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Simplicity is key in CRT

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Summary

Heart failure (HF) is a clinical syndrome entailing symptoms like shortness of breath, decreased exercise tolerance, fatigue and ankle swelling. Despite huge progress in the treatment of HF in the last couple of decades annual mortality is 1 in 10 and hospitalization 1 in 3 patients. Furthermore, quality of life of these patients remains low. One of the abnormalities that contribute to development of HF is abnormal, slow conduction of the electrical impulse within the heart, which leads to ineffective cardiac contraction.

When electrical conduction is normal, the specialized conduction tissue in the heart ensures a rapid and synchronous electrical activation of the myocardial cells and an coordinated contraction of the ventricles. In about one in three HF patients a defect in the electrical conduction is present.

A specific therapy is available to treat the electrical dyssynchrony: cardiac resynchronization therapy (CRT). To this purpose, a biventricular pacemaker; with electrodes in the right and left ventricle, is implanted. Large, randomized trials have shown that CRT improves the electrical synchrony and cardiac contractility. As a consequence symptoms decrease and prognosis improves. However, the benefit of a patient from CRT varies considerably, ranging from complete resolution of HF to worsening of the disease.

This thesis describes research aiming to improve the outcome of CRT through two approaches:

1. Improve the selection of patients that should receive CRT
2. Improve the clinical management of patients that receive CRT

Part I: Patient selection

The most common tool for patient selection in CRT is the electrocardiogram (ECG). The presence of a conduction disorder results in an increase in the total activation time of the ventricles, expressed as a longer duration of the QRS-complex on the ECG. Indeed, QRS duration was the first ECG marker for selection of CRT patients. However, not all QRS prolongation indicates dyssynchrony amenable to CRT, for example delayed activation in the right, rather than the left ventricle, or prolongation caused by non-conductive scar. Around ten years ago the morphology of the QRS complex was shown to be associated to response in CRT. Multiple studies showed that in patients with left bundle branch block (LBBB), response to CRT was significantly better than in non-LBBB patients. Ever since, prevailing guidelines have adopted LBBB as the leading criterion for patient selection in CRT. However, like QRS duration, LBBB QRS morphology has its limitations. Importantly, there are several definitions of LBBB. Moreover, qualification of LBBB is rather subjective.

In the first part of this thesis we have evaluated LBBB as a patient selection criterion in CRT. For this purpose, we have evaluated four currently used LBBB definitions. Four researchers assessed one hundred baseline ECGs of patients who underwent CRT implantation, applying the exact LBBB definitions. Next to this, four experienced cardiologists assessed the same ECGs for LBBB based on their clinical judgement. Finally, two researchers and two cardiologists assessed the ECGs twice for intra-observer variability. When two different reviewers assessed the same ECG, there was a one in five chance of discordance. When comparing the use of exact definitions to assessment by experienced

cardiologists, 2 in 5 judgements were discordant. Assessment of the same ECGs twice by one reviewer showed a discordant assessment of 1 in 10 ECGs. Translating these results to clinical practice, this means that assessment of LBBB is subject to large variability either when using exact definitions or clinical assessment. Moreover clinical assessment shows a large discordance with the assessment according to definitions used in trials, which puts major concerns at the translatability of trial results to current clinical practice.

When major differences exist in the qualification of LBBB, it is of major importance that every available definition has the same significance in CRT. In collaboration with Cardiocentro Ticino, Lugano, we evaluated the effect of the presence of LBBB on the baseline ECG according to different ECG definitions, on outcome in a group of over 300 CRT patients. Outcomes were time to death, time to HF hospitalization and echocardiographic reverse remodelling. Results from this study showed that the presence of LBBB according to some definitions did, and according to others did not relate to prognosis in CRT. This finding may be of major importance to clinical practice, excluding commonly used LBBB definitions from a role of importance in CRT.

