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The relation between local repolarization and T-wave morphology in heart failure patients

Francesco Maffessanti [a,1], Joris Wanten [b,2], Mark Potse [a,c,2,3], Francois Regoli [d,4], Maria Luce Caputo [d,4], Giulio Conte [d,4], Daniel Sürder [d,4], Annekatrin Illner [d,e,2], Rolf Krause [a,2], Tiziano Moccetti [d,3], Angelo Auricchio [a,d,1], Frits W. Prinzen [b,*,1]

[a] Center for Computational Medicine in Cardiology, USI, Lugano, Switzerland
[b] Maastricht University, Maastricht, The Netherlands
[c] INRIA Bordeaux Sud-Ouest & LIRYC - Institute of Cardiac Rhythmology, Bordeaux, France
[d] Cardiocentro Ticino, Lugano, Switzerland
[e] Otto von Guericke Universität, Magdeburg, Germany

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ABSTRACT

Background: Both duration and morphology of the T-wave are regarded important parameters describing repolarization of the ventricles. Conventionally, T-wave concordance is explained by an inverse relation between the time of depolarization (TD) and repolarization (TR). Little is known about T-wave morphology and TD-TR relations in patients with heart failure.

Methods: Electro-anatomic maps were obtained in the left (LV) and right ventricle (RV) and in the coronary sinus (CS) in patients with heart failure with narrow (nQRS, $n = 8$) and wide QRS complex with (LBBB, $n = 15$) and without left bundle branch block (non-LBBB, $n = 7$). TD and TR were determined from the thus acquired electrograms.

Results: In nQRS and non-LBBB patients, TD-TR relations had a slope between 0 and +1, indicating that repolarization followed the sequence of depolarization. In LBBB patients, repolarization occurred significantly earlier in the RV than in the LV, fitting with the idea that the discordant T-waves in LBBB are secondary to the abnormal depolarization sequence. However, the slopes of the TD-TR relations in the LV and CS were not significantly different from zero, indicating no major spatial gradient in LV repolarization, despite a considerable gradient in depolarization. Remarkable was also the large (~100 ms) transseptal gradient in repolarization. Values of the slopes of the TD-TR relation overlapped between the three patient groups, despite a difference in T-wave morphology between LBBB (all discordant) and nQRS patients (all flat/biphasic).

Conclusions: Discordant T-waves in LBBB patients are explained by interventricular dispersion in repolarization. T-wave morphology is determined by more factors than the TD-TR relation alone.

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1. Introduction

Both the duration and the morphology of the T-wave are regarded as important parameters that describe the repolarization of the ventricles. T-wave analysis is especially relevant to diagnosis of ischemia and (risk for) arrhythmia. However, the genesis of the T-wave is less well understood than that of the QRS complex.

In the normal heart a well-known feature of the T-wave is that it has the same polarity as the QRS complex, referred to as concordance of the T-wave. This concordance can only be understood if the main direction of repolarization is opposite to that of the preceding depolarization, in other words, that the latest depolarizing regions repolarize first. Indeed, many studies in animals and relatively healthy humans observed an inverse relation between the time of depolarization (TD) and repolarization (TR) of a region [1–3]. Less negative or even positive TD-TR relations have been observed in small groups of patients with aortic valve stenosis, coinciding with smaller or discordant T-waves [4,5]. Such T-wave abnormalities are regarded as signs of adverse electrical remodeling and increased risk for arrhythmias, which are likely related to the electrical remodeling that is known to occur in failing hearts [6].

In patients with a wide QRS complex the T-wave is mostly discordant. However, the basis of these discordant T-waves is not clear and

* Corresponding author at: Dept. of Physiology, Universiteitssingel 50, 6229 ER Maastricht, P.O. Box 616, 6200 MD Maastricht, The Netherlands.
E-mail address: frits.prinzen@maastrichtuniversity.nl (F.W. Prinzen).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[2] This author contributed to data analysis.
[3] This author contributed to the design of the study.
[4] This author contributed to data collection.

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neither whether such discordant T-waves should be regarded as adverse or whether they are simply a consequence of the extremely long depolarization time. The interest for the T-wave in patients with wide QRS complex is also growing, owing to recent publications reporting that the size of the T-wave is a good predictor of CRT response [7,8] and that a reduction in LV action potential duration following CRT is associated with a good echocardiographic response to CRT [9]. To the best of our knowledge, no studies have been investigating the cause of the discordant T-waves in patients with wide QRS complex.

