

Mapping and prevention of cardiac dyssynchrony

Citation for published version (APA):

Mafi Rad, M. (2016). *Mapping and prevention of cardiac dyssynchrony: towards better substrate identification and lead implantation*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20160916mm>

Document status and date:

Published: 01/01/2016

DOI:

[10.26481/dis.20160916mm](https://doi.org/10.26481/dis.20160916mm)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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Valorisation

At present, approximately 142.000 people in the Netherlands are suffering from heart failure. This has a great socio-economic impact on our society because heart failure leads to almost 30.000 hospital admissions and approximately 6800 deaths per year. The annual costs in 2011 were already estimated at 940 million euro's. The costs for the care of heart failure accounted for 11.4% of the total costs for cardiovascular disease and 1.1 % of the total health care costs in the Netherlands. It is estimated that the prevalence of heart failure will increase significantly in the coming years as a consequence of growth and ageing of the population, improved treatment and survival of patients with acute myocardial infarction and chronic coronary artery disease, and an increase in the prevalence of risk factors for heart failure such as diabetes and obesity.

A quarter to one-third of patients with heart failure has concomitant ventricular conduction abnormalities, most commonly due to a left bundle-branch block (LBBB). This conduction abnormality leads to a dyssynchronous electrical activation and contraction of the heart, which either causes or contributes to the left ventricular (LV) systolic dysfunction in these patients. The treatment of cardiac dyssynchrony has greatly improved with the advent of cardiac resynchronization therapy (CRT). This therapy improves the prognosis and reduces symptoms and the number of hospitalizations of patients with dyssynchronous heart failure. At present, approximately 3000 CRT pacemakers are implanted in the Netherlands each year. However, the issue remains that one-third to half of patients that receive a CRT pacemaker do not benefit from this therapy. This lack of response is not desirable for a treatment which involves a relatively expensive therapy and requires essentially irreversible implantation of a device and leads with potential risk of complications such as lead dislocations and infections. Improving identification of patients likely to benefit from this therapy and optimizing therapy delivery by better lead positioning are of utmost importance to improve the response rate of CRT.

In this thesis, a novel method of epicardial electroanatomic mapping (EAM) via the coronary veins was developed that can be used at the time of CRT implantation to determine the electrical activation sequence of the heart in patients with systolic heart failure and prolonged QRS duration. This new technique can be used to identify patients with delayed LV activation (the primary electrical substrate for CRT), who are more likely to benefit from CRT, and to target the LV lead to the latest activated region, a lead placement strategy that has been associated with improved outcome of CRT. This new coronary venous mapping technique provides detailed information on LV electrical activation without increasing the invasiveness of the CRT implantation procedure and at only minimal prolongation of procedure time. It therefore provides a middle ground between previously used mapping methods such as complete invasive endocardial EAM which is time-consuming and not without risk and simple electrical mapping with the LV lead, which provides only limited information on LV electrical activation. The results of this thesis suggest that coronary venous EAM has the potential to improve identification of patients likely to benefit from CRT and optimize therapy delivery by improving lead placement, thereby increasing the response rate to this therapy. Future studies are required to evaluate the actual impact of coronary venous EAM-guided patient selection and LV lead placement on CRT outcome and to assess the cost-effectiveness of this approach.

The data derived from coronary venous EAM were also used to demonstrate the potential of a relatively easy and noninvasive approach to identify patients with an appropriate electrical substrate for CRT using the area of the QRS complex (QRS_{AREA}) on the vectorcardiogram (VCG). At present, the key clinical markers to detect and evaluate the extent of LV activation delay remain the QRS duration and LBBB morphology on the surface electrocardiogram (ECG). Yet, QRS duration is a reflection of total ventricular activation and therefore not a reliable marker of delayed LV activation. Thus patient selection based on QRS duration alone will most likely

