NON-PHARMACOLOGICAL TECHNIQUES OF ANTIARRHYTHMIC THERAPY

PhD thesis

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I Introduction

Cardiac resynchronization therapy (CRT) is an important therapeutic option in the management of patients with symptomatic systolic heart failure (HF). Biventricular pacing significantly improves cardiac output, quality of life, and functional capacity in patients with congestive heart failure. However, the incidence of sudden cardiac death still remains high. Recent studies have shown that reversal of the normal myocardial activation sequence during epicardial pacing, as it occurs during conventional CRT, increases the transmural dispersion of repolarization (TDR) and causes ventricular arrhythmias. Biventricular pacing or left ventricular (LV) epicardial pacing may increase the QT interval and TDR, which have the potential to increase the risk of ventricular arrhythmias. Increased TDR as measured by Tpeak-Tend (Tp-Te) and Tp-Te/QT is associated with a higher incidence of ventricular arrhythmias in CRT-D patients. Therefore, it is important to determine CRT patients who are prone to have ventricular arrhythmias.

CRT with transseptal endocardial LV pacing is an alternative in patients where the conventional approach has failed. Endocardial pacing also leads more physiological activation. Experimental observations in humans suggest that potential arrhythmias can be avoided by stimulation of the LV endocardium. A recently published small case control study suggests that permanent biventricular pacing with LV endocardial lead placement through the interatrial septum is associated with fewer proarryhthmic ventricular characteristics when compared to CRT with a coronary sinus (CS) LV lead. Scott et al. (2011) evaluated seven patients with transseptal LV endocardial leads, 28 matched patients with CS LV leads, and eight patients with surgical LV epicardial leads. Significant postpacing reduction in Tp-Te and QT dispersion values were observed in the transseptal group compared to the CS group. In contrast, there were no differences between the surgical and CS groups in terms of the effect of CRT on these repolarization parameters. This small observational study with a case control design provides crucial information. However, finding a perfect match between small patient groups is not always possible and is a clear limitation. Differences in baseline characteristics between groups may have an impact on results.

In addition, different pacing configurations may also produce different vectorial activation and may affect ventricular repolarization patterns. Yang et al. (2012) reported a significant difference in the mechanical activation sequence between unipolar and bipolar LV pacing during CRT. They observed higher basal endocardial strain and more uniform global strain with bipolar pacing. The difference in the mechanical activation sequence between pacing polarities indicates differential activation of different layers of myocardium, which may have an impact on ventricular repolarization. There is an intrinsic repolarization difference among epicardium, mid myocardial M cells and endocardium. Delayed activation and repolarization of mid myocardial M cells during biventricular pacing leads to prominent increase in QT and TDR. These issues have raised concern as to whether the LV pacing polarity might play a role in the development of ventricular arrhythmias.

Although the impact of LV pacing polarity on contractile functions has been investigated, little is known about the role of pacing polarity on repolarization patterns. A novel quadripolar LV lead offers more pacing configurations, including six bipolar and four unipolar LV pacing options, and allows stimulation of the LV from different epicardial locations. The impact of pacing polarity and pacing sites from different perspectives (endocardial vs. epicardial and basal vs. non-basal) have not been investigated in the same patient group.

AF is the most common supraventricular arrhythmia in human and antiarrhythmic drugs used for rhythm control have limited success. Therefore, in the last decade pulmonary-vein isolation (PVI) became a corner stone for non-pharmacological treatment of AF. Radio-frequency (RF) catheter ablation is an effective therapy for AF and electroanatomic mapping (EAM) systems play important role on ablation procedures. Unfortunately, benefits of these tools are limited by biological factors. Significant changes in left atrium (LA) and pulmonary vein (PV) anatomy due to respiration have been reported. Beinart et al. recently demonstrated favorable effects of respiratory gating on electroanatomical map accuracy (2011). Respiratory compensated electroanatomical maps showed better correlation with pre-acquired computed tomography (CT) and magnetic resonance (MR) images. However, better correlation does not always mean better ablation results and impact of respiratory gating on AF ablation has not been studied yet.

