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Author	A. Yilmaz
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Summary and conclusions

The purpose of this thesis was to evaluate the effect of manual adjustment of rate adaptive pacemakers on exercise physiology and quality of life and to study some new aspects of cardiac resynchronization therapy. The first part of the thesis (Chapter 2 to 6) concerned studies in pacemaker patients on the effect of individual optimization of pacemaker sensors on exercise physiology and quality of life. The second part of the thesis (Chapter 7 to 9) described the effect of cardiac resynchronization therapy on cardiac function, the neurohumoral system and microcirculation in patients with heart failure.

Part I Studies on pacemaker sensors

Automatic functions are increasing in rate response pacemakers. Whether we can rely on these automatic functions in daily practice is limited described. We therefore reviewed in **chapter 2** the various types of sensors used in current pacemakers and tried to answer the question whether manual rate response optimization improves patient outcome and is still necessary given the existing automaticity in rate response pacemakers.

In **chapter 3** heart rate curves of healthy individuals (HI) from different age categories are described during the chronotropic assessment exercise protocol (CAEP) and 6- minute hall walk test (6-HWT). Heart rate (HR) at rest, HR at 1 minute of exercise, time to peak HR, maximal achieved HR, HR at 1,3 and 10 minutes recovery period, exercise duration, and METS or achieved distance (meters) were measured. The achieved HR at one minute of exercise was significantly higher and the time to peak HR significantly shorter during 6-HWT compared to CAEP, although the achieved maximal HR was comparable. There were no gender differences in HI randomized to 6-HWT and minimal gender differences in HI randomized to CAEP. The predicted maximal HR according to the Åstrand formula (220-age) was not significantly different compared to the achieved maximal HR in both tests. Thus, the Åstrand formula (220-age) can still be used for prediction of the maximal HR. The HR rate profiles described in this chapter can be used to further optimize of the pacemaker sensors. The 6-HWT is preferable for pacemaker sensor optimization.

Chapter 4 described the influence of individual optimization of sensors on quality of life (QOL) and exercise tolerance in a randomized, single blind study in patients with VVIR, DDDR or AAIR pacemakers. Patients with ≥ 75% pacing were randomized

to optimized sensor settings (OSS) or default sensor setting (DSS). Standardized optimization was performed using three different exercise tests. QOL questionnaires (QOL-q: Hacettepe, Karolinska and RAND-36) were used for evaluation of the sensor optimization. One month before and after optimization, exercise capacity using CAEP and the three QOL-q were assessed. We showed that one month after sensor optimization the achieved maximal HR and METS were significantly higher in OSS compared to DSS. Highest HR and METS were achieved in patients with pacemakers with accessible sensor algorithms. In patients with automatic slope settings, exercise capacity did not improve after sensor optimization. Surprisingly, QOL did not improve in OSS compared to DSS.

In **chapter 5** we investigated whether variation in HR during exercise affects the flow velocity in the middle cerebral artery and cardiac output. We therefore evaluated in patients with complete heart block and rate responsive pacemakers, the effect of DSS and OSS on blood pressure, stroke volume and mean flow velocity in the middle cerebral artery during graded ergometry cycling. For both OSS and DSS there was no significant increase in flow velocity in the middle cerebral artery during exercise. Stroke volume and cardiac output increased minimal with OSS compared to DSS.

We directly compared the chronotropic function of the peak endocardial acceleration (PEA) sensor to the activity sensor in **chapter 6**. Patients with ≥ 75% pacemaker driven HR and a PEA sensor and HC underwent a CAEP exercise test. The pacemakers were programmed in the default setting and VVIR mode, with adjustment of the upper sensor rate as an age related maximum value (220-age). The activity sensor was externally strapped on the thorax. We showed that the PEA sensor functions hypochonotropic during exercise programmed as a single sensor system. Although both groups had normal left ventricular functions, the exercise capacity of pacemaker patients was significantly lower than in HC. It is therefore preferable to combine the PEA sensor with an activity-based sensor in a dual sensor system.

