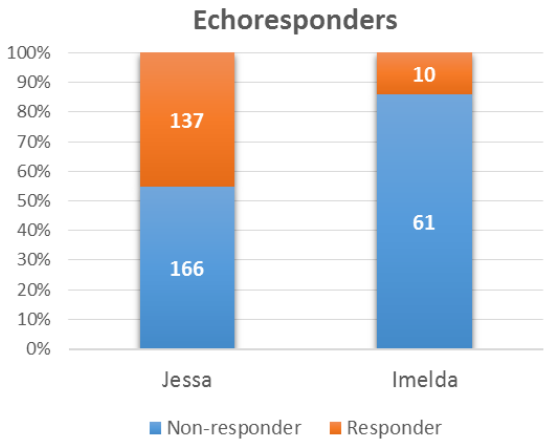


Figure 18 **Echo-responders per hospital.** *Less echo-responders in Imelda Hospital compared to Jessa Hospital(14.08%vs 54.78%)*

## 3.2 PART II: Exercise capacity improvement after CRT

### 3.2.1 Baseline characteristics

For this prospective study, five patients were included. One patient had to be excluded because of an plugged CRT implantation. For two patients no follow-up data was obtained caused by health deterioration of one patient and the other was not accessible anymore. Baseline characteristics and ergospirometry data are summarized in **Table 3**.

Table 3 **Baseline characteristics**

| | **Total population (n=4)** |
|---|---|
| **Men** | 50% (2) |
| **Age** | 59.5 ± 12.58 |
| **Ergospirometry parameters** | |
| Maximum load (W) | 110.25 ± 31.74 |
| HF (bpm) | 127.00 ± 37.74 |
| $VO_2$ max () | 16.00 ± 3.93 |
| Anaerobic threshold (W) | 54.75 ± 23.11 |
| $VE/VCO_2$ Slope (ml/kg) | 37.13 ± 3.35 |
| OUES (ml/kg) | 1309.67 ± 326.83 |

HF: Heart frequency; OUES: oxygen uptake efficiency slope; W: watt

### 3.2.2 The effect of CRT on exercise capacity after two and four months

First the influence of CRT on the OUES was examined. The oxygen uptake efficiency slope (OUES) was 1424 ± 260, 1459.5 ± 376.5 and 1559.5 ± 285.5mL/kg at baseline, two months and four months, respectively. All OUES were similar (Baseline vs 2M: P = 0.812; Baseline vs 4M: P = 0.118 and 2M vs 4M: P= 0.470) (**Figure 19**).

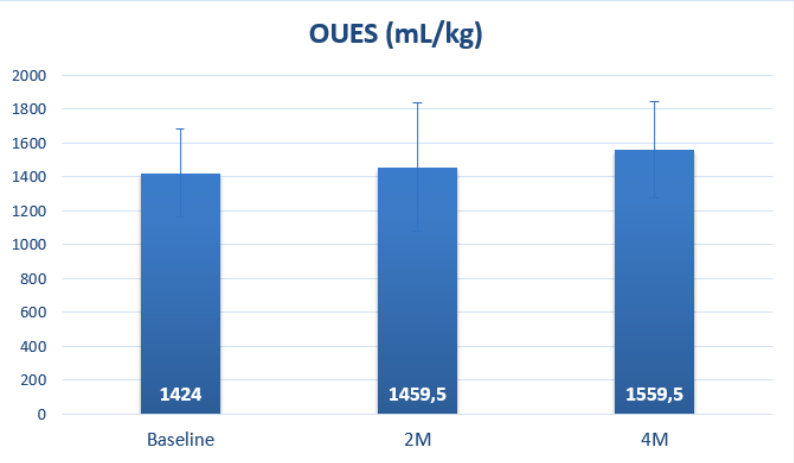


Figure 19 **OUES at baseline, two months and four months.** OUES at baseline was 1424 ± 260 mL/kg, 1459.5 ± 376.5 mL/kg at two months and 1559.5 ± 285.5 mL/kg after four months. No significant increase of OUES after two months (P = 0.812) and after four months (P =0.118). OUES at 2M and 4M was also similar (P =0.470). Data bars represent means ± SD.