We sought to confirm this result in a larger population. In order to get access to a large population of CRT patients we collaborated with the university medical centres of Utrecht and Groningen to create a retrospective CRT database ('MUG': Maastricht-Utrecht-Groningen) including every CRT treated patient in the past 15 years, including almost 2.000 patients. In an analyses of 1.500 of these patients, we found that, in contrast to the earlier mentioned study, the presence of LBBB according to any definition identified patients with better prognosis than the respective non-LBBB CRT patients. On average the LBBB patients had a 40% increased chance of being alive without a cardiac assist devices or transplantation, after 3 years of follow-up. When the individual criteria composing the LBBB definitions were evaluated, it appeared that every LBBB definition contained criteria without any association to outcome. Moreover only 3 criteria were independently associated to outcome. Combining these criteria however, did not improve diagnostic performance of LBBB. These findings support the use of LBBB, what ever the definition.

Despite the evidence for the superior prognosis of CRT patients with LBBB at baseline compared to non-LBBB CRT patients, patients without LBBB can certainly experience benefit from CRT. Earlier studies have shown that amongst non-LBBB patients, there are patients profiting considerably from CRT, but also patients experiencing significant harm from CRT. Prevailing guidelines, therefore are not clear on how to treat this patient group. The heterogeneous response to CRT may be explained by the existence of true left ventricular dyssynchrony in part of these patients, but the absence of dyssynchrony in others. In the latter, CRT may introduce dyssynchrony rather than cure it. In order to further investigate this hypothesis, we conducted a study in 23 patients without LBBB QRS morphology present on their baseline ECG, eligible for CRT. During implantation of the CRT-device in these patients, we assessed the duration of the very first start of the electrical activation of the ventricles until the local activation at the left ventricular lateral wall (measured in any possible CS tributary vein available). After all, in LBBB patients it has been shown that the left ventricular lateral wall is the area of latest activation, and the presence of late activation of the left ventricular lateral wall is associated to the effectiveness of CRT (independently from the presence of LBBB). Our study showed that in one in two patients without LBBB, there is significantly delayed activation of the left ventricular lateral wall. However, none of the tested ECG parameters were able to identify those patients with delayed activation present.
Up until this point this thesis has focussed on the limitations of the major criterion for patient selection in CRT, concluding that although various available LBBB definitions all seem associated to prognosis in CRT patients, variability in assessment seems (too) large. Moreover, it does not seem that the 12-lead ECG is able to further refine

the identification of patients able to benefit from CRT. Therefore in this thesis we assessed an alternative for the currently recommended ECG criteria.

Even though 12-lead ECG markers have their limitations, the ECG is a real time display of the electrical activation of the heart, and available to every physician involved in CRT. The derived marker(s) need to take into account the direction of the electrical activation more than QRS duration, and need to be less sensitive to subjectivity and variability than LBBB QRS morphology.

Vectorcardiographic analyses display the heart's electrical activation in three main directions as a 'vectorloop', earlier studies have shown this instrument to be usefull in assessing eligibility for CRT. Our group has shown that a vectorloop can reliably be constructed from the standard 12-lead ECG, and that a simple parameter, QRS area, can be calculated using the area under the QRS complex in these three directions. Smaller studies have shown that baseline large QRS area is associated to a good prognosis in CRT patients.

In the earlier mentioned MUG database, we have analysed the association of QRS area to the occurrence of events in CRT treated patients. In this cohort, it appeared that QRS area significantly improved identification of patients with good and bad outcome to CRT compared to the recommended combination of QRS duration and LBBB. QRS area provided additive diagnostic value combined with classic ECG criteria. Moreover, QRS area appeared to be equally effective in the subgroup of patient with non-LBBB QRS morphology. From these results we concluded that QRS area could be a valuable addition, or even better, alternative to currently used criteria in prevailing guidelines for CRT. To further establish the value of QRS area in patient selection for CRT, our group will conduct an analyses of QRS area in one of the large randomized CRT-trial data, including CRT-treated and non-treated patients. Therefore QRS area can truly be established as a marker of amenability to CRT. Moreover, if the results presented in this thesis prove to be reproducible, QRS area will be established on the same level of evidence as the classic criteria, justifying consideration for guideline recommendation. Another future step will be the evaluation of fully automated calculation of QRS area, to increase availability up to the level of QRS duration and morphology.