Part II Studies on biventricular pacing

To examine whether cardiac resynchronization therapy (CRT) induces favourable changes in the neurohumoral system, we measured in **chapter 7** in patients with heart failure, myocardial ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) uptake indices and brain natriuretic peptide (BNP) before and after 6 months of CRT. Furthermore, NYHA classification and echocardiographic indices were assessed. Six months of CRT resulted in 1) significant improvement in NYHA classification, 2) reduction in QRS width, LV end- diastolic diameter, LV end systolic diameter, septal to lateral delay and mitral regurgitation, 3) improvement of delayed ^{123}I-MIBG heart/mediastinal ratios and decrease of ^{123}I-MIBG washout and 4) decreased BNP levels. From these data we concluded that CRT induces favorable changes in the neurohumoral system.
Although it is known that CRT in heart failure patients improves systemic circulation, its acute effects on microcirculation are as yet unknown and improvement of the macrocirculation does not necessarily result in improvement of the microcirculation. **Chapter 8** describes the sub-lingual microcirculatory changes in heart failure patients due to CRT and right ventricular pacing by use of orthogonal polarization spectral (OPS) imaging. Six months of CRT resulted in a reduction in NYHA class and echocardiographic reverse remodeling. Acute microcirculatory changes were assessed by functional capillary density (FCD) and capillary velocity (CV) after previous six months of CRT. FCD and CV were measured sublingual after pacing 15 minutes in one of three pacing modalities (no pacing, RV only pacing, and biventricular pacing with a sensed AV interval of 100-120 msec). FCD was significantly higher in healthy controls compared to heart failure patients with right ventricular pacing and no pacing. CRT significantly increased FCD in heart failure patients compared to right ventricular pacing and no pacing. CV was normal in all patients with or without pacing.
In **chapter 9** we described in one of the first case reports, reversed remodeling of the left ventricle and left atrium after upgrading to biventricular pacing in a patient with worsening of mitral regurgitation and heart failure due to VVIR pacing after His bundle ablation and reviewed the literature concerning reversed remodeling after upgrading to biventricular pacing.

Interpretations and conclusions

The studies concerning individual optimization of pacemaker sensors on exercise physiology and quality of life that are described in this thesis lead to the following conclusions:

1. The majority of pacemaker sensors remain at the original programmed settings of the manufacturer, although there is evidence that individually adjustment of pacemaker sensors improves exercise capacity and quality of life.
2. Automatic features can be helpful in reducing the time needed to perform a follow-up of pacemakers, however individually adjustment of pacing sensors is still necessary.
3. The development of a sensor system that can simulate ideal sinus rhythm behavior remains a challenge for scientists and manufacturers.
4. International guidelines are needed to standardize pacemaker sensor optimization in all chronotropic incompetent patients.
5. Individual optimization of rate response pacemakers improves exercise capacity and increases maximum HR, although QOL remained unchanged.
6. Accessible pacemaker sensor algorithms are mandatory for individual optimization.
7. Pacemaker sensor optimization increased stroke volume and cardiac output minimally during exercise and had no measurable effect on flow velocity in the middle cerebral artery.
8. The PEA sensor functions hypochonotropic during exercise programmed as a single sensor system.

In conclusion, individual optimization of pacemaker sensors is necessary. Therefore accessible pacemaker sensor algorithms and clear international guidelines are of utmost importance. Combination of a physiologic and an activity based sensor in dual sensor systems mimics the sinus node behavior better than a single sensor system.

The conclusions of the second part of the thesis concerning the effects of cardiac resynchronization therapy on cardiac function, neurohumoral system and microcirculation in patients with heart failure are:

1. CRT induces favorable changes in the neurohumoral system in patients with

heart failure (BNP levels decreased, delayed ^{123}I-MIBG heart/mediastinal ratios improved and ^{123}I-MIBG washout decreased), parallel to significant functional improvement and echocardiographic reverse remodeling.

2. In CRT responders, CRT improves sub-lingual microcirculation in heart failure patients as assessed by OPS imaging.
3. The occasionally observed progressive mitral regurgitation and heart failure after right ventricular pacing following His-bundle ablation can be reversed by upgrading to VVIR biventricular pacing and in these circumstances upgrading should be considered.

In conclusion, cardiac resynchronization therapy improves the macrocirculation, the microcirculation and induces favorable changes in the neurohumoral system in patients with heart failure. Reversed remodeling of the left ventricle can be achieved with long- term CRT.