It was the aim of the present study to investigate the regional distribution of repolarization times within the ventricles in patients with heart failure and varying QRS complexes with specific attention to the relation between local depolarization and repolarization and to T-wave morphology on the ECG. We hypothesized that differences in QRS duration and morphology may influence the T-wave because experimental studies showed characteristic structural [10] and electrical remodeling in hearts with dyssynchronous heart failure [11].

2. Methods

2.1. Patient inclusion

Thirty consecutive patients with moderate-to-severe HF, LV ejection fraction <35%, and dilated cardiomyopathy of any etiology, referred to the Division of Cardiology, Fondazione Cardiocentro Ticino, for non-pharmacologic treatment were prospectively enrolled in this study. Twenty-two of them had a wide QRS complex and were candidate for CRT. These patients were divided into subgroups with left bundle branch block (LBBB, $n = 15$) and without LBBB (non-LBBB, $n = 7$). LBBB was defined according to the Strauss criteria [12]. The other patients had a narrow QRS complex, ischemic cardiomyopathy, and were candidate for stem-cell therapy (nQRS, $n = 8$).

All patients were on stable drug therapy with maximally tolerated doses of angiotensin-converting enzyme inhibitors or angiotensin-1 receptor blockers, diuretics, digitalis, aldosterone antagonists and beta-blockers (see Table 1 in Supplementary materials). All patients underwent standard 12-lead ECG (CS200 excellence, SchillerAG, Baar, Switzerland), a clinically indicated cardiac magnetic resonance (CMR) study (Magnetom Skyra, Siemens, Erlangen, Germany), and an electrophysiologic study including electroanatomic mapping (EAM) of the LV and RV and coronary angiography. Patient information was de-identified. All patients provided oral and written consent. The study was performed according to institutional ethics guidelines and approved by the institutional committee.

2.2. Electro-anatomic mapping

The electro-anatomic mapping system (Noga XP, Biologic Delivery Systems, Division of Biosense Webster a Johnson & Johnson Company) as well as the navigation and mapping methods were described previously [13].

In brief, a conventional 7F deflectable-tip mapping catheter (NogaStar, Biologic Delivery Systems, Division of Biosense Webster a Johnson & Johnson Company) was deployed in the LV via a retrograde aortic approach from the femoral artery. Moreover, in 15 patients with wide QRS complex also the RV and coronary sinus were mapped. Unipolar electrograms (UEGs) were recorded at a median of 107 (IQR 74–164) LV sites, 42 (33–62) RV sites and 55 (41–61) coronary sinus sites. A set of signal and catheter stability criteria was checked before a measurement point was accepted, following the standardized NOGA mapping criteria [13,14]. The sequentially recorded UEGs and position data were aligned using the simultaneously recorded 12-lead surface ECG.

2.3. Off-line data processing

After the mapping procedure, a secondary check of catheter stability criteria was performed taking into account large spatial gradients in, e.g., catheter trajectories. Also recordings of papillary muscles, which appear as internal protrusions to the endocardial reconstruction, were removed. Subsequently, the UEG were made available for custom off-line post-processing for which an analysis program was created in MATLAB (Mathworks, Natick, Massachusetts, USA). From the UEGs the local times of depolarization (TD) and repolarization (TR) were computed as the time of $(-dUEG/dt)_{max}$ and $(+dUEG/dt)_{max}$ in user-defined time windows including the QRS complex (Fig. 1, red) and the T wave (blue), respectively (Fig. S1). The earliest time of depolarization measured within a heart was used as reference for TD and TR (Fig. S1).

2.4. ECG analysis

Beside conventional measurement of QRS duration and QT-time, also variables were calculated that were derived from the vectorcardiogram, calculated from the digital 12-lead ECGs as described in detail elsewhere. Calculated were three dimensional QRSarea and Tarea, as descriptors of the size of these two ECG components [7,15]. In addition, the spatial angle between the mean direction of the QRS complex and T-wave (spatial QRS-T angle) was calculated. This angle quantifies the degree of concordance and discordance: perfect concordance would show as an angle = 0 and clear discordance as an angle of 180°. Finally, the morphology of the T-wave was classified as concordant, discordant, or flat/biphasic, the latter category being in between concordant and discordant.