Part II: Patient management

Care for HF patients treated with CRT is complex. It demands knowledge of HF disease management and device management of the treating physician. In clinical practice, however, these are subspecialties of different cardiologists. Therefore, in order to deliver optimal medical care, the fragile HF patient needs many consultations with different physicians and allied professionals. Some studies have shown that intensive and multidisciplinary follow-up care for CRT patients results in superior response to therapy, with better long term outcomes. However, taking into account the already vast burden on (local) health care systems, introducing such elaborate care processes does not seem sustainable on the long term. In order to tackle the issue of increasing health care burden, in general HF patient management, solutions have been suggested some time ago. Research has shown that substitution of specialist care by HF nurses is non-inferior. Thereafter, worldwide general HF clinics introduced nurse-lead HF clinics. Furthermore, checklists have proven to improve adherence with guidelines in HF care, subsequently leading to improved quality of care. None of the abovementioned interventions, have however found their way to present CRT practice.

In this thesis we describe the design and implementation of a care system which aims to optimize management of CRT patients in the sense of quality of care and governability in the future. Optimal quality of care is achieved by combining HF- and device knowledge into standardized checklists. Simultaneously making care for CRT patients efficient by standardizing and combining consultations and specialist-lead care. In order to achieve this, an international panel of physicians with extensive experience in CRT, and backgrounds in HF and device management, put together a consensus document. This document summarizes the minimal medical content of care system for CRT patients, to guarantee quality of care. This medical content is subscribed to different steps in CRT management; from patient selection to implantation of the device and follow-up thereafter. Quality of care is ensured by providing checklists relevant to each process step. Moreover efficient care was ensured by combining consultations and minimizing loss of information in the process. After designing a blueprint of the optimal care process, in 2014 we started implementing the CRT care pathway in the Maastricht University Medical Centre + (MUMC+). As process management in heath care is relatively new, the implementation was supervised by consultants specialized in lean process management, ensuring minimization of waste in the new process.. First step was the description of the current care process. Next to the evaluation of the minimal requirement for high quality of CRT care, determinants of efficient health care were evaluated. This showed that the CRT care process in the MUMC+ was high in quality, but inefficient, with a high burden for CRT patients, as well as the local health care system. In multiple phases the blueprint CRT care pathway was implemented to replace the old care process. This entailed reorganisation of planning and logistics, making recourses available and training of the healthcare professionals involved in the process. Unfortunately the final evaluation of the introduced CRT care pathway was not finished at the time this thesis was finished. However, for (inter)national symposia we have conducted multiple preliminary evaluations in small numbers of patients included up till then. These evaluations show important improvements in determinants of efficiency, including a clear reduction in consultations, referral-to-treatment times, and in-hospital days for implantation. Clinical outcomes like echocardiographic remodelling, patient reported HF complaints and HF hospitalization are non-inferior to the previous care process. However positive results on the identification of determinants of response to CRT and optimization of general HF treatment compared to the baseline assessment are encouraging for future evaluations of clinical outcomes in a larger group of patients. Moreover, individual patient and health care professional's comments over the years since implementation have been very positive.

In conclusion, the research presented in this thesis has shown that currently recommended aids in patient selection for CRT show low reproducibility and therefore add to the large diversity in patient response to CRT in clinical practice. Importantly, in this thesis we have shown that a large part of the patients that have a questionable indication for CRT according to current selection criteria, do show evidence of dyssynchrony amenable to CRT. The limitations laid bare for complex and subjective QRS morphology in this thesis, do not apply to the simple, quantitative QRS area. This new marker in CRT was shown to be strongly associated to outcome in CRT with better association than the currently recommended markers. The research in this thesis focussing on patient management in CRT presents a blueprint for efficient, multidisciplinary care that can be implemented in any HF clinic dealing with these patients, aiming for sustainable high quality of CRT care.