Evaluation of Multi-Lead ECG Markers to Track Changes in Dispersion of Ventricular Repolarization in the Intact Human Heart

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Abstract

Dispersion of ventricular repolarization (DRT) is an important factor contributing to the vulnerability to life-threatening arrhythmias. An accurate non-invasive methodology for its estimation would contribute to improve risk-prediction. We assessed 3 multi-lead ECG markers to track changes in DRT using intra-cardiac data recorded in patients with structurally normal ventricles. Changes in DRT were measured with intra-cardiac unipolar electrograms (UEG) simultaneously recorded in the RV endocardium (RVendo), LV endocardium (LVendo) and LV epicardium (coronary sinus, LVepi) in 10 patients. Standard S1S2 restitution protocols were conducted by pacing from the RVendo ($n = 8$), LVendo ($n = 10$) and LVepi ($n = 7$). DRT was measured as latest minus earliest repolarization time (RT). In the surface ECG, DRT was estimated from precordial and augmented limb leads as: (1) Interval between the earliest and the latest maximum upslope of the T-wave (ΔT_{up}); (2) Interval between median T-peak and median T-end ($T_{pe,med}$); (3) Interval between the earliest T-peak and latest T-end ($T_{pe,range}$). Intra-patient correlation with DRT changes was higher using ΔT_{up} (0.79, $0.66-0.89$) than $T_{pe,med}$ (0.61, $0.14-0.76$, $P = 0.001$) or $T_{pe,med}$ (0.71, $0.44-0.79$, $P = 0.054$).

1. Introduction

Ventricular repolarization dynamics modulate vulnerability to potentially life-threatening ventricular arrhythmias. The spatial organization of ventricular repolarization and its beat to beat variability is known to play an important role in determining susceptibility to arrhythmia and its non-invasive assessment can be useful for improving risk prediction. In particular, repolarization dispersion, i.e. the duration of the repolarization process from its beginning to its end, is known to be important [1]. Unfortunately, the link between the repolarization sequence and the morphology of the T-wave of the surface ECG in the intact human heart is still poorly characterized. In this study we assessed 3 multi-lead ECG markers to track changes in dispersion of repolarization using intra-cardiac data recorded in patients with structurally normal ventricles.

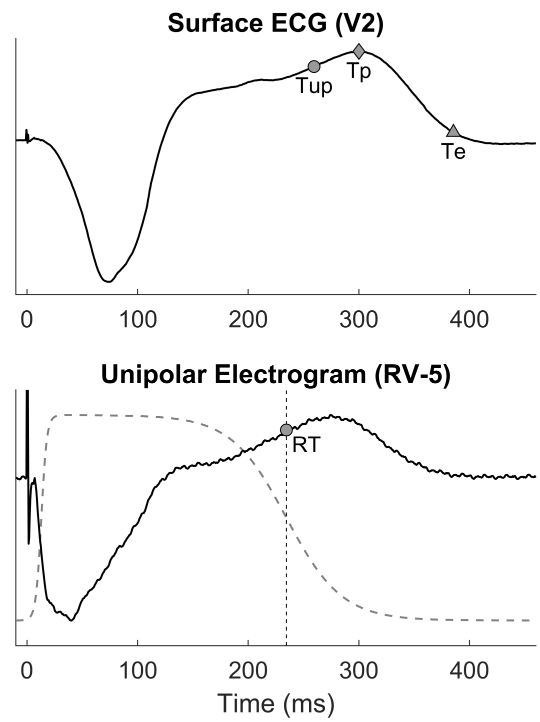

Figure 1. Repolarization markers in the surface ECG (above) and unipolar electrograms (below). Local repolarization time (RT) was measured at the maximum of the first derivative of the signal. Dashed line represents a stylized action potential.

2. Methods

Three decapolar catheters were used to simultaneously map the right ventricular endocardium (RVendo), left ventricular endocardium (LVendo) and left ventricular epicardium (coronary sinus, LVepi) in 10 patients undergoing an electrophysiological study for treatment of supra-ventricular tachycardia [2]. Unipolar electrograms (UEG, sampling frequency 2000 Hz, $0.05-500$ Hz) and the 12-lead ECG (sampling frequency 2000 Hz, $0.05-100$ Hz) were simultaneously recorded. All patients had a structurally normal heart and normal ECG. An standard S1S2 restitution protocol [2, 3] was conducted by pacing from the RVendo (in $n = 8$ patients), LVendo (in $n = 10$ patients) and LVepi (in $n = 7$ patients). Following a train of nine steady-state $S1S1$ stimuli at 600 ms, an extra stimulus at a shorter coupled pacing interval $S1S2$ was introduced. The $S1S2$ coupling interval was decremented in 50 ms steps from 1000 ms to 400 ms, then by 20 ms intervals between 380 and 400 ms, and thereafter in 5 ms steps until the effective refractory period (ERP) of the tissue. At ERP an S2 stimulus at 10 ms + ERP was applied followed by further decrementing S2 in steps of 2 ms.