2.5. Statistical analysis

For each patient, correlation analysis was performed to establish the quantitative relationship between TD on the one hand and TR on the other (Stata 13.1, Stata Corp, College Station, USA). The strength of this relation was quantified by Spearman's correlation coefficient (R). Significance in baseline characteristics and ECG variables between the three patient subgroups was evaluated using the Kruskal-Wallis test. A linear mixed model was used to evaluate the effect of subgroup and region on the slope of the TD-TR relation. A p-value <0.05 was considered significant.

3. Results

3.1. Baseline characteristics

Patients in the three subgroups all had heart failure with reduced ejection fraction, were in NYHA class II or III, and all but 2 patients were in sinus rhythm at the time of mapping. Most characteristics were similar between subgroups, but nQRS patients all had a history of ischemic heart disease, as compared to only 40% in the other subgroups (Table 1 in Supplementary Data).

QRS duration was (by definition) different between the three subgroups (Table 2 in Supplementary Data) and so were QRSarea and QTc interval. Tarea values tended to follow those of QRSarea. The spatial QRS-T angle, averaged over the entire QRS complex and T wave, was 150-160 degrees in the LBBB and non-LBBB groups, indicating almost opposite orientation of these two components of the ECG. This fitted with discordant T-waves in all LBBB patients and 4 out of 7 non-LBBB patients. In the nQRS patients the spatial QRS-T angle was significantly smaller than in the other patients and coincided with flat or biphasic T-waves. (Table 2 in Supplementary Data).

3.2. Spatial distribution of depolarization and repolarization

Fig. 1 displays the ECG and the distribution of EAM-derived depolarization and repolarization times of an LBBB and a non-LBBB patient for the RV endocardium, LV endocardium, and LV epicardium (coronary sinus). As expected, in the LBBB patient depolarization occurred earliest in the RV, followed by the LV endocardium and ultimately in the LV epicardium. Repolarization in the RV preceded that in the LV endocardium and epicardium, the LV epicardium repolarizing slightly before the LV endocardium. In this patient, the T-wave was discordant and RV repolarization occurred before the peak of the T-wave, whereas LV repolarization occurred at or after the peak of the T-wave. In the non-LBBB patient the RV and LV endocardium were activated more or less simultaneously, while a later activation was noted in the CS. In the RV and LV endocardium the repolarization occurred throughout the T-wave, while repolarization near the coronary sinus occurred close to the peak of the T-wave (Fig. 1).

Fig. 2 displays the spatial distribution of TD and TR in one patient with LBBB, one with non-LBBB and one with nQRS. Depolarization of the LBBB patient showed the well-known pattern of early RV activation, a transseptal activation delay >30 ms and a gradual activation from the LV surface of the septum to the LV lateral wall [16]. In this patient repolarization within the RV and within the LV was almost simultaneous, but there was a large interventricular delay in repolarization. In contrast, in the non-LBBB patient repolarization followed the sequence of depolarization in both ventricles and the same was true for the LV of the nQRS patient.

3.3. TD-TR relations

The aforementioned repolarization patterns can be further described by the relation between TD and TR. Spearman correlation coefficients of

