Branching out

Summary

Normal activation of the cardiac ventricles comes about through a specialized, high-velocity conduction system. The first part of this system is the His bundle, which consists of a left and a right bundle branch. Conduction through these branches enables synchronized and fast activation of both left and right ventricles (LV and RV, respectively).

If one of the bundle branches is damaged, left bundle branch block (LBBB) or right bundle branch block (RBBB) occurs, and activation of the affected ventricle has to come about by means of slower conduction through the working myocardium. For this reason, activation and contraction of the affected ventricle (and in particular, its free wall) are delayed.

Over time, this activation pattern has multiple adverse consequences for the myocardium at the molecular and cellular level (e.g. changes to ion channels related to depolarization and repolarization) and at the organ level (e.g. asymmetric hypertrophy and cardiac dilatation). Progression of all these events leads to worsened cardiac function and more severe conduction delay, starting a vicious circle that can culminate in heart failure.

Cardiac resynchronization therapy (CRT) may reverse this vicious circle. This treatment involves implanting a pacemaker and placing electrodes in the right atrium and in both LV and RV. Resynchronisation through (almost) simultaneous stimulation of both ventricles can cause both acute and long-term improvements in cardiac function, which in turn lead to lower risk of heart failure hospitalisations and death, in particular in patients with heart failure and LBBB.

However, several aspects of this treatment are less well understood. First of all, while the effects of CRT on cardiac depolarization have been studied in considerable detail, much less is known about the effects of CRT on repolarization. Furthermore, much is yet to be learned about the efficacy of CRT in the context of structural heart disease, such as mitral regurgitation (MR) or congenital heart disease. The aim of the research described in this thesis was to branch out into these territories, hopefully yielding deeper understanding of the effects and potential applications of CRT.

Repolarization remodelling during CRT

Several studies have found that CRT may affect cardiac repolarization. This effect of CRT is particularly important since dispersion of repolarization has been linked to a higher risk of

cardiac arrhythmias. However, until now, the time course of repolarization remodelling after CRT has not been studied in detail, nor has the relation with contractile remodelling been elucidated.

In **chapter 3** we explored the effects of CRT on repolarization by measuring T wave morphology changes after CRT, by relating these changes to mechanical remodelling and by interpreting these results using a patient-specific computational model. We found that changes in repolarization parameters (such as T wave area) already reached a plateau within 5 to 14 days after initiation of CRT. However, some parameters showed contradicting results, which may be explained by the different aspects of repolarization represented by these parameters. Left ventricular ejection fraction and systolic septal strain increased between 2 weeks and 6 months of CRT, suggesting that electrical changes precede mechanical changes.

The observed changes in the T wave were largely reproduced in a patient-specific computer model that assumed an inverse relation between CRT-induced change in activation time and adaptation in action potential duration. The latter changes resulted in a reduction in dispersion of repolarization during chronic CRT as compared to acute CRT.

A more detailed investigation of the link between repolarization remodelling and functional improvement following CRT is described in **chapter 4**. We analysed vectorcardiograms from 76 patients, both prior to the start of CRT and after six months of treatment. Then, we stratified the patients into two subgroups: those with a T area change smaller (LOW, indicative of relatively little repolarization remodelling) and larger (HIGH, indicative of more repolarization remodelling) than the median T area change. At baseline, the groups demonstrated comparable vectorcardiographic (e.g. QRS and T area) and clinical characteristics. After 6 months, most repolarization parameters were still comparable between the groups, except for T area and amplitude. Patients in the HIGH subgroup showed a larger increase in left ventricular ejection fraction than those in the LOW subgroup, suggesting a link between repolarization remodelling and mechanical changes. However, arrhythmia incidence was low and did not differ between the subgroups. Larger studies are required to confirm the link between T area and left ventricular ejection fraction, and to explore whether there is also a link between repolarization remodelling and clinical improvement or arrhythmia incidence.