Local repolarization times (RT) was measured from the UEG at the maximum of the first derivative, $\max(dV/dt)$, of the signal during the T-wave (Fig. 1). This is a standard measurement supported by experimental [4] and theoretical [5] studies, and largely adopted in human electrophysiological research [2, 6, 7]. Total dispersion of repolarization (ΔRT) was measured in the beats following the short-coupled intervals as the interval between the earliest to the latest repolarization time (RT). Body surface ECG was analyzed with custom software as in previous studies [8, 9] to measure the following ECG markers: T_{up}, time of the maximum of the first derivative during the T-wave upslope, $\arg\max(dV/dt)$ (as for local RT estimate in the UEG), T-wave peak (Tp) and T-wave end (Te), which was measured using the tangent method (Fig. 1). All markers were visually inspected and corrected if needed. The following markers of dispersion of repolarization were derived from inter-lead analysis of precordial and augmented limb leads of the surface ECG:

- 1. Interval between the earliest and the latest maximum upslope of the T-wave (ΔT_{up});
- 2. Interval between the earliest T-peak and latest T-end ($T_{pe,range}$).
- 3. Interval between median T-peak and median T-end ($T_{pe,med}$);

The Spearman's correlation coefficient between ΔRT and the surface ECG estimates of ΔRT was measured per each $S1S2$ restitution curve ($n = 25$). Results are show as median and Q1-Q3 interval.

3. Results

An example of surface ECG and intra-cardiac UEG during RV pacing is shown in Fig 2. Local RT was early in the RV-apex and late in the LV-base. As expected [5], UEGs showed upright T-wave in the RV (early RT) and inverted T-wave in the LV (late RT). Interestingly, Tup was early

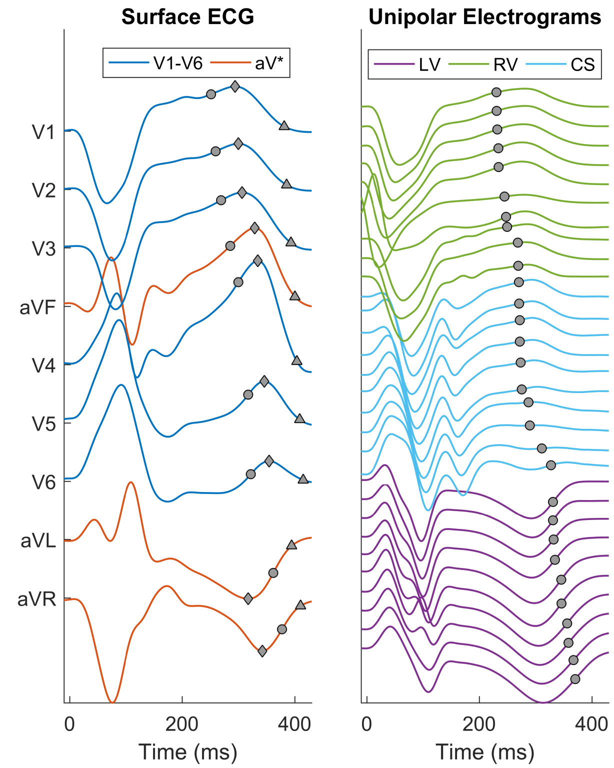

Figure 2. Intrac-ardiac (right) and corresponding surface (left) recordings during RV apical pacing. Local repolarization time (RT) is early in the RV and late in the LV (right). A similar pattern is observed for Tup on the ECG (left). Note the similar morphology between RV UEG and V1-V2.

in V1-V2, where the T-wave resembled the T-wave of RV UEGs, and late in V6 and aVL.

Representative examples of the correlation between ΔRT measured from the intrac-ardiac UEGs and estimated from the surface ECG as ΔT_{up} is shown in Fig. 3, which shows the changes of ΔRT and ΔT_{up} as a function of pacing interval (left) as well as their scatter-plot (right). As expected [3], dispersion of repolarization initially decreases with decreasing pacing interval and then increases for pacing interval lower than 350 ms as a result of the engagement of conduction velocity restitution. In both patients, the correlation coefficient was $\rho \approx 0.90$.

