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Ventricular activation patterns in conduction abnormalities and during different pacing modes

Insight from electroanatomical mapping

Academic Dissertation

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1. INTRODUCTION

Congestive heart failure is a progressive disease that is caused by left ventricular dysfunction and leads to impaired exercise tolerance, worsening of quality of life and shortened life expectancy. Despite substantial advances in pharmacological therapy, heart failure remains disabling disease with high morbidity and mortality rates. Ventricular dysfunction is often linked to ventricular dilatation, which in turn, may cause ventricular conduction delays and further worsening of the cardiac function. Recent decade has witnessed the advent of cardiac resynchronization therapy (CRT), a therapeutic modality based on the premise that preexcitation of late activating regions by cardiac pacing may restore impaired left ventricular synchrony.

To this date, many studies have confirmed that implementation of CRT improves the symptoms, quality of life, exercise capacity, systolic function and also prognosis in patients with severe heart failure and conduction abnormalities. Despite these encouraging results, certain proportion of patients remains clinically unimproved and several issues regarding CRT remain the matter of debate, mainly the criteria for identification of responders, selection of stimulation modality (biventricular, single-site left ventricular and right ventricular bifocal pacing), optimal lead positioning and exact mechanisms responsible for hemodynamic improvement.

Thus, the introduction of CRT has revived interest in complex conduction abnormalities that form the basis for dyssynchronious contraction. This dissertation consists of the set of publications that focus on electrical activation sequences in the failing heart. The goal of these studies was to identify individual characteristics that affect electrical activation and thus possibly determine the success of CRT.

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2. HISTORICAL OVERVIEW AND CURRENT PERSPECTIVES

Methods describing electrical activation patterns

Various methods have been designed to map ventricular activation. Despite being invented more than hundred years ago, the standard electrocardiography (ECG) still remains the cornerstone of these techniques. Based on its principles, other methods have been developed that use mathematic algorithms for reconstruction of electric impulse propagation: e.g. description of cardiac electric axis – vectorography[1] or recording from the thorax as the body surface mapping[2;3]. In general, these non-invasive techniques are limited by their spatial and time resolution. Thus, the detail characterization of the activation sequence course in human was obtained by invasive techniques that allowed acquisition of electrical information directly from endocardium and/or epicardium.

The first "pioneering" work that described propagation of activation sequence invasively in human heart was performed in early seventies by Durrer *et al.*[4], who studied perfused hearts in car accident victims. Additional data were brought by intraoperative mapping in 80s. During the cardiac surgery specially designed sock with build-in electrodes was pulled over the heart and used to describe of epicardial activation[5-7]. Development of catheter techniques allowed deeper insight into conduction abnormalities[8-11] and modern catheter-based mapping systems enabled three-dimensional computer reconstruction of mapped cavities with superimposed activation sequence[12;13].

Factors influencing conduction velocity in the ventricles

The complex three-dimensional muscular structure of cardiac wall is responsible for heterogeneous conduction properties in both epi- and endocardium as well as in different ventricular segments. Conduction within the heart is thus even under normal circumstances anisotropic and its velocity is determined by four main factors:

(1) Although the propagation in conduction system is fast (3-4m/s)[14], the conduction within myocardial cells itself is relatively slow (0,3-1m/s)[15]. In case of Purkinje cells and/or conduction system damage, the electrical impulse is conducted by myocytes and thus, at least four times slower.

(2) Distribution of conduction system in ventricles is heterogeneous, e.g. in left ventricular inferobasal segment is its density relatively lower and this can explain minor conduction abnormalities observed in patients after inferior myocardial infarction[10].

(3) The velocity of conduction is almost two times faster in the direction along the myofibres than across[15] and the architecture of myocardial fibres in heart is rather complex. Longitudinal fibres are distributed mainly subendocardially and subepicardially, circular fibres are located in the mid portion of myocardial wall, mostly in basal segments[16].

(4) Conduction in the endocardial layer is faster when compared with the rest of the myocardial wall, even if the myofibres are not a part of the specialized conduction system[17]. This may be illustrated by slower left ventricular activation during epicardial pacing when compared to pacing from the endocardium[18].

