Dynamics of Ventricular Electrophysiology Are Unmasked Through Noninvasive Electrocardiographic Imaging

DOI: 10.23919/CinC53138.2021.9662863
Handle: http://hdl.handle.net/1942/37299

Dynamics of Ventricular Electrophysiology Are Unmasked Through Noninvasive Electrocardiographic Imaging

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Abstract

Dynamic variability of ventricular activation and recovery can be a physiological phenomenon, but is also known to increase susceptibility to arrhythmias. It has been extensively studied on the 12-lead electrocardiogram (ECG), but subtle (patho)physiological variations may be challenging to detect and localize due to the limited spatial resolution. Electrocardiographic imaging (ECGI) could be a useful noninvasive high-resolution mapping technique to investigate ventricular dynamics in more detail. Ventricular activation and recovery times (ATs and RTs) were examined using ECGI in 10 normal subjects. Zero-th order Tikhonov regularization was used in combination with a spatiotemporal estimation method to determine ATs and RTs. Dynamics were defined as standard deviations of ventricular ATs and RTs over three beats. Dynamics were higher for recovery than for activation during sinus rhythm, and significantly exaggerated after ventricular ectopy. Left ventricular areas were less dynamic than right ventricular areas. Since arrhythmias may arise due to an increase in ventricular dynamics in the diseased heart, these results provide an important basis for future research on ventricular dynamics and arrhythmias.

1. Introduction

The temporal variability of ventricular activation and recovery during sinus rhythm has been studied extensively on clinical electrocardiograms (ECG), but has not been studied directly on the heart at high spatial resolution. Electrocardiographic imaging (ECGI) enables to noninvasively project electrical activation and recovery on the heart surface based on the combination of body-surface mapping and a patient-specific torso-heart geometry. ECGI has previously been validated by our group [1] and others. To set a standard for future research on dynamic ventricular parameters such as RR interval, rate-dependent aberrant conduction, T-wave variability, we investigated variations of activation and recovery in normal human subjects at rest through ECGI.

2. Methods

2.1. Patient selection

The study was approved by the Medical Ethics Committee of Maastricht University Medical Center. All subjects gave written informed consent. 10 Subjects with atypical chest pain underwent a cardiac CT-scan as part of routine clinical care but proved negative for any cardiac pathology on full examination and after follow-up.

2.2. BSPM and geometry

A CT scan was performed with intravenous iodine contrast medium and the diastolic phase of the torso-heart geometry was reconstructed. Subsequently, segmentation of the ventricular epicardium was performed manually. Geometries were reduced to a median of 1967 (1842-2100) nodes. Prior to the CT scan, a body-surface potential map (BSPM) was recorded. Recordings were made using a 256-channel acquisition system of which 184±9 were used on average, with a 2048-Hz sampling rate (BioSemi, Amsterdam, The Netherlands). For each subject, three consecutive sinus beats and three sinus beats occurring within minutes from each other were analyzed.

2.2. Preprocessing and reconstruction

Baseline drift and 50Hz noise were removed from the BSPM. The STT-segment was filtered with a 2nd order 40Hz lowpass Butterworth filter. Subsequently, inverse reconstructions of epicardial potentials were performed using an epicardium-only formulation of ECGI [1], with zero-th order Tikhonov regularization. The median value of the regularization parameter (lambda) was used for each

separate beat. A spatiotemporal estimation method was then used to determine the activation and recovery times (ATs and RTs) from the reconstructed epicardial electrograms [1].

Subsequently, a median filter with a 15mm radius was applied to calculated RTs. Lastly, to correct for unreliable RTs in regions of low-amplitude T-waves, RTs which fell outside of the largest area of positive derivative of the T-wave were blanked and spatially interpolated. ATs and RTs are expressed relative to the start of QRS on the 12-lead ECG. Our previously developed algorithm UNISYS [2] was used for standardized analysis of different segments of the ventricles. Epicardial bullseyes were separated into 20 segments, see Fig. 1. Dynamics were assessed by calculating standard deviations (SD) of ATs and RTs for each location relative to the first AT, over three beats. This was done for both three consecutive beats, and three beats within minutes from each other, all with similar RR intervals. Average SDs were calculated for each segment.