Group analysis showed that changes in ΔRT from cycle length equal to 1000 ms to effective refractory period (240, 223-250 ms) were equal to 94.4 ± 36.9 ms. Intra-patient correlation between changes in ΔRT and changes in surface ECG markers was equal to 0.79 $(0.66-0.89)$ for ΔT_{up}, 0.71 $(0.44-0.79)$ for $T_{pe,range}$ and 0.61 $(0.14-0.76)$ for $T_{pe,med}$ (Fig. 4). Group differences were significant ($P = 0.017$, Kruskal-Wallis test) and pair-wise comparison showed that ΔT_{up} correlated significantly bet-

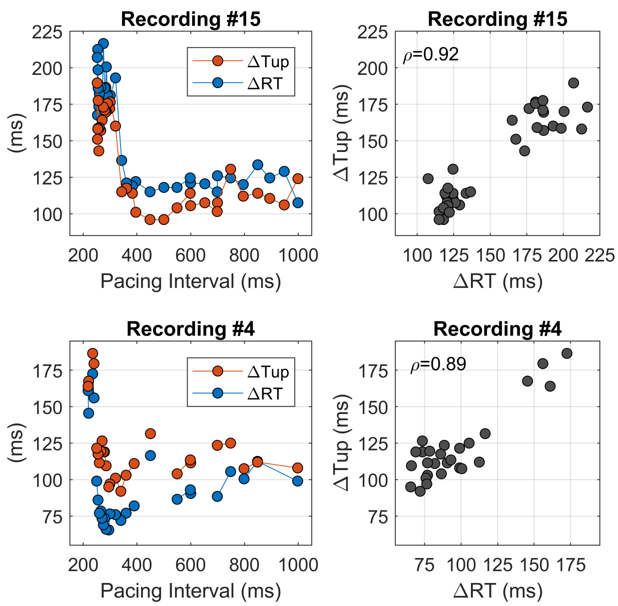

Figure 3. Relation between dispersion or repolarization measured with intra-cardiac unipolar electrograms (ΔRT) and estimated from the surface ECG as ΔT_{up}. Left: Changes of both ΔRT and ΔT_{up} as a function of pacing interval. Right: Scatter-plot showing tight correlation between ΔRT and ΔT_{up}, with correlation coefficient $\rho > 0.89$.

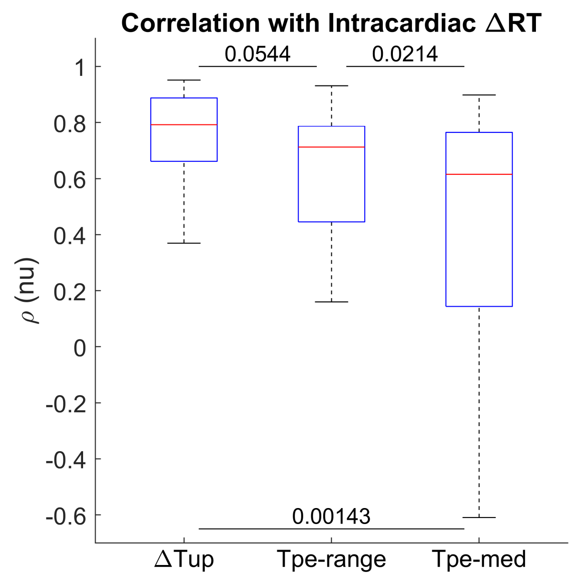

Figure 4. Distribution of the intra-patient correlation coefficient ρ between dispersion or repolarization measured with intra-cardiac unipolar electrograms (ΔRT) and estimated from the surface ECG in $n = 25$ restitution protocols (across 10 patients). Pair-wise different are measured with the Wilcoxon signed-rank test, with p-values reported above horizontal lines.

ter than $T_{pe,med}$ ($P = 0.001$) and almost significantly better than $T_{pe,range}$ ($P = 0.054$) with ΔRT (Fig. 4).

4. Discussion

This study assessed three surface ECG markers to track changes of dispersion of ventricular repolarization in the intact human heart. The main result is that ΔT_{up}, i.e. the interval between the earliest and latest Tup, measured as $\arg\max(dV/dt)_{max}$, tracks changes in dispersion of repolarization with high intra-patient correlation.

The underlying hypothesis of this study is that a unipolar surface ECG lead can be interpreted as a unipolar electrogram at a distance, therefore providing information about regional repolarization of the most proximal cardiac segment. For instance, early and late RV repolarization often corresponded to upright and inverted (or biphasic) T-waves in V1-V2, respectively, while early and late LV repolarization often corresponded to upright and inverted (or biphasic) T-waves in V5-V6.

Our results are in partial agreement with the results of a recent and elegant porcine study [10].

Our study focused on markers to track changes in the dispersion of repolarization and the results were based on intra-patient correlation. This was intended to reduce the bias introduced by the fact that the intra-cardiac mapping did not cover the entire endocardial and epicardial surfaces of the heart, which may have resulted in an under-estimation of the *true* dispersion of repolarization. The extent of this bias depends on the geometrical configuration of the catheters with respect to the repolarization sequence and may be different in each patient.

The results of this study have implications for cardiac risk assessment, and ΔT_{up} should be compared and/or integrated with/to other ECG repolarization indices [11–13]. Future studies could also assess the capability of ΔT_{up} to track beat-to-beat repolarization variability [14–16].

In conclusion, multi-lead index ΔT_{up} tracks changes in dispersion of repolarization with high intra-patient correlation.

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