Normal ventricular activation sequence and anatomy of conduction system

Normal ventricular activation sequence starts when the electric impulse travels from the atrioventricular (AV) node to the bundle of His. The bundle then divides into the right and left bundles of Tawara with subsequent branching into separated fascicles that finally terminate in the larger network of subendocardially positioned Purkinje cells. The impairment at any level of this system (AV node, His bundle, fascicles and distal network of Purkinje cells) leads to specific changes in the activation sequence and prolongs the duration of ventricular activation.

Traditionally, three main fascicles of the conduction system are described (i.e. right, left anterior and posterior). However, as the portion of the left fascicle may activate the

interventricular septum, some authors describe this extension as the fourth fascicle[19]. The right bundle is anatomically well-defined structure coursing from interventricular septum via muscular bundle "moderator band" toward the right ventricular anterior wall. The left bundle and particularly posterior fascicle form rather diffuse fan-like structure[20;21].

Under normal circumstances, the activation of both ventricles is rapid and synchronous, with left ventricular activation slightly preceding activation of the right ventricle (about 10ms). The electrical impulse is conducted from endocardium to epicardium[4]. In the left ventricle, the activation starts from three separated sites that correspond to the terminations of the fascicles (the lower portion of septum, the midseptum and the anterior wall near the base of the papillary muscle). The activation then spreads radially so that the apex and the left ventricular lateral wall are activated within the terminal portion of the QRS complex[8]. In the right ventricle the activation spreads from interventricular septum and anterior wall (site of insertion of moderator band). Activation of the interventricular septum occurs mainly from the left bundle creating negative deflection of the initial portions of the QRS complex in the leads I and aVL (septal q).

Intraventricular conduction disturbances

The widening of the QRS complex may arise from two main reasons. First, the damage of specialized subendocardial conduction system leads to slowing of conduction within the ventricle. Secondly, the impaired conduction in one of the main bundles (left or right) leads to distortion of interventricular synchronicity (i.e. activation of one ventricle is delayed as the electric impulse conducts through the interventricular septum)[22].

Conduction abnormalities result in typical patterns of the QRS complex on the 12-lead ECG that allowed definition of criteria for "blocks" in separated fascicles[23]. Despite the widespread use of the term "block", the conduction within the damaged fascicle can be only slowed rather than completely discontinued. Especially in cases of complex conduction

disturbances the ventricular activation reflects combination of multiple conduction defects and may result in "bizarre" QRS complexes on the 12-lead ECG.

Classification of conduction abnormalities

Conduction defects within the right fascicle – right bundle branch block (RBBB) can be classified according to the level of conduction block into three types: *proximal, distal and terminal*. The first type is the most common with conduction blocked at the level of the His bundle. In such case, both ventricles are activated from the left bundle only. In *distal RBBB*, the early activation of the right site of the interventricular septum is preserved and the conduction is interrupted at the level of the "moderator band". This type of conduction abnormality can be observed mainly after cardiac surgery, when the muscular cord is often damaged (e.g. surgical correction of the congenital heart disease). *Terminal block* is the second most frequent type of RBBB. Conduction through the right bundle is preserved, including early activation of the right ventricular anterior wall, and the site of block is located within the right ventricle. This type of block may occur in patients after correction of tetralogy of Fallot[24] or in those with arrhythmogenic dysplasia of the right ventricle.

Abnormalities within the left ventricular conduction system are much less defined and the term left bundle branch block (LBBB) describes a spectrum of disorders that share slowed conduction throughout the interventricular septum. In complete LBBB the interventricular septum is activated from the right ventricle. This results in absence of the septal q in the leads I and aVL on the standard ECG. In addition, activation of the left ventricle is delayed by 52±17ms[9]. Both velocity and character of subsequent conduction then depend on the type of myocardial pathology.