$VO_2$ max was 19.2 ± 1.3, 19.4 ± 4.7 and 19.9 ± 2.7 mL/kg at baseline, two months and four months, respectively. No significant increase was seen after two and four months (p-value= 0.963, 0.502 respectively). The $VO_2$ max after two and four months were also similar (P-value= 0.492) (**Figure 20**).

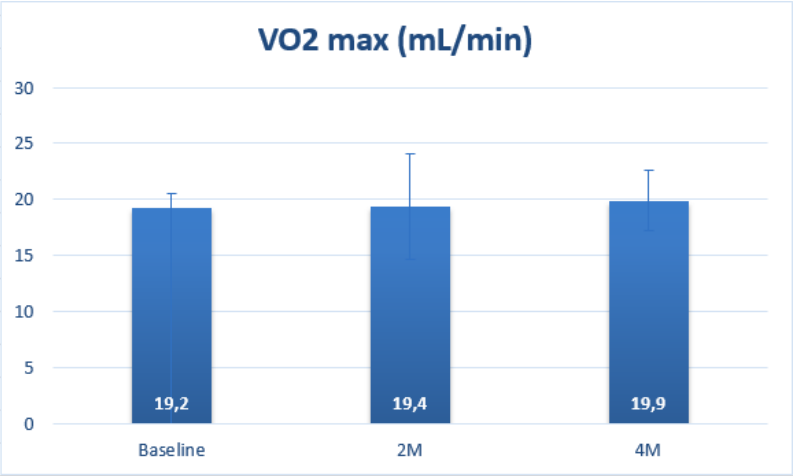


Figure 20 **$VO_2$ max at baseline, two months and four months.** *$VO_2$ max at baseline was 19.2 ± 1.3 mL/kg, 19.4 ± 4.7 mL/kg at two months and 19.9 ± 2.7 mL/kg after four months. No significant increase of VO2 max after two months (P = 0.963) and after four months (P =0.502). $VO_2$ max at 2M and 4M was also similar (P =0.492). Data bars represent mean ± SD.*

# 4 Discussion

Cardiac resynchronization therapy has demonstrated to improve survival in patients with heart failure and LBBB (14). Resynchronizing cardiac hemodynamics between atria and ventricles decreased mortality and hospitalizations. This study confirmed the successful clinical application of this relatively new heart failure therapy in a real-live population in two major heart centers of Belgium and compared the differences between these centra in a search for parameters that affect survival after CRT. The main finding of this study is that despite major differences in implantation and follow-up there is no significant difference in survival between both centers. Intriguingly the Jessa patients had a better recuperation of the left ventricular function by ultrasound echocardiography after CRT without effect on survival.

## 4.1 PART I: Parameters that affect the survival after CRT

### 4.1.1 Reflection of real-world CRT population

The study population included all consecutive patients who received a CRT-P or CRT-D device implantation in two major cardiac centers of Belgium between 2006 -2016. This real-live population might differ from major randomized controlled trials that have excluded some important groups (COMPANION, CARE-HF, REVERSE,..) (44). Very elderly patients, patients with atrial fibrillation and patients who had already a previous device implantation are some examples. 30.7% of our study population was older than 75 years at the time of implantation and 19.4% had atrial fibrillation. Including these groups in this study contributed to a study population that reflects the real-world CRT population.

The survival rate after one year was 95 % and 42.1% after ten years. These one-year results were in line with previous studies where overall survival ranged from about 90 % to 98% (14, 45-47). The ten-year survival rate and mortality were likewise comparable to other published studies (45, 48). When these findings are depicted into a figure with HF patients without CRT implantation, at both five-year and ten-year follow-up, the advantage of the implantation could be estimated (10-year follow-up: 42.1% vs 26.7%) (41). However, it also shows that despite the major advantages on mortality, there still is a substantial gap between healthy non-HF subjects and CRT patients (75% vs 42.1%) (42).