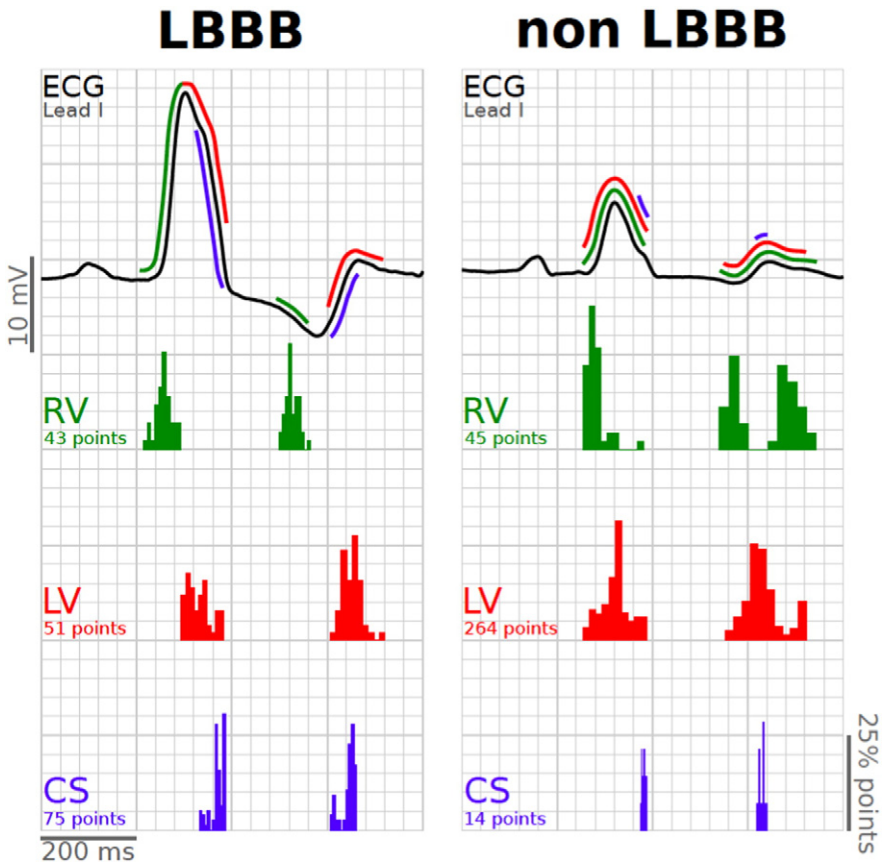


Fig. 1. ECG (upper) and distribution of RV (green), LV (red) and CS (blue) depolarization and repolarization times in an LBBB (left) and a non-LBBB patient (right).

these relations were 0.51 ± 0.24, lower values coinciding with flat TD-TR relations. In the LBBB patient depicted in Fig. 3, the repolarization times in the LV endocardium and epicardium were virtually independent of the sequence of activation. As a consequence, the LV endocardial and epicardial TD-TR slopes were flat. In contrast, the corresponding slope for the RV endocardium was slightly positive. It can be observed from the figure that the ~100 ms earlier depolarization in the RV was associated with earlier repolarization in the RV than in the LV, despite the positive RV slope. In an attempt to better relate TD-TR relations to T-wave morphology, also the slope of the TD-TR relation, calculated from all data points in this heart was calculated. Due to the large difference in TR between the RV and LV, the slope of this combined regression line (black line) was clearly positive.

In the non-LBBB patient the slopes for all three regions were similar and positive and so was the slope of the combined regression line. The regression line of the LV endocardium of the nQRS patient was also clearly positive.

The median TD-TR relations for all patients in the three subgroups are displayed in the lower panels of Fig. 3. These data illustrate that in the LBBB patients repolarization occurred generally earlier in the RV than in the LV. In the non-LBBB patients a relatively early repolarization was observed in the LV epicardial regions.

The slope of the TD-TR relation in LBBB patients was not significantly different from zero in the LV endocardium and epicardium, but was positive in the RV (Fig. S2, Supplementary Data). The slope of the TD-TR relation, based on all data points, was also significantly larger than zero. This indicates low intra-LV dispersion of repolarization but significant interventricular dispersion of repolarization. In non-LBBB patients LV endocardial TD-TR relations also had a near zero slope, whereas positive slopes were observed for the other regions. In the LV of the nQRS patients there was a significantly positive slope in the LV endocardium, denoting later repolarization in later activated regions. It is also Important to note the large standard deviation of the slopes of the TD-TR relations in all regions and subgroups, indicating considerable interindividual differences.

4. Discussion

The major findings in the present study are that 1) in patients with heart failure there is either a flat or a slightly positive TD-TR relation (slopes between 0 and 1), implying that the sequence of repolarization follows that of depolarization, but with a smaller dispersion than in depolarization, 2) the discordant T-wave in LBBB patients seems to be related to interventricular dispersion of repolarization combined with a remarkable lack of spatial gradient in repolarization in the LV and a large transseptal gradient of repolarization, 3) there is a large variation in the slope of the TD-TR relations between patients with the same T-wave morphology, suggesting that T-wave morphology may be determined by more factors than the slope of the TD-TR relation alone.