II Objectives

Based upon information, mentioned above, the objective of the present work was the following:

1. Recent studies have shown that reversal of the normal myocardial activation sequence during epicardial pacing, as it occurs during conventional CRT, increases the TDR. In the first study, we evaluated the proarryhthmic repolarisation characteristics of endocardial and epi-cardial biventricular pacing in the same CRT patient group.

2. The impact of pacing polarity and pacing sites from different perspectives (endocardial vs. epicardial and

basal vs. non-basal) have not been investigated in the same patient group. In the second study, we investigated the impact of LV pacing polarity and epicardial pacing site on repolarization parameters by using quadripolar LV lead.

3. Electroanatomical mapping systems play an important role on ablation procedures. However, impact of respiratory gating on electroanatomical mapping and image integration guided AF ablation procedures have not been investigated. Therefore, we assessed the impact of respiratory gating on electroanatomic mapping and image integration guided AF ablation procedures.

III Methods

1. Evaluating the effects of endocardial vs. epicardial LV pacing

Seven patients who had transseptal endocardial left ventricle (LV) lead placement, in whom epicardial CRT had failed due to coronary sinus (CS) lead dislodgement after successful implantation, were admitted to the study. LV endocardial leads were implanted through the interatrial septum in a lateral position. ECGs were scanned before and after successful epicardial and endocardial biventricular pacing and analyzed using digital callipers. ECG markers of TDR (Tp-Te and Tp-Te/QT ratio) were measured and compared.

2. Evaluating the effects of bipolar vs. unipolar and basal vs. non-basal LV pacing

Twenty patients, who had CRT-D implantation with quadripolar LV lead were admitted to the study. Two bipolar pacing vectors (D1-M2, P4-M2) and two unipolar vectors, also called extended bipolar pacing vectors (D1-RVcoil, P4-RVcoil), were selected for comparison. After successful implantation, the final LV lead electrode positions were recorded under fluoro-scopy. ECG markers of TDR (Tp-Te and Tp-Te/QT ratio) were measured and compared.

3. Evaluating the effects of respiratory gating on AF ablation

One-hundred-forty consecutive patients undergoing pulmonary vein isolation were admitted to study. Respiratory gating module (AccuResp algorithm, Carto3, Biosense Webster) was enabled in 70 patients and disabled in 70 patients during procedures. Total procedure times, fluoroscopy times, RF application durations and electroanatomical map reconstruction times were recorded and compared.

IV Results

1. Evaluating the effects of endocardial vs. epicardial LV pacing

Between September 2007 and March 2014, 48 patients in our center had transseptal endocardial LV lead placement. Thirteen of them had a CS lead dislodgement history after successful conventional CRT implantation and epicardial pacing. Five patients who did not have analyzable CRT ECGs and one patient who had CRT upgrade from RV pacing were excluded.

Baseline QRS durations (161.7±15.9 vs. 162.2±17.8 ms, p=0.95), QTc intervals (435.6±56.9 vs. 444.6±44.5 ms, p=0.73), Tp-Te values (107.1±20.5 vs. 108.5±17.6 ms, p=0.89) and Tp-Te/QT ratios (0.24±0.05 vs. 0.24±0.03, p=0.88) were similar before epi and endo CRT.

In all patients QRS intervals reduced significantly following both epi and endo CRT (161.71±16 vs. 133.42±15, p<0.01; 162.28±18 vs. 133.14±8 ms, p<0.01 respectively). Although QRS interval reductions were similar (-28.3±11.6 vs. -29.1±11.4 ms, p=0.89), epi CRT was associated with a significant increase in Tp-Te values (17.1±19.5 vs. -12.6±18.9 ms, p=0.01) and Tp-Te/QT ratios (0.03±0.04 vs. -0.02±0.03, p=0.04) compared to endo CRT. Differences in QTc interval changes were not significant (14.4±37.5 vs. -17.0±45.2 ms, p=0.19).