### 4.1.2 Pre-implantation characteristics influence the outcome after CRT

First women with heart failure and LBBB had a significant better survival after CRT than men. A multi-variable analysis showed that both groups were only different in the frequency of ischemic heart disease: Women were more likely to have a non-ischemic dilated cardiomyopathy (DCM: 72.8% vs ICM: 27.2%), in contrast to men (DCM: 42% vs ICM 57%). Comparable results were seen by Bogale *et al,* which can indicate that a lower prevalence of ICM decreases the mortality rate (46). However, a better survival in women is also seen in several other heart failure studies after one – five and ten-year follow-

up (49, 50). These findings were not reported in both COMPANION and CARE-HF were the mortality was similar between both sexes (14, 51). Our findings may suggest that women have a better intrinsic prognosis and outcome after CRT. This highlights the importance of including women in randomized controlled studies where they are often under-represented.

Next, a difference in survival between ICM and DCM was demonstrated. Patients with DCM had a lower mortality rate. This was as well confirmed by Bagole *et al (46).* However, Wikstrom *et al.* compared in their study ischemic HF and non-ischemic HF in patients with a CRT and medical therapy. They concluded that patients with ischemic HF (both CRT and medical therapy) had similar mortality rates after CRT (52). Other randomized trials reported similar mortality rates from CRT for DCM and ICM patients (14, 47).

Hypertension was a risk factor that showed significant differences in survival. In the early stages after CRT implantation, hypertension is associated with a higher mortality. However, intriguingly after 8 years a cross-over occurred to demonstrate a better survival in patient with hypertension. The ability to generate a high blood pressure might at a certain point reflect the preservation of the functional capacity of the heart muscle and allow heart failure medication to be increased more profoundly to target doses.

Biton *et al.* stated that CRT has incremental clinical benefits in patients with lower baseline systolic blood pressure (SBP) values. Note that Biton did not make a difference between hypertension or not, but emphasizes the baseline SBP values. This study reported that patients with a SBP > 110 mmHg had a lower mortality rate compared to patients with a SBP between 110 and 136, and > 136 mmHg (53). These data eventually confirm the results of our study and a possible explanation for these differences is the increase of SBP caused by CRT (54).

Next to hypertension, the influence of diabetes mellitus was investigated. In contrast to many other trials, no difference in survival was seen in CRT patients with or without diabetes. Several studies stated that the mortality rate for patients with diabetes is higher than non-diabetic patients. (55). This could be explained by the poorer health conditions of these patients (having hypertension, more renal problems,..). However, a long-term study resulted in similar survival rates between diabetic and non-diabetic patients (56). An unambiguous conclusion cannot be formulated according to the outcome of diabetic patients.

AF patients are rarely included in randomized trials. In this study similar survival rates were seen for patients with a sinus rhythm and AF. One possible explanation is the high number of His-ablation performed by these patients. Indeed after His-ablation, the intrinsic own heart rate in AF patients is

blocked to allow the CRT device to control the HR at all times and to insure continuous biventricular pacing. Similar survival rates between AF and sinus rhythm were observed in several other studies (45, 57, 58). On the other hand, a randomized trial did not obtain benefits for this group of patients by implanting a CRT (59). AF patients could also be more represented in trials to gain better insights into the influence of AF on the outcome after CRT. These data suggest that sinus rhythm should not be a requisite to induce CRT.

Finally, the influence of heart rate was examined in two groups: HR > and < 60 bpm. The maximum heart rate in the group > 60 bpm was 100 bpm which is in the range of a normal heart rate of an adult. Mortality rate between patients with a HR > 60 bpm and < 60 bpm at rest were similar. These findings are in contrast with Laskey *et al.* They stated that a HR between 79 and 147 bpm had a lower survival than a HR between 33 and 67 bpm (60). Another HR trial in HF also showed a better survival at lower HR (61)

### 4.1.3 Type of device and device settings influence survival after CRT

Next, the emphasis was set on the lead-implantation-route and device settings. As expected, a higher survival rate was seen in patients with CRT-D. The great majority of patients received a CRT-D. This additional survival benefit of the cardiac internal defibrillator was also seen in the CARE-HF and COMPANION studies (51, 62). The fact that many of these patients die from arrhythmias earlier than from heart failure might explain this difference.

