Branching out

Impact

The main goal of this thesis was to investigate aspects of cardiac resynchronization therapy (CRT) that have not yet been studied in detail. To this end we examined the effects of CRT on ventricular repolarization, as well as the use of this therapy in the context of structural mitral regurgitation (MR) and congenital heart disease.

Scientific impact

Relatively little is known about changes in the course of repolarization in the context of CRT. Our data provide new information in this area. Note that impulse conduction has attracted most attention in the field of CRT (assessed using the electrocardiogram (ECG) or mapping techniques), but that the processes related to conduction of the depolarization wave are relatively simple. In contrast, myocardial repolarization is an extremely complex process involving multiple ion channels, some of which (e.g. calcium channels) are also related to cardiac contraction. The finding that relatively simple measurements using the (ECG-based) vectorcardiogram provide novel information about repolarization dispersion, in particular during brief interruption of CRT, may open the door to further scientific studies on repolarization processes in the field.

These ECG-based repolarization investigations may be supported by patient-specific modelling. In **chapter 3** an example of such an approach has been given. The full ECG (QRS complex and T wave) of a patient before start of CRT was fitted to a combined cardiac and thoracic geometrical model with ventricular conduction modelled using the Eikonal approach and simulated ECG based on the lead-field theory. Repeating this approach in a larger cohort may show differences between patients in the pre-CRT repolarization pattern.

The model was also capable of reproducing clinically observed T waves after medium-term follow-up. The change in T wave between the situation before initiation of CRT and after medium-term treatment could be explained by assuming a relation between the change in local activation time (AT) after CRT and the change in local action potential duration (APD) (ΔAT – ΔAPD relation). Repeating these exercises in a larger cohort may provide evidence for interindividual differences in electrophysiological adaptations of the ventricles after CRT that may relate to response to this treatment. The latter studies may be refined by applying locally different ΔAT – ΔAPD relations and by including scar in the model.

On the other hand, the lack of full understanding of the mechanisms of repolarization remodelling calls for more basic scientific studies. These could include electrophysiological

measurements in cardiomyocytes that underwent long-term stretching. Another approach can be to use computer models with direct coupling of electrophysiological and mechanical properties[1].

Clinical impact

Although the studies we performed either involved animals or relatively small numbers of patients, we hope they may be a starting point for new inquiries. One could, for example, study the link between repolarization remodelling and echocardiographic response in a larger population, and also investigate whether there may be a correlation with clinical benefit. The use of more detailed techniques to assess repolarization (e.g. ECG imaging) could be useful in this context. From a functional perspective, it also makes sense to further investigate whether remodelling of repolarization leads to better relaxation with longer-lasting CRT.

In the long term, a better understanding of the different conditions where CRT may be beneficial would be useful. If it were to be proven effective in right bundle branch block, for example, a potentially successful application in larger numbers of patients could be realized.

If repolarization remodelling would prove to be linked to clinical outcome, the relatively short time scale at which repolarization remodelling occurs (approximately 2 weeks) could enable faster fine-tuning of CRT settings, potentially improving its therapeutic effect.

Finally, our findings may contribute to a better understanding of how CRT impacts the heart. This, in turn, may help to find ways to further increase CRT efficacy, which may be advantageous since approximately one third of patients who receive this therapy do not respond[2]. If the mechanism or signalling pathway behind the potential link between electrical and mechanical remodelling were to be elucidated, this might serve as a target for drug development. Enhancing the response to CRT by influencing this electromechanical link could hopefully lead to further improvements in treating cardiac dyssynchrony.

References

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2. Daubert JC, Saxon L, Adamson PB, Auricchio A, Berger RD, Beshai JF, *et al.* 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: Implant and follow-up recommendations and management. *Europace* 2012;**14**:1236–86.