result in a substantial number of patients receiving a CRT device without deriving any detectable benefit. Classification of QRS morphology (LBBB or not) faces the problem of being operator dependent due to the presence of different LBBB definitions in the literature and the subjective interpretation of QRS notching and slurring. In addition, the refined LBBB definition is highly specific for delayed LV activation, but lacks sufficient sensitivity. As a consequence, a substantial number of patients that have delayed LV activation are not identified as such, and in these patients, CRT may be withheld erroneously. The present thesis demonstrates that vectorcardiographic QRS_{AREA} identifies delayed LV activation better than the conventional electrical markers QRS duration and LBBB morphology. The great practical benefit of QRS_{AREA} is that this parameter is measured in an objective manner and quantified as a continuous variable, as opposed to LBBB, which is a dichotomous measurement that is subject to the use of different definitions and subjective interpretations. Another practical feature of QRS_{AREA} is that it can be easily derived from the standard 12-lead ECG since most commercially available ECG machines have algorithms to construct VCGs from standard 12-lead ECGs. The simple and non-invasive nature of VCG analysis combined with the excellent diagnostic performance of QRS_{AREA} for delayed LV activation implies that this parameter can be easily used in clinical practice to identify appropriate CRT candidates before CRT implantation. This may potentially improve the response to this therapy and prevent ineffective and costly CRT device implantations with potential risk of complications. In addition, it may allow application of CRT in a substantial number of patients to whom treatment is currently wrongfully denied based on current guideline criteria.

A second topic in this thesis is the prevention of cardiac dyssynchrony, as caused by right ventricular (RV) pacing. Cardiac dyssynchrony is not only observed in patients with conduction disorders but also in patients receiving RV pacing because of symptomatic bradycardia. At present, approximately 8000 patients in the Netherlands are implanted with a pacemaker for anti-bradycardia treatment each year. Especially in patients with pre-existent impaired LV pump function, pacing-induced dyssynchrony can cause further deterioration of pump function and increase the risk of heart failure. Several studies have suggested that an upgrade of RV pacing to biventricular pacing or de novo implantation of a biventricular device in patients with atrio-ventricular block and reduced ejection fraction reverses or prevents pacing-induced dyssynchrony and further deterioration of cardiac function. Yet, the benefit of biventricular pacing comes at the expense of a more complex and time-consuming procedure, a higher rate of complications, failed implantations with the consequent need for re-operation, a shorter battery life and additional costs.

In this thesis, a first-in-man study was performed on the use of LV septal pacing for antibradycardia treatment, in order to prevent RV pacing-induced dyssynchrony. The feasibility of permanently implanting an LV septal lead using a transvenous approach through the interventricular septum has previously only been demonstrated in animal experimental studies. These animal studies showed that LV septal pacing leads to a more physiological sequence of left ventricular electrical activation and contraction. In this thesis, the results of the previous animal studies were translated into clinical practice by demonstrating the feasibility and safety of permanently implanting an LV septal lead using a transvenous approach through the interventricular septum in a cohort of 10 patients. Similar to the pre-clinical findings, the study showed that LV septal pacing induces less electrical dyssynchrony and provides acute hemodynamic benefit as compared to conventional RV apex pacing. These results suggest that this new pacing method could serve as a better alternative for RV apex pacing in patients with a conventional indication for antibradycardia pacing. If clinical experience with the

trans-interventricular septal lead placement approach turns out to be positive and if subsequent larger and prospective studies indicate that the acute hemodynamic benefit of LV septal pacing translates into preservation of LV pump function on the longer term, the LV septum may become the preferred site for anti-bradycardia pacing. This may reduce the number of patients that develop heart failure due to pacing-induced dyssynchrony. In addition, the study results suggest that LV septal pacing could serve as an easier, less complication- and failure-sensitive and more cost-effective alternative for biventricular pacing to prevent pacing induced-dyssynchrony in patients requiring pacing because of symptomatic bradycardia.

Another possible application of LV septal pacing might be CRT. Recent research has shown that pacing at the LV septum, also decreases electrical dyssynchrony and accordingly improves LV systolic function to a similar degree as conventional biventricular pacing in canine hearts with LBBB and heart failure patient with LBBB. The beneficial effects of LV septal pacing in dyssynchronous hearts and the promising results of permanent LV septal lead implantation via the trans-interventricular septal route demonstrated in the present thesis suggest that LV septal pacing could become an equal alternative for biventricular pacing in CRT. Yet, compared with biventricular pacing, this approach would allow CRT to be performed using a single ventricular lead in combination with a simpler 2-chamber pacemaker, thereby reducing the complication rate as well as implantation costs and prolonging battery life. Yet, this requires further investigation in preferably large randomized controlled trials that directly compare LV septal pacing and biventricular pacing with regard to long-term effect on left ventricular pump function, clinical outcome with particular focus on complication- and re-operation rates, and cost-effectiveness.

In conclusion, the research performed in this thesis could lead to improvement of the treatment and prevention of cardiac dyssynchrony. This may reduce death and morbidity due to dyssynchronous heart failure and the health care costs associated with this disease.