For the insertion method, endocardial versus epicardial, survival curves are overlapping over a ten-year period. Studies have been performed on the response to CRT between both groups, but about survival little is known (63, 64). It is important to realize that not every difference in response to CRT will have an impact on survival.

Biventricular pacing should ideally be present 100 % of the time to achieve the best effect and response on the CRT. However, our results did not show a significance difference between >95% and <95% of biventricular pacing. Limited data was available about the percentage of biventricular pacing in the study population, which might have resulted in differences that did not reach significance. A higher survival trend was seen in the >95% group. The exact cut-off percentage is not unambiguous: Hayes *et al.* already showed a difference of survival > < 98% whereas another study concluded that patients with biventricular pacing < 92% had a lower survival rate compared to patients that were biventricular paced <92% (65, 66).

A higher survival was seen in patients with a short AV sense interval (< 110 ms). Most of the patients had AV sense intervals <110 ms, but a number of patients had an AV sense interval of 120 ms or above. Ultrasound Doppler was used to optimize sensed and paced AV intervals. These adjusted AV settings

might improve response after CRT. No differences in mortality rate were seen for AV pace intervals > and < 150 ms. Additionally, other cut-off values were chosen (140 and 160 ms, data not shown), but survival stayed similar. These AV sense and pace intervals are optimized to avoid LV contraction before complete filling (67). The goal of this AV optimization is to increase LV diastolic filling time. This might allow left atrial pressures to increase only at higher heart rates and thus improve exercise capacity. AV optimization has shown to decrease the number of non-responders (68). However, their influence on survival after CRT has to our knowledge not yet been reported.

### 1.1.1 Endocardial LV lead placement has advantages over epicardial LV lead placement

Baseline ejection fraction were similar in both hospitals. However, after CRT implantation a significant increase of LVEF was seen in the Jessa patients with an mean increase of about 12 %. Imelda patients had an increase of 2.22%. This results in a significant difference in echo-responders without benefit on survival after ten years. A multi-variable analysis showed insertion method was the only parameter that had a significant effect on change in ejection fraction. Changes in echo measurements between hospitals are not likely to be the cause of this difference because of the similar baseline data. This may suggest that endocardial LV lead placement or patient tailored optimization of CRT parameters increases the LVEF much more than the epicardial LV lead placement and the absence of AV optimization. Ginks *et al.* concluded that endocardial LV lead pacing was superior to epicardial and had more benefits in cardiac hemodynamics (63). Another study revealed that endocardial LV lead placement resulted in a narrower QRS complexes after implantation (64). These effects may have an physiological explanation (69).

These findings may raise the question whether endocardial or epicardial LV lead placement should be preferred. However it remains difficult to explain why survival outcome after ten years, is not affected by a better LVEF.

## 4.2 PART II: Exercise capacity after CRT

Next to survival and LV function, the improvement of exercise capacity after CRT was investigated. One of the goals of this study was to gain more insights into which parameters influence exercise capacity after CRT. However, due to a very few patients that were eligible to CRT in the last months in Jessa, only a limited number could be included in this part of the study. Results will therefore have to be interpreted with caution.

The small sample size was not only the result of few patients that were eligible to an implantation but also the limited number of patients who could undergo an ergospirometry test (e.g. exclusion due to a knee replacement). It is important to mention that the patients in this study followed an exercise training program in ReGo after CRT implantation.

No significant differences of OUES and $VO_2$ max at the three time-points could be shown. This may indicate that the exercise capacity did not improve after two and four months, but again, the sample size is likely too small to draw a real conclusion. However, for OUES a small increase was seen after two months and a bigger increase after four months. This trend could suggest that in a bigger study population some real differences in exercise capacity would be seen. In a randomized controlled study it has been demonstrated that significant improvements are seen three months after CRT implantation (70). It is desirable to repeat this study with more patients to examine which parameters affect exercise capacity and whether it would significant improve after CRT.