In clinical electrocardiology, LBBB is traditionally classified according to the mean electrical axis[25]. In uncomplicated LBBB the axis typically ranges between -30 and +105 degrees. Left axis deviation reflects left ventricular dysfunction. LBBB with right axis

deviation occurs rarely and is usually intermittent in nature. It can be observed in patients with right ventricular volume overload[26]. However, detailed mapping studies found only weak correlation between the vector of electrical axis gained from 12-lead ECG and the activation sequence[9]. Similarly, no correlation was found between the vector of electrical axis in LBBB and left ventricular ejection fraction[27].

The influence of underlying heart disease

While ventricular activation in patients with dilated cardiomyopathy (DCM) is considered to be homogeneous, post-infarction scars in patients with coronary heart disease (CAD) result in localized slowing of conduction. In this respect, Hatala et *al.*[28] described three different activation patterns in CAD patients according to location of myocardial infarction. The so-called "radial activation pattern" was observed in patients with inferior scar. In this case propagation omitted the inferior wall. The "counterclock-wise activation pattern" was typical in patients with anterior myocardial infarction. Anterior scar in these patients created a line of block and the rest of the left ventricle was activated through the inferior wall. "Variable pattern" was described in patients with multiple scars. In these subjects the activation propagated variably with the lateral wall being most commonly the latest.

Relationship between conduction disturbances and mechanical function

Conduction abnormalities were considered for a long time only an epiphenomenon of the dilatation of the heart. Nowadays, there is a mounting evidence that ventricular conduction delays have an important impact on systolic and diastolic ventricular function and thus may further contribute to progression of heart failure[29]. Indeed, conduction abnormalities and the QRS width represent a significant risk factor with adverse effect on mortality in patients with advanced heart failure[30].

Resulting dyscoordinated ventricular contraction leads to tilting of the left ventricle and increases regional myocardial wall stress. Contraction of early-activated segments is not

followed by a raise in intraventricular pressure since the other regions remain inactive. These lately activated segments are then exposed to passive distension and contract subsequently with a higher preload. In the late systolic phase, activation of these regions leads in turn to distension of the early-activated segments[31]. Such a late distension may lead to disruption of myocardial cross-bridges and thus, can result in further decrease in contractility.

The loss of synchronicity has also adverse consequences for myocardial metabolism and energetic consumption. Although the early-activated segments have lower energetic consumption, the use of energy is ineffective since the contraction does not lead to the rise of intraventricular pressure. On the contrary, the late-activated segments contract with high energetic demand that results in compensatory asymmetric hypertrophy[32]. Alteration of the left ventricular geometry together with late activation of lateral papillary muscle then worsens mitral regurgitation.

To summarize, dyssynchronious activation and contraction thus lead to a significant impairment of ejection fraction, rise of energetic consumption and worsening of mitral regurgitation[33;34].

Cardiac resynchronization therapy

Cardiac resynchronization therapy has evolved as a result of efforts to restore synchronicity of contraction in subjects with conduction abnormalities. The main principle of CRT is creation of "electrical bypass" by stimulation of the late activated segments (mostly in the region of left ventricular lateral free wall). The left ventricle is then activated via two separated wavefronts (one arising from the conduction system and the second from the tip of pacing lead) that fuse together.

Although the first report assessing hemodynamic performance of left ventricular pacing can be traced back to 1983[35], it took nearly 13 years for the first systematic analysis to appear[36]. Since then, several hemodynamic studies have shown that CRT can markedly

improve cardiac output, increase systolic pressure, lower pulmonary wedge pressure[37;38] and enhance left ventricular contractility as assessed by maximal rate of blood pressure rise (dP/dt)[39;40]. Importantly, CRT leads to the hemodynamic improvement with concomitant reduction of myocardial energy consumption[41] and sympathetic activity[42].

Those acute hemodynamic studies were then followed by clinical trials evaluating multisite pacing as the treatment option for patients with advanced heart failure and conduction abnormalities. To date, several placebo controlled studies have been completed: PATH-CHF trial[43], MUSTIC[44], MIRACLE[45] and COMPANION[46]. These studies confirmed sustained improvement in exercise tolerance, quality of life score and NYHA functional class. The last of these studies also reported reduced hospitalization[47] and indicated that CRT, especially in conjunction with implantable cardioverter-defibrillator, may significantly reduce mortality in patients with failing heart. Only recently, the CARE-HF trial[48] proved that even sole resynchronization may improve prognosis of heart failure patients. The study randomized 813 patients to optimal pharmacological therapy or CRT and proved significant reduction of mortality in patients receiving CRT device. Importantly, all these benefits are in addition to those afforded by standard pharmacologic therapy.