4.1. TD-TR slopes in patients with heart failure

These data are the first to show the dispersion in repolarization in patients with heart failure and reduced LV ejection fraction. The flat to moderately positive TD-TR relations are comparable to those observed in patients with aortic stenosis [4] and in patients with arrhythmias [17]. In contrast, negative TD-TR relations have been reported in relatively normal hearts [1,4,18]. Altogether these data seem to indicate that in healthy hearts the sequence of repolarization is opposite to the

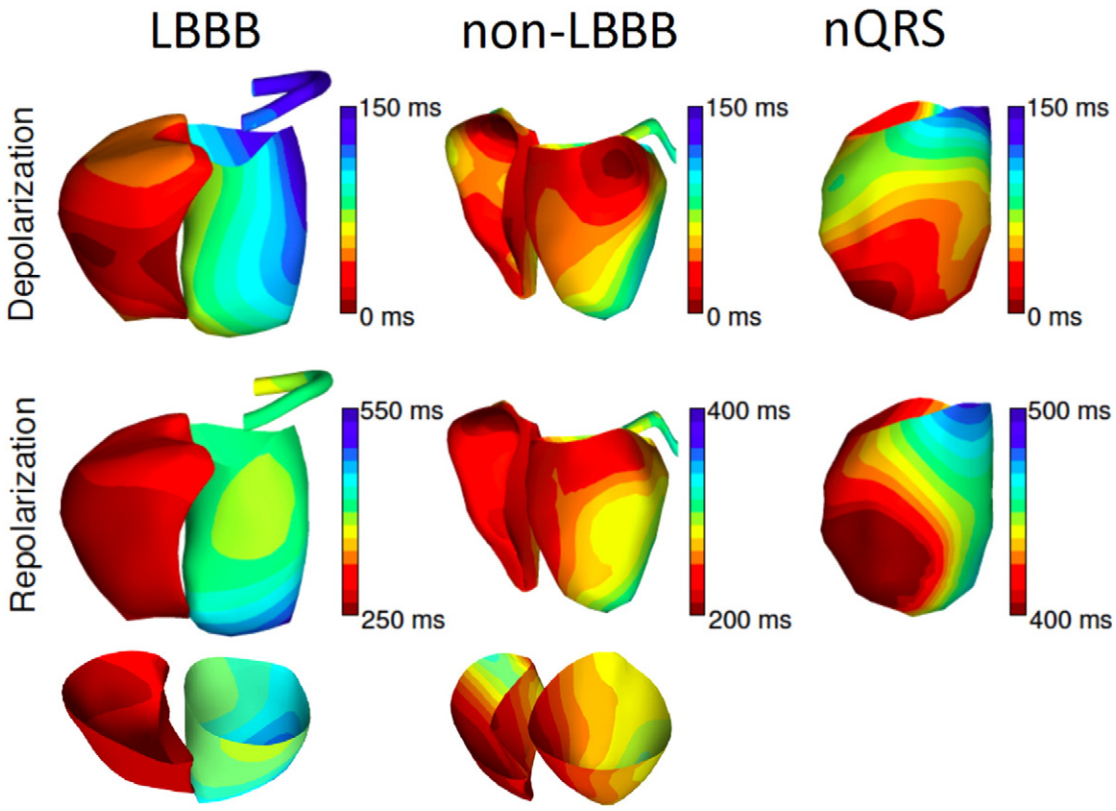


Fig. 2. 3D-depolarization (top) and repolarization maps (bottom) from patients with LBBB, non-LBBB, and nQRS. The shapes indicate the endocardial contours of the RV and LV and the course of the coronary sinus. For the LBBB and non-LBBB patient a cross-section through the LV and RV is also presented in order to depict the considerable transseptal gradient in repolarization in the LBBB patient. In the nQRS patient only the LV was mapped. Isochrones were calculated taking the original data points and interpolating them in time and space.

sequence of depolarization (negative TD-TR slope) whereas in various kinds of compromised hearts repolarization follows depolarization (slope > 0), albeit that the dispersion of repolarization is generally smaller than that of depolarization (slope < +1).

The previous studies were mostly limited to the LV [1,4,17,18], or RV [17] alone, whereas in the present study most patients with wide QRS complex were mapped in both ventricles, thus providing a more comprehensive view on repolarization. The first studies in this field used epicardial mapping [1,4,18] but later studies also used endocardial mapping [17,18] showing no significant differences in the TD-TR relation with epicardial mapping.

The recent study by Opthof et al. is unique in that it used detailed RV and LV measurements in all layers [2].