# 5 Conclusion

The data obtained in this study have an added value to the comprehension of the outcome after CRT implantation. First of all, this study confirmed the advantages of CRT in two major heart centra in Belgium. No significant difference was reported between both hospitals, although they differ from insertion method and follow-up. However, differences were seen in change in ejection fraction and echo-responders by ultrasound echocardiography between the two hospitals. These differences may be a result of differences in insertion method of the LV lead and the follow-up (presence or absence of AV optimization). These findings may raise the question whether a specific LV lead placement should be preferred.

Furthermore, there was a significant higher survival in women and patients with non-ischemic dilated cardiomyopathy and without hypertension. These findings increases the knowledge about patient's chances to survive. Additionally, device type and device settings had an effect on survival of the patients. Gaining insights into which device settings are more preferable, it will allow more personalized therapy in a patient group with poor outcomes.

No real conclusion could be reported about the exercise capacity after CRT due to a too small sample size. But OUES tend to have an increase after two and four months which suggests that repeating this study design in a bigger study population will lead to real differences.

In the future more trials should be performed including the patient groups that are underrepresented to reflect the real-world CRT population. It would be desirable if patients of heart centers with differences in implantation methods and follow-up could be compared in survival and response after CRT to obtain the most preferable implantation method, follow-up and device settings.

# References


1. Besterman EMM. William Harvey and his discovery of the circulation of the blood. West Indian Medical Journal. 2004;53(6):425-6.
2. Skinner H. Coronary blood flow. Oxford Journals for Medicine & Health. 2005;5(2):4.
3. Gray H. Anatomy of the human body. Twentieth ed. Philadelphia: Lea & Febiger; 1918, 2000.
4. Fukuta H, Little WC. The cardiac cycle and the physiologic basis of left ventricular contraction, ejection, relaxation, and filling. Heart Fail Clin. 2008;4(1):1-11.
5. Yan GX, Lankipalli RS, Burke JF, Musco S, Kowey PR. Ventricular repolarization components on the electrocardiogram - Cellular basis and clinical significance. Journal of the American College of Cardiology. 2003;42(3):401-9.
6. Gezondheid AZe. Hart- en vaatziekten Brussels: Vlaamse Overheid; 2010 [Available from: https://www.zorg-en-gezondheid.be/Ziektes/Ziektelijst-A-Z/Hart--en-vaatziekten/.
7. Watson RDS, Gibbs CR, Lip GYH. ABC of heart failure - Clinical features and complications. British Medical Journal. 2000;320(7229):236-9.
8. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol. 2011;8(1):30-41.
9. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics-2015 Update A Report From the American Heart Association. Circulation. 2015;131(4):E29-E322.
10. Yusuf S. EFFECT OF ENALAPRIL ON SURVIVAL IN PATIENTS WITH REDUCED LEFT-VENTRICULAR EJECTION FRACTIONS AND CONGESTIVE-HEART-FAILURE. New England Journal of Medicine. 1991;325(5):293-302.
11. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. New England Journal of Medicine. 1996;334(21):1349-55.
12. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. New England Journal of Medicine. 1999;341(10):709-17.
13. Perry G, Brown E, Thornton R, Shiva T, Hubbard J, Reddy KR, et al. The effect of digoxin on mortality and morbidity in patients with heart failure. New England Journal of Medicine. 1997;336(8):525-33.
14. Cleland JGF, Daubert J, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. New England Journal of Medicine. 2005;352(15):1539-49.
15. Moynahan M, Faris OP, Lewis BM. Cardiac resynchronization devices - The food and drug administration's regulatory considerations. Journal of the American College of Cardiology. 2005;46(12):2325-8.
16. Jeevanantham V, Daubert JP, Zareba W. Cardiac resynchronization therapy in heart failure patients: An update. Cardiology Journal. 2009;16(3):197-209.
17. McAlister FA, Ezekowitz J, Hooton N, Ben V, Spooner C, Dryden DM, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction - A systematic review. Jama-Journal of the American Medical Association. 2007;297(22):2502-14.
18. Cazeau S, Ritter P, Jauvert G, Alonso C, Lazarus A. Cardiac resynchronization therapy: technical issues. European Heart Journal Supplements. 2003;5(I):83-7.
19. Freemantle N, Tharmanathan P, Calvert MJ, Abraham WT, Ghosh J, Cleland JGF. Cardiac resynchronisation for patients with heart failure due to left ventricular systolic dysfunction - a systematic review and meta-analysis. European Journal of Heart Failure. 2006;8(4):433-40.
20. Ypenburg C, Lancellotti P, Tops LF, Boersma E, Bleeker GB, Holman ER, et al. Mechanism of improvement in mitral regurgitation after cardiac resynchronization therapy. European Heart Journal. 2008;29(6):757-65.
21. Rajappan K. Permanent pacemaker implantation technique: part II. Heart. 2009;95(4):334-42.

