Pacing the heart

Impact

Since the experiments of Galvani in the second half of the 18th century and the development of the pacemaker in the 1950s, pacemaker implantation is an increasingly common technique in cardiology. In the Netherlands, between 10,000 and 15,000 pacemakers are implanted each year. Pacemakers are used in treatment of patients suffering from bradycardia and patients with heart failure and disorders of the heart's natural, rapid conduction system. Especially heart failure takes a large part of the total healthcare budget, as it requires chronic treatment and leads to frequent hospitalizations. In the Netherlands, more than 250,000 people suffer from heart failure and total healthcare costs due to heart failure were more than 800 million euros in 2017. Up to one third of heart failure patients exhibit conduction disorders, mainly left bundle branch block (LBBB). In these patients, biventricular pacing (BVP) has proven to be an effective treatment, improving both symptoms and survival.

In patients suffering from bradycardia and who require chronic pacing therapy, the right ventricular (RV) apex is an anatomical location frequently used for implantation of the ventricular pacing lead. When implanting the pacemaker lead transvenously, the apex of the RV is the easiest to reach and the most stable position. However, pacing the RV apex results in a very non-physiological ventricular activation. This non-physiological ventricular activation through RV apex pacing can lead to adverse effects such as increased incidence of atrial fibrillation, higher mortality and more frequent heart failure hospitalization. Already quite some research has been performed with the goal to find alternatives to RV apex pacing. The most recently studied technique is left bundle branch pacing (LBBAP). In LBBAP, the interventricular septum is paced at a site deep within the septum near the left ventricular (LV) endocardium. The septal myocardium can be paced with (left bundle branch pacing) and without (LV septum pacing) direct capture of the left conduction system.

The main objectives of this thesis were: 1) to investigate whether adding LV pacing locations could improve response to BVP, 2) to study the safety and feasibility of LBBAP as alternative to RV pacing, and 3) to investigate the differences between LV septal pacing and left bundle branch pacing within LBBAP. In this chapter we summarize the clinical, scientific and societal impact of the main findings of this thesis.

Clinical impact

In **chapter 5** we showed that, the modified transseptal implantation technique used in LVSP and LBBAP is feasible and safe. Therefore, LBBAP seems a safe and effective alternative to RV apex pacing in anti-bradycardia pacing. Additionally, we demonstrate a learning curve for permanent LBBAP implantation, even with implanters already experienced in HBP. The results suggest that at least 50-100 procedures are required for implanters to become experienced. Inexperienced implanters potentially cause more perforations into the LV cavity.

In **chapter 6**, we reproduced the findings of **chapter 5** on a very large scale. **Chapter 6** includes patients in whom LBBAP device implantation was attempted at 14 different European centres, comprising over 2500 patients with varying pacing indications. The results show that LBBAP is indeed a feasible and safe technique regardless of the pacing indication. Also, lead implantation success rate, defined as a deep intraseptal lead position with paced QRS complex including a terminal R/r wave in lead V1, was 92.4% (1698/1837) for bradyarrhythmia and 82.2% (572/696) for heart failure indications. While these results are promising for a technique that was introduced less than 5 years ago, this finding suggests that there is a need for improvement and adaptation of implantation tools for specific patient subpopulations. The complication rate of LBBAP implantation was found to be similar to conventional BVP.

In **chapters 5**, **7** and **8** we compared LVSP and LBBP and found that the decrease in ventricular dyssynchrony compared to RV pacing is similar for both modalities. Compared to RV pacing, already a large reduction in dyssynchrony is achieved during LVSP while LBBBP provides only a small additional decrease. These findings suggest that LVSP may be enough to avoid detrimental effects of ventricular pacing. The effort of additional left bundle branch capture comes at the cost of extended procedure and radiation time and potential higher complications rate such as LV perforation. Largescale, randomized trials are required to determine if and in which subpopulations LBBP results in beneficial long-term outcome compared to LVSP.

Scientific impact

In **chapter 3**, both electrophysiological and hemodynamic effects of conventional BVP and multi-LV pacing were investigated. In contrast to most clinical studies, we compared multiple LV pacing locations within the same heart. Also, we compared multi-point pacing and multi-vein pacing within the same heart. Our results show that the reduction in activation time achieved by adding LV pacing sites, does not translate into hemodynamic benefit. We demonstrated that the additional benefit of multi-LV pacing depends on the initial response produced by BVP with that corresponding LV site. Future patient studies investigating multi-LV pacing should therefore compare, within the same patient, conventional BVP yielding the best hemodynamic response with both multipoint and multi-vein pacing. However, given the increasing evidence of equal benefit of BVP and LBBAP, it may be questioned whether adding LV leads, if any, should be combined with LBBAP rather than RV pacing.

The results of **chapters 5**, **7** and **8** indicate that LVSP and LBBP provide a similar degree of ventricular synchronous activation compared to RV pacing. The results also show a small but statistically significant difference in (left) ventricular synchrony in favor of LBBP. An important question remains whether this statistically significant difference

translates into long-term clinically significant difference. Does LBBP, where the LV is activated in a manner closest to nature's physiology, provide beneficial outcome in patients compared to LV septal " only" pacing? And if this is not the case, should we then not always apply LVSP as it is the most straightforward technique? The good acute effects of LVSP/LBBP urge for more long term randomized studies, especially comparing RV vs. LBBAP in brady and LBBAP vs. BVP in heart failure patients.
Another question that deserves scientific investigation is whether LVSP/LBBP creates less dispersion of repolarization. Several reports indicate a pro-arrhythmic effect of BVP, therefore BVP is not infrequently combined with ICD. If repolarization is better preserved, such ICD may be required less frequently.

Societal impact
The potential societal impact of the thesis mainly relates to the improvement of pacemaker therapy. By improving and optimizing chronic pacemaker therapies, patients are better treated and experience less symptoms. For instance, the incidence of pacemaker induced cardiomyopathy (PICM) can be reduced by applying more physiological techniques such as LBBP. This will lead to less hospitalizations and less health care costs. By reducing PICM, there will also be less need for ICD, which also reduces costs. In case LBBAP turns out to be a safe and effective alternative to BVP, it will be a cheaper alternative as it required only one instead of two ventricular leads. Lastly, better understanding of LBBAP might lead to insight into which subpopulations of patients requiring chronic pacing benefit specifically from either LVSP or LBBP. This might contribute to decrease in health care costs through shorter implantation duration and therefore shorter waiting times.