Recommendations and future directions

Part I

Our results might have a number of implications for the clinician. Today, most pacemakers are programmed in the default setting of the manufacturer. We recommend individual optimization in all chronotropic incompetent patients. After the implantation of a pacemaker, carefully follow- up of the patients is needed. The function of the pacemaker sensors has to be evaluated and optimized using an exercise test. We feel that in-hospital exercise tests are artificial, especially the treadmill and bicycle tests. We recommend therefore the use of e.g. a hall walk test with stair climbing, which resembles closer daily life activities than other in- hospital tests. Ideally, the sensor function should be measured directly during daily living activities with for example holter registration. In addition, investigating the effects of programming sequence (e.g. first threshold adjustment followed by slope adjustment) of rate response parameters is very important, although time consuming and strenuous for the patients. Development of tools for home monitoring of the separate rate response parameters can be helpful to gain more insight in this issue.

The achieved rate profile during treadmill exercise testing resulting from dual sensor pacing (with complementary properties) is improved over single sensor pacing because sensor combination provides improvement in speed, proportionality, sensitivity and specificity. As consequence, we recommend to use dual sensor systems with a combination of an accelerometer and a physiologic sensor (minute ventilation, QT, peak endocardial acceleration) in chronotropic incompetent patients.
In our study described in chapter four, QOL-q remained unchanged after one month of individual optimization of rate response pacemakers. An explanation for the failure to improve QOL after sensor optimization could be the relatively good baseline functional capacity, because patients with relative preserved functional capacity at enrollment show the lowest improvement in health related issues. Another reason could be the partly inadequate questioning of specific pacemaker patient related symptoms with the used QOL-q in this study. Therefore, we advise to use the Aquarel QOL-Q, which is a recently developed pacemaker patient specific QOL-q and we feel that future research to improve QOL-q related to pacemaker patients has still several challenges. Insight in the interpretation of the QOL-q scores in relation with classical used clinical parameters such as NYHA classification is important.

Part II

Furthermore, the automaticity in rate response pacemakers is increasing tremendously. Although, automaticity can reduce pacemaker follow- up time, accessible pacemakers remain needed for individually adjustment of the rate response parameters. Whether automatic adjustment is better than manual adjustment should be investigated in randomized trials.
The results of our studies concerning the effects of CRT on neurohumoral system and microcirculatory changes form a step forward in the unraveling of the working mechanisms of CRT in heart failure patients. To get more insight in this issue we suggest to replicate these studies in both responders and non-responders to CRT. It would be of interest to know whether microrocirculatory changes at implant could predict beneficial response to CRT and whether CRT induces beneficial long-term microcirculatory changes. In addition, nowadays patients are selected for CRT mainly on electrocardiographic criteria. The standard EKG is less reliable in the

characterization of the extent of dyssynchrony, since even patients with normal QRS duration on EKG can have marked dyssynchrony, while 20-30% of patients with wide QRS complexes do not respond to CRT. We therefore recommend to select patients using advanced tissue-doppler imaging techniques, because this technique is likely to improve the response rate to CRT.

Furthermore, the deleterious effects of right ventricular pacing (RV) are now well documented. Considering the large magnitude of the deleterious effects of RV pacing we strongly suggest '*to go away of the RV*' or to minimize RV pacing using algorithms such as search hysteresis and mode switching. We think that left ventricular pacing using the coronary sinus is a more physiologic pacing site also for conservative pacing indications (sick sinus syndrome, AV-block) as for the modern pacing indications (resynchronization therapy) in patients with already reduced left ventricular function and/or mitral valve insufficency. More studies are needed to identify patients who are at high risk for deterioration with RV pacing. Improving the technique for pacemaker lead implantation in the coronary sinus (to reduce lead implant time) will widen the indication for left ventricular pacing.

Finally, extrapolating from recent developments, J Warren Harthorne (professor in medicine Massachusetts General Hospital, Boston, USA, writer of the book 'the future of cardiac pacing'), has suggested, that the future will give us "implantable computers that will serve as an electronic service center" able to communicate with various organ systems " to rouse flagging performance of heart, cerebral, respiratory, gastrointestinal, genitourinary, and musculoskeletal function" Electrostimulation has evolved so far since its beginning that this description does not seem entirely outside the realm of the possible.