22. Leclercq C, Kass DA. Retiming the failing heart: Principles and current clinical status of cardiac resynchronization. Journal of the American College of Cardiology. 2002;39(2):194-201.
23. Glikson M. Cardiac Resynchronization Therapy - How to Overcome High Left Ventricular Pacing Thresholds and Avoid Phrenic Nerve Stimulation HOSPITAL CHRONICLES. 2006:3.
24. Mair H, Jansens JL, Lattouf OM, Reichart B, Dabritz S. Epicardial lead implantation techniques for biventricular pacing via left lateral mini-thoracotomy, video-assisted thoracoscopy, and robotic approach. Heart Surgery Forum. 2003;6(5):412-7.
25. Auricchio A, Prinzen FW. Non-responders to cardiac resynchronization therapy: the magnitude of the problem and the issues. Circ J. 2011;75(3):521-7.
26. Killu AM, Wu JH, Friedman PA, Shen WK, Webster TL, Brooke KL, et al. Outcomes of cardiac resynchronization therapy in the elderly. Pacing Clin Electrophysiol. 2013;36(6):664-72.
27. Goldenberg I, Kutyifa V, Moss AJ. Survival with cardiac-resynchronization therapy. N Engl J Med. 2014;371(5):477-8.
28. Gorcsan J, Oyenuga O, Habib PJ, Tanaka H, Adelstein EC, Hara H, et al. Relationship of echocardiographic dyssynchrony to long-term survival after cardiac resynchronization therapy. Circulation. 2010;122(19):1910-8.
29. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol. 2008;52(23):1834-43.
30. Parthenakis FI, Patrianakos AP, Simantirakis EN, Vardas PE. CRT and exercise capacity the impact of mitral valve in heart failure: regurgitation. Europace. 2008;10:96-100.
31. Wasserman K, Whipp BJ, Davis JA. Respiratory physiology of exercise: metabolism, gas exchange, and ventilatory control. Int Rev Physiol. 1981;23:149-211.
32. Shimizu M, Myers J, Buchanan N, Walsh D, Kraemer M, McAuley P, et al. THE VENTILATORY THRESHOLD - METHOD, PROTOCOL, AND EVALUATOR AGREEMENT. American Heart Journal. 1991;122(2):509-16.
33. Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, Tauchi N, et al. Oxygen uptake efficiency slope: A new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. Journal of the American College of Cardiology. 1996;28(6):1567-72.
34. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: An index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. Journal of the American College of Cardiology. 2000;36(1):194-201.
35. Marinov B, Kostianev S. Exercise performance and oxygen uptake efficiency slope in obese children performing standardized exercise. Acta Physiol Pharmacol Bulg. 2003;27(2-3):59-64.
36. Van Laethem C, Bartunek J, Goethals M, Nellens P, Andries E, Vanderheyden M. Oxygen uptake efficiency slope, a new submaximal parameter in evaluating exercise capacity in chronic heart failure patients. American Heart Journal. 2005;149(1):175-80.
37. De Marco T, Wolfel E, Feldman AM, Lowes B, Higginbotham MB, Ghali JK, et al. Impact of cardiac resynchronization therapy on exercise performance, functional capacity, and quality of life in systolic heart failure with QRS prolongation: COMPANION trial sub-study. J Card Fail. 2008;14(1):9-18.
38. Mastenbroek MH, Sant JV, Versteeg H, Cramer MJ, Doevendans PA, Pedersen SS, et al. Relationship Between Reverse Remodeling and Cardiopulmonary Exercise Capacity in Heart Failure Patients Undergoing Cardiac Resynchronization Therapy. J Card Fail. 2015.
39. M.C. I, C. A, P. C, O. S, T. L, O. C, et al. Exercise training after cardiac resynchronization in chronic heart failure. Results of a pilot study. Paris, France: Cardiologia del Ejercicio - Sports Cardiology; 2003. p. 7.
40. Defoor J, Schepers D, Reybrouck T, Fagard R, Vanhees L. Oxygen uptake efficiency slope in coronary artery disease: clinical use and response to training. Int J Sports Med. 2006;27(9):730-7.