4.2. RV as dominant factor in determining the discordant T-wave

According to the canonic theory a disconcordant T-wave is explained by a positive slope of the TD-TR relation [1]. The currently observed flat TD-TR relations in the LV of LBBB patients are hard to reconcile with their discordant T-waves. On the other hand, the considerably earlier RV than LV repolarization may explain the discordant T-waves, because in LBBB there is a consistently earlier depolarization as well as repolarization in the RV than in the LV. Such link between depolarization and repolarization sequences fits with the idea of "secondary T-wave changes" i.e. T-wave changes secondary to the abnormal activation.

The supposed strong influence of the RV on the total T-wave may look surprising, because RV mass is approximately one third of LV mass. However, according to the solid angle theory [19] the body surface ECG potentials are solely determined by the potentials derived from the surface of the ventricles and the surface of the RV is of similar size as that of the LV.

An intriguing aspect of the observed interventricular difference in repolarization times is the large repolarization difference across the interventricular septum of LBBB patients. More research is required to better understand the cause of this large gradient as well as its consequence for arrhythmogenesis. Currently, there is no evidence that LBBB increases the risk for arrhythmia as compared to non-LBBB [20].

4.3. Minor spatial gradients in repolarization in the LV of LBBB hearts

Maybe the most remarkable finding in this study was the minor spatial gradient in repolarization in the LV of the LBBB patients. In hearts with LBBB there are large differences in mechanical loading, degree of hypertrophy and expression of ion channels between the early activated septum and late activated lateral wall [21,10,22,11].

The lack of major repolarization gradients in the LV, despite the ~100 ms time differences in depolarization, indicates that beside the "secondary" T-wave changes, other processes must have occurred in the LV. Indeed, it is known that during longer lasting LBBB and RV pacing, further changes in repolarization develop: the amplitude of the T-wave decreases over a period of weeks [23–25], indicating a kind of "electrical remodeling". The first evidence for such remodeling came from studies on "cardiac memory", where T-wave abnormalities were described after the return to sinus rhythm following a period of ventricular pacing [26,27]. Other animal studies showed that the "normal" negative TD-APD (APD = action potential duration) relation disappears directly after starting RV pacing, but that after a few hours of continued RV pacing, this negative TD-APD relation reappears again, indicating regional changes in APD and thus "primary" T-wave changes [28] In the present study, all patients with LBBB had this conduction abnormality for many months, indicating that relevant electrical remodeling had most likely occurred.