Based on the above data, CRT has become the current standard in therapy of patients with heart failure and conduction disturbances. Nowadays, the resynchronization is achieved mostly by biventricular pacing (i.e. simultaneous stimulation by two endovasally implanted electrodes), when one lead is positioned in the right ventricle and the second is placed retrogradely via the coronary sinus on the left ventricular lateral wall. However, other pacing modalities such as right ventricular bifocal[49] (i.e. placement of electrodes into the right ventricular apex and outflow tract) or single-site left ventricular pacing[50] have been proposed as alternatives and their role within the framework of CRT or optimal pacing site has to be determined.

Similarly, a central issue for CRT remains the identification of the candidates most likely to benefit. Originally, the most frequently used indication criterion in clinical trials was the QRS width (i.e. QRS > 120 to 150ms)[44-46]. Although the baseline QRS width was documented to correlate with hemodynamic and clinical improvement after installment of CRT, several clinical trials showed that a substantial portion of patients selected solely by QRS width remains unimproved[45]. Thus, different techniques have been designed and evaluated to assess the ventricular dyssynchrony and to select the appropriate candidates. Direct analysis of mechanical dyssynchrony may be feasible by means of tissue Doppler strain analysis[51;52], magnetic resonance imaging[53] or Doppler echocardiographic indexes[54;55].

3. PREVIEW OF THE INVESTIGATIONS

Since the 12-lead electrocardiogram (ECG) appears to be of limited value in description of complex intraventricular conduction disturbances, more elaborate mapping techniques have to be employed to provide further insight into activation patterns underlying the LBBB and other conduction disturbances in the failing heart. In this respect, the left ventricular activation was studied using the intraoperative epicardial[28;56] or catheter-based endocardial mapping[9;57]. However, the variability of individual activation patterns and their importance for successful application of CRT are not yet fully understood.

Secondly, several studies have evaluated hemodynamic performance of different pacing modalities both in human[37] or in animal models[58;59]. Despite this, only limited information is available on changes in ventricular activation sequences caused by pacing from various sites.

4. THE AIMS OF THE STUDIES

The present thesis has following objectives:

1. to analyze the ventricular activation patterns in patients eligible for CRT with respect to the underlying heart disease and/or QRS morphology on the surface ECG
2. to quantify changes in ventricular activation patterns during different pacing modes and identify factors that affect activation
3. to compare the hemodynamic performance during left ventricular single-site pacing and biventricular pacing and correlate the degree of electrical synchronicity (assessed by QRS width) with hemodynamic performance

5. *METHODS*

Concept of electroanatomical mapping

The first publication (**Appendix 1.**) provides the review on the principles, clinical utility and limitations of the electroanatomical mapping system (CARTO, Biosense Webster). This catheter-based endocardial mapping technique allows three-dimensional computer reconstruction of mapped cardiac chambers with superimposed activation sequence and distribution of local voltage. The principle of this electroanatomical mapping can be briefly summarized as follows. The mapped cavity is entered with a special mapping catheter (NAVISTAR) retrogradely via femoral artery (the left ventricle) or antegradely via femoral vein (the right ventricle). Exact position of the catheter inside the heart is calculated by measuring the intensity of the magnetic field emitted under the patient's table. Location accuracy is established with accuracy ≤ 1mm relatively to reference sensor tapped to the patient's chest. The combination of local electrogram recordings together with different catheter positions allows the construction of three-dimensional computer maps with color-coded projection of electrical activation and/or voltage on the surface.