CRT during MR

CRT may beneficially impact MR during ventricular dyssynchrony through several mechanisms. For example, resynchronization of contraction leads to faster build-up of pressure, while resynchronization of the papillary muscles may result in improved positioning of the valve

leaflets. While both short-term and long-term effects of CRT during MR have been reported, it is not yet clear whether CRT can also be beneficial during structural MR, i.e. MR that is not due to dyssynchrony but due to damage to the mitral valve apparatus. Moreover, it is not known which pacing mode would be most beneficial in this context.

In **chapter 5** we explored this topic using an animal model of chronic LBBB+MR. We compared these animals with a control group of animals with only LBBB. Over time, echocardiographic and haemodynamic measurements indicated that LV end-diastolic volume was significantly larger in MR+LBBB dogs than in LBBB animals, while LV end-diastolic pressure also tended to be higher in the former. Therefore, the MR+LBBB model represents a dilated, dyssynchronous cardiomyopathy with MR.

After 16 weeks of LBBB, haemodynamic measurements were performed during three pacing modes: biventricular (BiV) pacing, LV pacing with a short atrioventricular (AV) delay (LV_{short}) and LV pacing with an AV delay aimed at fusion with intrinsic activation (LV_{fusion}). All pacing modes significantly increased the maximum rate of LV pressure rise ($LVdP/dt_{max}$) in the LBBB dogs. In the MR+LBBB group BiV pacing tended to increase $LVdP/dt_{max}$ and significantly reduced LV end-diastolic pressure. The different pacing modes had comparable effects.

These data suggest that CRT can be beneficial in LBBB even in the context of structural MR. However, extrapolating results from acute animal studies to long-term clinical effect should be done with care, especially since we did not measure forward blood flow into the aorta.

Conduction properties in patients with repaired Tetralogy of Fallot

In addition to its beneficial effects on the LV in LBBB, CRT has also been explored in patients with RBBB. A particular situation in which this has been attempted is after surgical repair of Tetralogy of Fallot (ToF), a type of congenital heart disease.

In patients with ToF, a potentially life-threatening combination of abnormalities is present in the heart. Very often, surgery is performed within the first year of life to repair these defects. The complicated repair surgery can lead to RBBB, while pressure and volume overload of the RV may also be present postoperatively.

Patients with repaired ToF (rToF) show both mechanical and electrical dyssynchrony. This suggests that resynchronization of the RV could be beneficial. RBBB is an obvious candidate cause of this dyssynchrony. However, fibrosis due to the combined pressure/volume overload

or due to surgical scars may also play a role. The distinction between these causes of dyssynchrony is important, since the presence of fibrotic tissue may preclude successful resynchronization through CRT.

In **chapter 6** we investigated the cause of cardiac conduction delays in patients with rToF by analysing electrical mapping data that was recorded at Toronto General Hospital. During medically indicated cardiac surgery, more than two decades after ToF repair surgery, cardiac electrical activation was recorded both during sinus rhythm and during ventricular pacing. Thirteen patients with rToF were mapped using an endocardial RV balloon array. Epicardial mapping was performed in 4 of these patients, and also in 2 patients with LBBB and 2 patients without either LBBB or RBBB (non-BBB). We found that structural lines of block were rare in patients with rToF and that pacing did not increase dispersion of endocardial and epicardial activation of the RV free wall. Moreover, epicardial activation dispersion in both ventricles during pacing was quite comparable for all three groups. This suggests that myocardial conduction properties in rToF patients do not preclude successful resynchronization through CRT.

Conclusions

Our results indicate that repolarization remodelling after start of CRT occurs rapidly (within 5-14 days) and, based on simulations in a patient-specific computational model, leads to lower dispersion of repolarization. Additionally, more repolarization remodelling may be linked to a better echocardiographic response to CRT.

We also found evidence that CRT still increases LV pump function in the presence of structural MR, even though CRT most likely does not directly influence this kind of MR.

Finally, our studies show that structural conduction blocks are rare in patients with rToF and that tissue properties of the right ventricular free wall are comparable between rToF patients and LBBB or non-BBB patients.