3. Results

3.1. Patient characteristics

Table 1 shows the subject characteristics. Mean age was 58±7 years. 2 Subjects were male, and mean left ventricular ejection fraction (LVEF) was 60%. Mean PQ interval was 156±15ms, mean QRS duration was 89±8ms, and mean QTc interval was 414±19ms.

Table 1. Patient characteristics

Subject ID (sex)	Age (y)	LVEF (%)	PQ (ms)	QRS (ms)	QTc (ms)
1 (F)	60	61	152	88	431
2 (F)	65	61	156	94	404
3 (M)	65	69	180	98	398
4 (F)	56	53	154	92	419
5 (F)	67	N/A	164	80	406
6 (F)	53	60	146	84	399
7 (F)	53	67	142	82	389
8 (F)	52	61	130	94	442
9 (F)	62	56	178	78	411
10 (M)	48	55	158	100	442

3.2. Baseline activation and recovery

Average activation duration (AT_{max}-AT_{min}) over all 10 subjects was 36ms. Average recovery dispersion (RT_{max}-RT_{min}) was 85ms. Activation and especially recovery isochrones showed pronounced differences between subjects. However, overall, within an individual these were qualitatively similar through time; both for consecutive beats and within minutes (representative examples for three individuals in Fig. 2). These results suggest a high inter-person variability of activation and recovery, but a

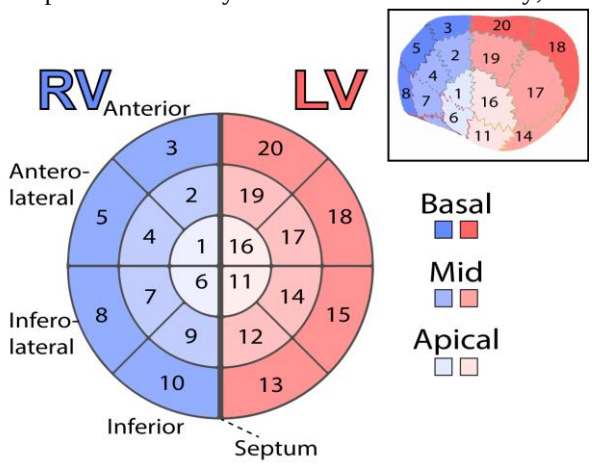

Figure 1: anatomical division of segments through UNISYS. RV/LV: right/left ventricle.

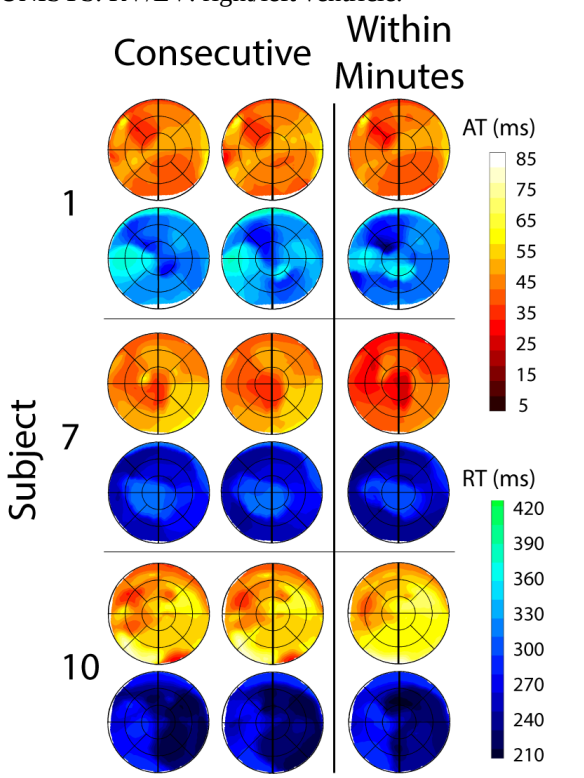

Figure 2: AT and RT isochrones for subjects 1, 7 and 10. 2/3 consecutive beats and 1/3 beats within minutes from each other are shown.