6. RESULTS

Spectrum of conduction abnormalities in patients eligible for CRT

The first clinical study **(Appendix 2.)** describes endocardial activation patterns in 26 patients with left ventricular conduction disturbances and QRS duration of more than 130ms. Its main contribution lies in characterization of variability of inter- and intraventricular delays underlying these conduction abnormalities. The QRS duration reflects a total time needed for complete ventricular activation and therefore, incorporates both interventricular (i.e. interval between onsets of activation between the right and left ventricle) or intraventricular (prolongation of activation within the ventricle) conduction delays. In this respect, different combinations of conduction disturbances may be encountered despite the same or similar QRS duration: from the case of true LBBB with long interventricular conduction delay and only minor left ventricular conduction problem to the case with severely damaged and dilated left ventricle, nearly normal conduction via the left fascicle and dominant intraventricular delay.

Detailed analysis of our data revealed considerable differences in individual delays that were not identifiable from the 12-lead ECG recording. Although there is not a difference in duration of transseptal duration in the LBBB with respect to the underlying disease[9], in most of our patients the interventricular conduction delay did not reach the true complete LBBB. Importantly, the patients with CAD presented predominantly with only LBBB-like pattern, characterized with nearly normal transseptal conduction and major conduction delay localized within the left ventricle around the scar area. Similarly, total left ventricular activation time was significantly longer in these patients as compared with those with dilated cardiomyopathy (DCM). The latter group presented rather with homogeneous endocardial conduction with the latest activation region located on the lateral wall. The variability of activation patterns and

their significance for resynchronization therapy has been summarized in the letter to editor (**Appendix 3**).

So far, clinical implications that would reflect the above described variability of activation patterns with either dominant inter- or intraventricular conduction delays are not that obvious. Although we observed different nature of conduction abnormalities with respect to the underlying heart disease, there is not a difference in acute hemodynamic outcome of biventricular pacing between CAD and non-CAD patients[60]. This may reflect the fact that biventricular pacing corrects both inter- and intraventricular asynchrony. In this respect, Pěnička *et al.*[55] recently used pulsed-wave tissue Doppler imaging for assessment of mechanical inter- and intraventricular delays in CRT candidates and found that the sum of both parameters was the best predictor of functional recovery after resynchronization. This combined parameter, in addition, correlated significantly with the improvement of left ventricular ejection fraction and end-diastolic volume. Although electrical and mechanical inter- and intraventricular delays do not directly equal, our work provides clue that these mechanical delays have very good electrical correlate.

Activation pattern during different pacing modes

The second original publication **(Appendix 4)** provides description of characteristic left ventricular activation patterns in 20 patients assigned to biventricular, single-site left ventricular or right ventricular bifocal pacing. In each patient the endocardial mapping was performed in studied pacing mode and during baseline conduction abnormality.

Study showed that only biventricular pacing produced the most substantial changes as documented by shortening of the left ventricular activation, minimization of the interventricular delay. Single-site left ventricular pacing was associated with similar characteristics provided by fusion of the pacing wavefront with spontaneous septal activation.

The right ventricular bifocal pacing resulted only in a mild shortening of left ventricular activation that was outweighed by an increase in the interventricular delay. Moreover, the activation pattern during bifocal pacing still resembled the LBBB. From this point of view this pacing modality cannot be considered as an equal alternative to biventricular pacing. Finally, the study demonstrated that the single-site right ventricular apical pacing caused apicobasal left ventricular activation and led to the highest degree of inter- and intraventricular asynchrony.

One of the original observations of the study appears to be description of the role of fusion of spontaneous conduction and pacing on left ventricular activation patterns during different pacing modes. The presence of fusion seems to be crucial for potential clinical benefit of single-site left ventricular pacing, however, it may have practical implications even during biventricular pacing as it leads to variable septal activation patterns.

Hemodynamic performance of biventricular and left ventricular pacing

The last study **(Appendix 5)** compared hemodynamic performance of single-site left ventricular pacing and biventricular pacing as assessed by stress test echocardiography. The study included 26 patients with sinus rhythm that underwent exercise testing during randomly selected mode with cross-over the next day. The cardiac output was measured using Doppler echocardiography calculating the VTI (velocity time integral) formula in the left ventricular outflow tract.