41. Hobbs FDR, Roalfe AK, Davis RC, Davies MK, Hare R, MidReC. Prognosis of all-cause heart failure and borderline left ventricular systolic dysfunction: 5 year mortality follow-up of the Echocardiographic Heart of England Screening Study (ECHOES). European Heart Journal. 2007;28(9):1128-34.
42. Taylor CJ, Roalfe AK, Iles R, Hobbs FDR. Ten-year prognosis of heart failure in the community: follow-up data from the Echocardiographic Heart of England Screening (ECHOES) study. European Journal of Heart Failure. 2012;14(2):176-84.
43. Kamireddy S, Agarwal SK, Adelstein E, Jain S, Saba S. Correlation of Electrical and Mechanical Reverse Remodeling after Cardiac Resynchronization Therapy. Annals of Noninvasive Electrocardiology. 2009;14(2):153-7.
44. Dickstein K, Bogale N, Priori S, Auricchio A, Cleland JG, Gitt A, et al. The European cardiac resynchronization therapy survey. European Heart Journal. 2009;30(20):2450-60.
45. Zabarovskaja S, Gadler F, Braunschweig F, Stahlberg M, Hornsten J, Linde C, et al. Women have better long-term prognosis than men after cardiac resynchronization therapy. Europace. 2012;14(8):1148-55.
46. Bogale N, Priori S, Cleland JGF, Brugada J, Linde C, Auricchio A, et al. The European CRT Survey: 1 year (9-15 months) follow-up results. European Journal of Heart Failure. 2012;14(1):61-73.
47. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events. New England Journal of Medicine. 2009;361(14):1329-38.
48. Gasparini M, Leclercq C, Yu CM, Auricchio A, Steinberg JS, Lamp B, et al. Absolute survival after cardiac resynchronization therapy according to baseline QRS duration: A multinational 10-year experience: Data from the Multicenter International CRT Study. American Heart Journal. 2014;167(2):203-+.
49. Ho KKL, Anderson KM, Kannel WB, Grossman W, Levy D. SURVIVAL AFTER THE ONSET OF CONGESTIVE-HEART-FAILURE IN FRAMINGHAM HEART-STUDY SUBJECTS. Circulation. 1993;88(1):107-15.
50. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KKL, et al. Long-term trends in the incidence of and survival with heart failure. New England Journal of Medicine. 2002;347(18):1397-402.
51. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. New England Journal of Medicine. 2004;350(21):2140-50.
52. Wikstrom G, Blomstrom-Lundqvist C, Andren B, Lonnerholm S, Blomstrom P, Freemantle N, et al. The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE-HF trial. European Heart Journal. 2009;30(7):782-8.
53. Biton Y, Moss AJ, Kutyifa V, Mathias A, Sherazi S, Zareba W, et al. Inverse Relationship of Blood Pressure to Long-Term Outcomes and Benefit of Cardiac Resynchronization Therapy in Patients With Mild Heart Failure A Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy Long-Term Follow-Up Substudy. Circulation-Heart Failure. 2015;8(5):921-6.
54. Ather S, Bangalore S, Vemuri S, Cao LB, Bozkurt B, Messerli FH. Trials on the Effect of Cardiac Resynchronization on Arterial Blood Pressure in Patients With Heart Failure. American Journal of Cardiology. 2011;107(4):561-8.
55. Sun JP, Chinchoy E, Perlic G, Popovic ZB, Li Z, Grimm RA, et al. Acute optimization of cardiac resynchronization therapy using novel echocardiographic indices: Optimization of A-V and V-V intervals. Circulation. 2003;108(17):7-.
56. Fantoni C, Regoli F, Ghanem A, Raffa S, Klersy C, Sorgente A, et al. Long-term outcome in diabetic heart failure patients treated with cardiac resynchronization therapy. European Journal of Heart Failure. 2008;10(3):298-307.
57. Auricchio A, Metra M, Gasparini M, Lamp B, Klersy C, Curnis A, et al. Long-term survival of patients with heart failure and ventricular conduction delay treated with cardiac resynchronization therapy. American Journal of Cardiology. 2007;99(2):232-8.

