

Something old, something new

Citation for published version (APA):

Engels, E. B. (2016). *Something old, something new: vectorcardiographic loop size and response to cardiac resynchronization therapy*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20161019ee>

Document status and date:

Published: 01/01/2016

DOI:

[10.26481/dis.20161019ee](https://doi.org/10.26481/dis.20161019ee)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Valorization

In the Netherlands, approximately 150,000 people suffer from heart failure (HF). Annually approximately 7000 patients die due to HF and there are around 30,000 HF hospitalizations.¹ These hospital admissions and treatment of patients with severe symptoms are associated with high costs. In 2007 the costs for HF amounted 455 million euros, of which 60% was due to hospitalizations.

In approximately 25% of all HF patients², the electrical conduction pattern is disturbed leading to a dyssynchronous electrical activation and contraction of the right and left ventricle (LV), resulting in a reduced pump function. In 2001 a new therapy was approved by the FDA, cardiac resynchronization therapy (CRT), which aims to resynchronize the right and left ventricle leading to a better pump function of the heart. In the last few years, the CRT implantation rate was >2000/year in the Netherlands alone.³ CRT has been shown to improve cardiac pump function and quality of life, and reduce HF symptoms, hospitalization, and mortality at the population level.⁴ However, benefits at the individual level vary considerably. On the one hand, ~20% of patients that are implanted according to current guidelines^{5,6} show complete normalization of LVEF whereas a significant portion (30-50%) of patients benefit little from this therapy.⁷ Such lack of response is especially undesirable since CRT requires the implantation of a costly device during an invasive procedure. Improved patient selection and optimal programming of the CRT device could lead to a higher response rate to CRT.

Improving patient selection

In this thesis it was shown that the baseline value of QRS_{area} and T_{area} , both indices derived from the vectorcardiogram (VCG), are good predictors of response to CRT. They perform better than the established criteria QRS duration and certain LBBB criteria. Patients with a higher baseline value of QRS_{area} or T_{area} have a higher change of CRT response, making both variables good measures to improve patient selection for CRT. The advantage of these measures is that they are easily obtained and widely applicable.

As was pointed out in **chapter 3** it is justified to synthesize a VCG from a 12-lead electrocardiogram (ECG) using the Kors matrix. This conversion can be applied to almost any 12-lead ECG, with the only requirement being that either a common running lead or a common reference point, such as a pacing artefact, must be present. Ideally, the ECGs are stored

digitally but semi-digital ECGs as stored in a pdf-file or even paper ECGs could also be used to calculate the QRS_{area} and T_{area} . As we described in this thesis, the pdf-files contain vector-graphics that embed the digital information of the displayed ECG. The digital information can thus be extracted, making it possible to synthesize a VCG and calculate the QRS_{area} and T_{area} . For scanned ECGs, the program ECGscan (AMPS LLC, New York, NY, USA) can be used to digitize the ECGs. This enables retrospective as well as prospective VCG analysis of routinely recorded 12-lead ECGs in large patient populations.

VCG indices like QRS_{area} and T_{area} can also be calculated in a prospective manner. Most commercially available ECG machines already have algorithms to construct a VCG from standard 12-lead ECGs and the beginning and ending of the QRS complex and T-wave are often indicated. The excellent predictive power of QRS_{area} and T_{area} for CRT response indicates that these parameters deserve to be applied more frequently in clinical practice to identify appropriate candidates for CRT.

Furthermore, if the predictive power of these VCG indices is proven in larger clinical trials, they may be included in the official guidelines as a selection criterion for CRT implantation. The present thesis provides important supportive data for this introduction.

Optimal programming of the CRT device

Beside optimal patient selection, optimal programming of the CRT device settings can also play an important role in increasing the response rate to CRT. Currently, all available tools to optimize CRT device settings are time-consuming and/or subject to noise, leading to the use of the ‘out-of-the-box’ default settings by a vast majority of cardiologists. Furthermore, the optimization can often only be performed during in-hospital visits, while the optimal setting might change over time or during different levels of activity.

CRT is often employed by pacing both the right and left ventricle of the heart (biventricular [BiV] pacing). However, several acute⁸ and chronic⁹ studies have demonstrated that in patients with sinus rhythm and intact AV conduction, LV-only pacing can be at least as effective as BiV pacing. CRT using LV-only pacing has been shown to be most effective when the paced LV impulse is properly timed with respect to the intrinsic activation of the right ventricle (RV), ensuring appropriate fusion with intrinsically conducted activation wave fronts. In **chapter 8** of this thesis, we showed that using either the normal VCG or an electrogram (EGM) based VCG (EGM-VCG) that can be extracted from the EGM signals measured from the unused implanted electrodes, this exact optimal timing can easily be found. The point at which the maximal QRS vector amplitude changes or flips direction was equal to the onset of intrinsic activation of the RV.

A few years ago, the ADAPTIVECRT™ (trademark of Medtronic, Inc.) algorithm has been developed that switches between BiV pacing and LV only pacing depending on con-

duction measurements.¹⁰ When LV only pacing is applied, the ADAPTIVECRT™ algorithm aims to perform fusion pacing which estimates the delay between atrial activation and intrinsic RV activation (A-RV) based on an average, general relation. With the VCG or EGM-VCG the A-RV can be determined individually, making it more precise. It does so by obtaining information during LV-only pacing at different AV-delays, while the ADAPTIVECRT™ estimates A-RV using measurements performed when CRT is turned off. Furthermore, the VCG and EGM-VCG methods are more robust than the ADAPTIVECRT™ algorithm since they are independent of the exact position of the RV lead and of LV latency. Therefore, the ADAPTIVECRT™ algorithm could be improved by using the VCG or EGM-VCG to find the exact A-RV. The idea of using the VCG or EGM-VCG to find the exact A-RV and using it to individualize the ADAPTIVECRT™ algorithm is already part of a patent application in collaboration with Medtronic, Inc. To do so, there are two options. First, a single determination of A-RV, at time of implant or shortly after, could be performed using the regular ECG from which a VCG and subsequently the maximal QRS vector amplitude can be calculated. The exact difference in timing between A-RV_{sense}, the delay between atrial activation and the moment of sensing of activation on the RV lead, and A-RV can be programmed in the device instead of the estimated difference relation used in the current ADAPTIVECRT™ algorithm. This would only require adding the constant delay to the algorithm. A second option would be to extract the A-RV from the EGM-VCG. The algorithm needed to find A-RV can be embedded in the CRT device, making automatic and continuous optimization possible. Again, the difference between A-RV_{sense} and A-RV can be determined every few days, and the ADAPTIVECRT™ algorithm can perform its usual continuous optimization with this timing difference embedded.

The methods proposed here can be used to objectively and easily tailor the ADAPTIVECRT™ algorithm, possibly leading to a further increase in hemodynamic response by CRT. It does so without spending additional current, purely by optimizing fusion pacing, which benefits from the natural activation of the RV. Because of the high potential of the VCG or EGM-VCG to improve the ADAPTIVECRT™ algorithm, this idea was patented together with Medtronic, Inc.

Conclusion

The findings of this thesis provide valuable tools to improve patient selection for CRT and CRT device optimization, which have been derived from extensive basic and clinical research prior to and during this thesis. These tools can be easily embedded in already existing systems, either ECG machines or devices. Therefore, findings from the present study may well have significant practical implications.

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