2. Evaluating the effects of bipolar vs. unipolar and basal vs. non-basal LV pacing

The protocol was successfully completed in 20 of the 26 patients. Bipolar LV pacing was associated with a significantly better Tp-Te value than unipolar pacing from both sides of the LV. (Basal, unipolar vs. bipolar, 119.1±36.7 vs. 97.6±27.9 ms, $p<0.05$; non-basal, unipolar vs. bipolar, 117.9±36.3 vs. 98.6±20.4 ms, $p<0.05$). Pacing from basal and non-basal segments of LV had no differential effect on repolarization parameters (Bipolar Tp-Te, basal vs. non-basal, 97.6±27.9 vs. 98.6±20.4 ms, $p=0.89$; unipolar Tp-Te, basal vs. non-basal, 119.1±36.7 vs. 117.9±36.3 ms, $p=0.92$). The mean baseline Tp-Te/QT ratio was 0.25±0.05. Although Tp-Te/QT ratios were lower with bipolar pacing, the differences were not significant (Basal, unipolar vs. bipolar, 0.26±0.06 vs. 0.23±0.06, $p=0.14$; non-basal, unipolar vs. bipolar, 0.28±0.10 vs. 0.23±0.03, $p=0.06$). There was no significant change between QTc intervals.

QRS intervals in all patients reduced significantly following both unipolar and bipolar CRT ($p<0.01$). However, QRS reduction was more prominent with bipolar pacing than with unipolar pacing (Basal, unipolar vs. bipolar, 135.1±17.8 vs. 119.3±14.5 ms, $p<0.01$; non-basal, unipolar vs. bipolar, 134.4±15.7 vs. 121.9±10.3 ms, $p<0.01$). Interestingly, LV pacing location had no impact on QRS duration (Bipolar, basal vs. non-basal, 119.3±14.5 vs. 121.9±10.3 ms, p=0.53; unipolar, basal vs. non-basal, 135.1±17.8 vs. 134.4±15.7 ms, p=0.89).

3. Evaluating the effects of respiratory gating on AF ablation procedures

We enrolled 140 patients who underwent AF ablation for the first time. In respiratory gated group (70 patients, mean age 59±10 years, 21 female) underwent procedures after enabling AccuResp module. In nongated group (70 patients, mean age 56±10 years, 25 females) procedures were performed using the same EAM system without enabling the AccuResp module.

Durations from the beginning of the procedure to beginning of the EAM reconstruction were similar in both groups [median 22 (IQR 17-27) vs. median 21 (IQR 16-25), p=0.40] min.

In gated group electroanatomical maps reconstructed within median 14 (IQR 12-16) vs. median 13 (IQR 10-18) min in non-gated group (p=0.19).

Significantly shorter ablation times were observed in respiratory gated group [median 37 (IQR 32-53) vs. median 48 (IQR 39-65) min, $p<0.05$]. However, total RF application durations were not different between two groups [median 1554 (IQR 1213-2196) vs. median 1802 (IQR 1344-2448) s, $p=0.11$].

A significant reduction in total procedure times [median 77 (IQR 66-95) vs. median 82 (IQR 72-104) min, $p<0.05$] and fluoroscopy times [median 14 (IQR 9-17) vs. median 16 (IQR 12-22) min, $p<0.05$] were observed in the respiratory gated group.

V Conclusion

1. Transseptal LV endocardial pacing is associated with better arrhythmogenic repolarization characteristics than epicardial pacing in CRT. Larger clinical studies are needed to determine whether these effects may contribute to reduction of arrhythmias.

2. LV pacing polarity significantly affects repolarization patterns regardless of pacing site. Bipolar LV pacing is

associated with better ventricular repolarization characteristics compared to unipolar LV pacing. The LV pacing site, from the perspective of basal and non-basal segments, has no differential effect on repolarization parameters. Quadripolar LV leads offer ten left ventricular pacing configurations, and unipolar (extended bipolar) LV pacing is widely used to overcome technical issues such as phrenic nerve capture and stimulation thresholds. Randomized controlled studies comparing the bipolar and unipolar LV pacing are needed to determine whether these changes are related to arrhythmic risk in patients with CRT.

3. Respiratory gated electroanatomic mapping significantly improves ablation and fluoroscopy times during AF ablation. Beside these advantages, using automatic respiratory gating module does not prolong mapping times.

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