58. van Bommel RJ, Borleffs CJW, Ypenburg C, Marsan NA, Delgado V, Bertini M, et al. Morbidity and mortality in heart failure patients treated with cardiac resynchronization therapy: influence of pre-implantation characteristics on long-term outcome. European Heart Journal. 2010;31(22):2783-90.
59. Tang ASL, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Cardiac-Resynchronization Therapy for Mild-to-Moderate Heart Failure. New England Journal of Medicine. 2010;363(25):2385-95.
60. Laskey WK, Alomari I, Cox M, Schulte PJ, Zhao X, Hernandez AF, et al. Heart Rate at Hospital Discharge in Patients With Heart Failure Is Associated With Mortality and Rehospitalization. Journal of the American Heart Association. 2015;4(4).
61. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376(9744):875-85.
62. Yao GQ, Freemantle N, Calvert MJ, Bryan S, Daubert JC, Cleland JGF. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. European Heart Journal. 2007;28(1):42-51.
63. Ginks MR, Lambiase PD, Duckett SG, Bostock J, Chinchapatnam P, Rhode K, et al. A Simultaneous X-Ray/MRI and Noncontact Mapping Study of the Acute Hemodynamic Effect of Left Ventricular Endocardial and Epicardial Cardiac Resynchronization Therapy in Humans. Circulation-Heart Failure. 2011;4(2):170-9.
64. Garrigue S, Jais P, Espil G, Labeque JN, Hocini M, Shah DC, et al. Comparison of chronic biventricular pacing between epicardial and endocardial left ventricular stimulation using Doppler tissue imaging in patients with heart failure. American Journal of Cardiology. 2001;88(8):858-62.
65. Hayes DL, Boehmer JP, Day JD, Gilliam FR, Heidenreich PA, Seth M, et al. Cardiac resynchronization therapy and the relationship of percent biventricular pacing to symptoms and survival. Heart Rhythm. 2011;8(9):1469-75.
66. Koplan BA, Kaplan AJ, Weiner S, Jones PW, Seth M, Christman SA. Heart Failure Decompensation and All-Cause Mortality in Relation to Percent Biventricular Pacing in Patients With Heart Failure Is a Goal of 100% Biventricular Pacing Necessary? Journal of the American College of Cardiology. 2009;53(4):355-60.
67. Pastromas S, Manolis AS. Cardiac resynchronization therapy: Dire need for targeted left ventricular lead placement and optimal device programming. World J Cardiol. 2014;6(12):1270-7.
68. Mullens W, Kepa J, De Vusser P, Vercammen J, Rivero-Ayerza M, Wagner P, et al. Importance of Adjunctive Heart Failure Optimization Immediately After Implantation to Improve Long-Term Outcomes With Cardiac Resynchronization Therapy. American Journal of Cardiology. 2011;108(3):409-15.
69. Hyde ER, Behar JM, Claridge S, Jackson T, Lee AWC, Remme EW, et al. Beneficial Effect on Cardiac Resynchronization From Left Ventricular Endocardial Pacing Is Mediated by Early Access to High Conduction Velocity Tissue Electrophysiological Simulation Study. Circulation-Arrhythmia and Electrophysiology. 2015;8(5):1164-72.
70. Patwala AY, Woods PR, Sharp L, Goldspink DF, Tan LB, Wright DJ. Maximizing Patient Benefit From Cardiac Resynchronization Therapy With the Addition of Structured Exercise Training A Randomized Controlled Study. Journal of the American College of Cardiology. 2009;53(25):2332-9.

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