3.3. Dynamics

Differences between subjects and segments were pronounced (see Figs. 3 and 4). Overall, SD of ATs and RTs were similar for consecutive beats compared

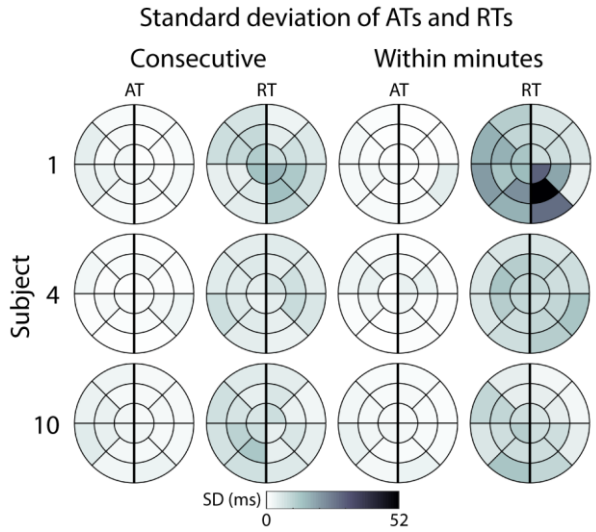

Figure 3: standard deviation of ATs and RTs for three consecutive beats and for three beats within minutes from each other, in subjects 1, 4 and 10.

low intra-person variation.

to within minutes. For activation, left ventricular (LV) anterior/anterolateral (A/AL) segments were the least variable segments, followed by LV inferior/inferolateral (I/IL), RV A/AL and RV I/IL segments, respectively. For recovery, LV I/IL segments were the least variable segments, followed by LV A/AL, RV I/IL and RV A/AL segments, respectively. Two subjects had ventricular extrasystoles (VES). After a VES, dynamics in repolarization (SD of RTs) greatly increased from 14ms to 21ms in subject 5, and from 9ms to 18ms in subject 8 (see Fig. 5). This marks a pronounced increase from measurements at rest (see Fig. 4).

4. Discussion

We previously investigated the dependency of ECGI on technical implementations (electrode displacement, using a static diastolic geometry, using less electrodes) [1], [3]. For a single application, the 'technical variability' of ECGI results appeared to be limited, which allows for using ECGI to investigate 'physiological variability'. Here, for the first time, we quantitatively and systematically assessed ventricular activation and recovery and their dynamics in 10 normal subjects. Moreover, for two subjects, dynamics around a VES were analyzed.

Dynamics of recovery as shown by ECGI were greatly increased around a VES, which would be physiologically expected through abrupt changes in RR or a different activation/recovery pattern. Interestingly, dynamics did not increase homogenously throughout the epicardium and was different between subjects; dynamics increased mainly for LV segments for subject 5, and inferior segments in subject 8. Moreover, dynamics appeared to increase in certain segments for subject 5 even before the VES, which could imply a potential value for ECGI to predict upcoming arrhythmic phenomena. Indeed, it is known that repolarization dynamics may precede arrhythmias [4]. In-depth analysis of dynamics around a

