Pacing the heart

Summary

Under physiological conditions, biventricular depolarization occurs fast and synchronous. In particular, the synchronicity is key in maintaining (lifelong) normal cardiac pump function. In case of disease of the cardiac conduction system this synchronicity can be impaired causing decline in function, adverse structural remodeling and increased risk of heart failure. In order to either counter symptoms or to prevent heart failure, patients with conduction system disease can be treated with pacemaker therapy. The most commonly applied technique is right ventricular (RV) apex pacing, since this particular location is easily accessible and safe. Unfortunately, in some patients this RV (apex) pacing induces adverse remodeling and heart failure. In search of preventing these pacing induced negative effects different pacing strategies have been applied.

Chapter 2 describes how the adverse effects of ventricular dyssynchrony induced by RV pacing has led to alternative pacing strategies, such as biventricular (BVP), His bundle (HBP), LV septal (LVSP) and left bundle branch pacing (LBBP). Although among these alternative pacing sites HBP is theoretically the ideal strategy as it comes closest to a physiologic ventricular activation, its application requires more skills and is associated with the most complications. In LVSP and LBBP, commonly referred to as LBBAP, where the ventricular pacing lead is advanced through the interventricular septum to its left side, creates ventricular activation that is only slightly more dyssynchronous. LBBAP related research is rapidly expanding and studies have shown that LBBAP is feasible, safe and encounters less limitations than HBP.

The acute electrophysiological and hemodynamic effects of multi-LV pacing were investigated in a preclinical study that is described in **chapter 3**. As shown in chapter 2, one way of preventing RV pacing induced adverse outcome, is combining RV pacing with LV pacing, also referred to as BVP. To further improve the response rate to BVP, multi-LV pacing (or tri-ventricular pacing) was proposed. Only a small number of clinical trials investigating multi-LV pacing have been conducted with conflicting results. **Chapter 3** provides insight into the question whether capturing a larger LV tissue area by pacing multiple electrodes provides better resynchronization compared to RV and conventional BVP and, as a consequence, cardiac function. Results show that different types of multi-LV pacing create a similar degree of electrical resynchronization and hemodynamic effect, which are larger if interelectrode distance is large. However, multi-LV pacing only increases the benefit of conventional BVP if the LV lead used for BVP provides poor response.

Chapter 4 presents a comprehensive review on the physiology and the practicality of LVSP. In this review, we describe how animal studies as well as patient studies have demonstrated that LV function is maintained during LVSP at levels comparable to sinus rhythm with normal conduction. Left ventricular activation, however, is more synchronous during LBBP compared to LVSP, but LBBP produces a higher level of intraventricular dyssynchrony compared to LVSP. An important practical consideration: while LVSP is fairly straight-forward to perform, targeting the left bundle branch area may be more challenging.

In **chapter 5**, the safety and feasibility of LBBAP is described in the first 80 patients implanted with this technique in The Netherlands (Maastricht University Medical Center+). Results demonstrate that LBBAP is a safe and feasible technique (success rate 96%), with a clear learning curve that seems to flatten after 40-60 implantations. Capture of the left conduction system is obtained in two-thirds of patients. Compared to RVSP, LBBAP largely maintains ventricular electrical synchrony to values close to intrinsic (narrow QRS) rhythm.

In **chapter 6**, we combined our local registry with other experienced centers forming the largest registry-based observational study that included patients in whom LBBAP device implantation was attempted at 14 European centers, for any indication. The study comprised over 2500 patients and LBBAP lead implantation success rate for bradyarrhythmia and heart failure indications was 92.4% and 82.2%, respectively. Independent predictors of LBBAP lead implantation failure were heart failure, broad baseline QRS and left ventricular end-diastolic diameter. The predominant LBBAP capture type was left bundle fascicular capture (70%). The results show that safety and success rate in heart failure patients need to be improved.

After extensively have demonstrated safety and efficacy, in **chapter** 7 the electrical ventricular synchrony is directly compared between direct LBBP and LVSP in a multi-center population. ECG and VCG indices demonstrate that both LVSP and LBBP improve ventricular dyssynchrony considerably as compared to RVSP, to values close to normal ventricular activation. LBBP results in a small, but significant, improvement in ventricular synchrony as compared to LVSP.

In **chapter 8**, the design and the preliminary results of the first ten patients are described of the MASTER-LV trial (***M****echA****n****i****S****tic insigh****T****s in l****E****ft bundle b****R****anch and* ***L****eft* ***V****entricular septal pacing*). This trial was designed to evaluate acute hemodynamic and electrical effects of deep septal pacing with (LBBP) and without (LVSP) direct stimulation of the left bundle branch. In patients with different permanent pacemaker indications, a more synchronous ventricular activation during pacing can be achieved by both LVSP and

LBBP compared to RV pacing. Preliminary results show that differences in the acute hemodynamic effect of RV pacing and LBBAP are small. There seems to be a trend towards a slightly higher systolic blood pressure during LVSP and non-selective LBBP.