No significant differences were revealed between both groups either in heart rate or in blood pressure at rest and during any step of exercise. However, single-site left ventricular pacing was associated with higher cardiac output at rest and low-level exercise. This observation is in concordance with previous acute hemodynamic studies[37;39]. One possible explanation of this phenomenon may be that in presence of fusion with spontaneous

conduction the left ventricular activation patterns is similar during both modes, while the contraction of the right ventricle is not adversely affected by right ventricular pacing. Secondly, the single-site left ventricular pacing has been shown to remove the interventricular interaction[61](the preexcited left ventricle starts to fill before the right ventricle, which in turn prolongs diastolic filling, reduces mitral regurgitation and increases cardiac output).

Interestingly, the superior hemodynamic effect of left ventricular pacing was in our study predominantly confined to patients with DCM. This may be, at least in part, explained by the different nature of conduction abnormalities in these patients. As described above, the DCM subjects often have predominant interventricular conduction delay, while the conduction within the left ventricle is rather preserved and homogeneous. In such patients, single-site left ventricular pacing removes the delay between both ventricles, while the left ventricle is activated relatively rapidly. On the other hand, CAD patients appear to have more expressed intraventricular delay that is caused by the presence post-infarction scars. In this situation, it may be more important to activate the left ventricle from more sites.

Finally, no correlation was found in the study between QRS width (as a potential marker of electrical synchronicity) and the cardiac output. This highlights the complex relationship between electrical activation and mechanical function. Mechanical dyssynchrony and delayed segmental contraction may exist even in patients with narrow QRS complex[62] and thus, independently from electrical activation. On the other hand, electrical resynchronization of nonviable and noncontracting region will not provide, despite QRS narrowing, any hemodynamic improve. For these reasons, the markers for selection of CRT candidates should be derived from methods that assess mechanical rather than electrical dyssynchrony[51;52;54;55].

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7. CONCLUSIONS

The thesis consists of a set of publications that focused on ventricular activation patterns in the failing heart. Although the eletroanatomical mapping system cannot be used in clinical practice on a routine basis, it enabled detailed analysis of activation sequences far beyond the standard ECG. It revealed wide spectrum of activation patterns in patients with conduction abnormalities that may consist of variable inter- and intraventricular conduction delays. Importantly, substantial differences were present with respect to the underlying heart disease. DCM patients presented rather with complete LBBB and homogeneous endocardial activation pattern with the latest activated region positioned laterally for LBBB. In contrast, patients with CAD displayed on the ECG predominantly a nonspecific conduction abnormality and had rather heterogeneous endocardial activation with individual location of the late activated region. This variability of activation patterns supports the concept of individually tailored CRT with the position of the pacing lead targeted to the region with the latest activation and highest dyssychrony. Secondly, as those differences are not identifieable from the standard ECG, this method and the QRS width should not be used as a solely parameter for selection of CRT candidates.

When comparing the activation patterns during different pacing modes, biventricular pacing produced the highest degree of electrical resynchronization. For a similar degree of resynchronization during single-site left ventricular pacing, the presence of fusion with spontaneous activation was required. In contrast, the potential resynchronization benefit gained by right ventricular bifocal pacing was outweighed by the creation of interventricular dyssynchrony and thus, this pacing mode cannot be considered as an equal alternative to the biventricular pacing. Finally, the right ventricular apical pacing led to the highest degree of inter- and intraventricular electrical asynchrony and should be avoided in the failing heart.

The clinical implications of these studies are somehow limited by the fact that the correlation of electrical synchronicity with hemodynamic performance is not direct. The potential benefit derived from CRT can be nowadays better predicted by methods that assess the degree of mechanical rather than electrical dyssynchrony. However, the quantification of electrical activation patterns forms the solid background for understanding the principles and mechanisms underlying the effect of CRT and for elucidation of the complex relationship between electrical and mechanical dyssynchrony.

In conclusion, characteristic ventricular activation patterns can be observed in patients with failing heart and conduction abnormalities both during spontaneous activation and different pacing modes. Multiple factors affect the resulting activation pattern and its hemodynamic impact and this underscores the complexity of left ventricular dyssynchrony and the array of variables that determine the success of cardiac resynchronization therapy.

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9. LIST OF AUTHOR'S PUBLICATIONS

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