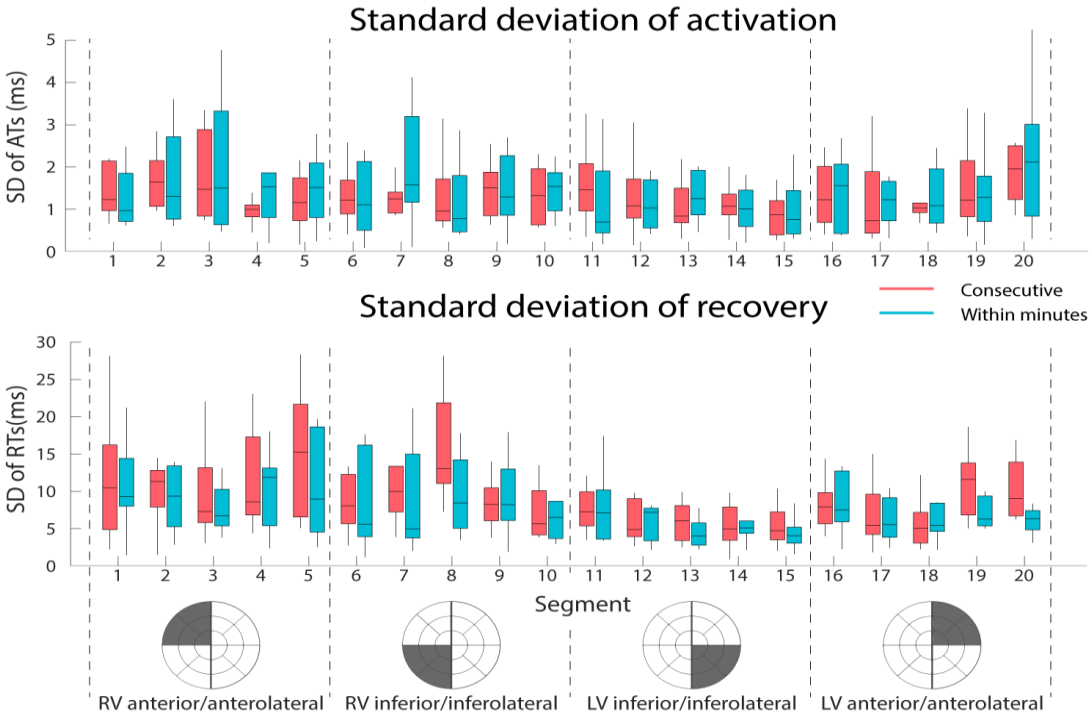

Figure 4: standard deviations of ATs and RTs per segment. Segments denoted in Figure 1. LV/RV: left/right ventricle.

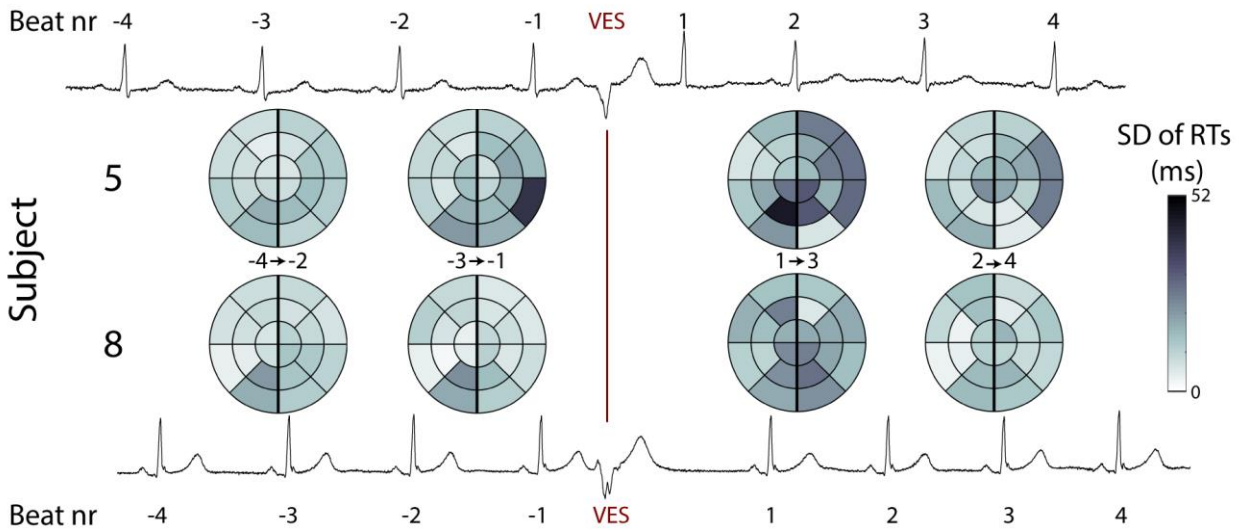

Figure 5: Dynamics) of recovery patterns (SDs of RTs) before and after a VES in subjects 5 and 8. Each beat is denoted with a number. Dynamics were calculated over three beats, i.e. beats -4 to -2, -3 to -1, etc. As visible in both subjects, dynamics increase after a VES. In subject 5, dynamics also increase before the VES.

VES through ECGI may uncover previously concealed dynamic pathologies.

Activation and especially recovery patterns were different throughout subjects, but stable within one subject. These inter-subject differences are qualitatively consistent with earlier findings [5]. However, dynamics of recovery were not assessed before. Recovery was about 5-fold more variable than activation, most likely since activation takes less time and spreads by neighboring cells through the conduction system, while repolarization takes a longer time and is a more local phenomenon. LV segments were less dynamic in recovery than right ventricular (RV) segments. This could possibly be due to differences in sympathetic innervation or ion channel expression.

Even though not addressed in this study, short-time changes in breathing may be a factor of influence in this study and would require more future research. This could also hold for other confounding factors such as small RR differences and noise which could cause the regularization parameter (lambda value) to vary between beats, even though this parameter was fairly stable in between beats. We deliberately chose to use the median lambda value for each beat, since this method was validated earlier [1] and reflects a real-life situation.

Future goals are to further expand this research to pathology involving dynamics such as T-wave variability. Even though SDs over three beats were analyzed here, many other measures could be used such as ventricular conduction stability (VCoS) or short-term variability (STV) [4]. The dynamics shown here around a VES suggest that ECGI would be fit to investigate arrhythmic events. Research involving STV and our current finding in subject 5 both hint towards the potential use of ECGI for short-term risk stratification of upcoming arrhythmias.

5. Conclusion

This is the first study to systematically and noninvasively investigate dynamics of both depolarization and repolarization on a temporal and spatial scale. ECGI revealed many dynamic aspects of ventricular electrophysiology, even in these normal individuals. Our study shows that ECGI would be a promising tool to uncover dynamic pathology that may form a substrate for ventricular arrhythmias.

6. References

[1] M. J. M. Cluitmans *et al.*, "In Vivo Validation of Electrocardiographic Imaging," *JACC Clin. Electrophysiol.*, vol. 3, no. 3, pp. 232–242, 2017.

[2] J. Stoks, U. Chau Nguyen, R. Peeters, P. Volders, and M. Cluitmans, "An Open-Source Algorithm for Standardized Bullseye Visualization of High-Resolution Cardiac Ventricular Data: UNISYS," *Comput. Cardiol.* vol. 47, Dec. 2020.

[3] M. J. M. Cluitmans *et al.*, "In-vivo Evaluation of Reduced-Lead-Systems in Noninvasive Reconstruction and Localization of Cardiac Electrical Activity," *Comput. Cardiol.*, vol. 42, pp. 221–224, 2015.

[4] M. B. Thomsen *et al.*, "Increased Short-Term Variability of Repolarization Predicts dS-Sotalol–Induced Torsades de Pointes in Dogs," *Circulation*, vol. 110, no. 16, pp. 2453–2459, Oct. 2004.

[5] C. Ramanathan, P. Jia, R. Ghanem, K. Ryu, and Y. Rudy, "Activation and Repolarization of the Normal Human Heart Under Complete Physiological Conditions," *Proc. Natl. Acad. Sci.*, vol. 103, no. 16, pp. 6309–6314, Apr. 2006.

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