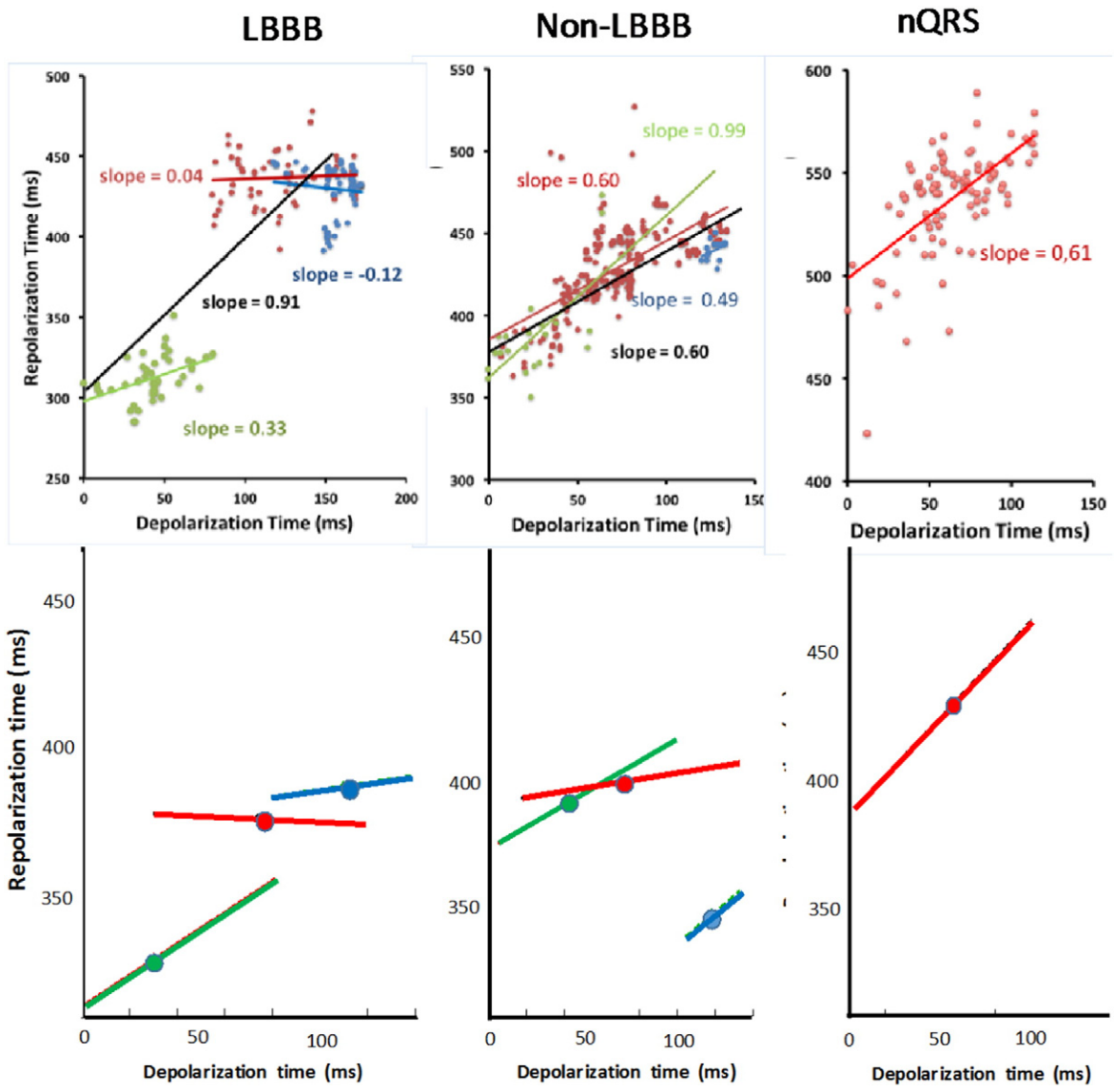


Fig. 3. Examples of individual plots of repolarization time as a function of depolarization time (top) and mean TD-TR relations (bottom) in LBBB (left) non-LBBB (middle) and nQRS patients (right). In the upper row slopes of the RV (green), LV (red) and CS data (blue) are indicated as well as the slope of the relation when using all data combined (black). In the lower row the lines are based on the mean slope and intercept of all patients in the subgroups; the extent of the lines is based on the full range of data and the dots mark the median values.

4.4. Variability in slopes despite consistent T-wave morphology

While the TD-TR relations provide some insight in the genesis of the T-wave, the data also shows that uncertainties remain. After all, the error bars in Fig. S2 show considerable interindividual differences in the TD-TR slope. Similar variability has been reported in other studies. Fig. 4 combines our data with those from previous human studies. There is a large variation in the TD-TR slope, many patients showing a TD-TR relation not fitting the canonic theory. The TD-TR slope ranged between −2 and +1 in the patients with a concordant T-wave and between −0.5 and +1 in patients with a discordant T-wave.

Obviously, as can be appreciated from Fig. 2, there is a substantial spread of the individual data within each region of a ventricle, which limits the accuracy of the determination of the TD-TR slope. However, the interindividual variations in slopes seem too large to be explained only by such variability. Therefore, while on average the TD-TR slope is indeed larger (less negative, more positive) in failing hearts than in non-failing hearts, there is overlap in individual patients, despite clear differences in the T-wave polarity and morphology.

These data indicate that the TD-TR relation provides only partial explanation for the T-wave polarity and morphology. Clearly, a significant amount of research is required to further resolve the unknown aspects of repolarization that are concealed in the T-wave.

4.5. Results in a broader perspective

Because repolarization of the heart is hard to measure in vivo, a great deal of the information on repolarization is derived from in vitro experiments (isolated cells and wedge preparations).

Such preparations have the disadvantage that electrotonic interaction between cells is completely (isolated cells) or partly (wedge preparations) lost. This may explain discrepancies in the presence of a discordant T-wave between in vivo experiments and wedge preparations [29,30]. A similar discrepancy exists with respect to action potentials in LBBB hearts. In isolated hearts APD was shown to be longer in cells isolated from the late-activated LV lateral wall than in those isolated from the earlier activated anterior wall [11] whereas the virtually synchronous repolarization in our LBBB patients implies a shorter APD

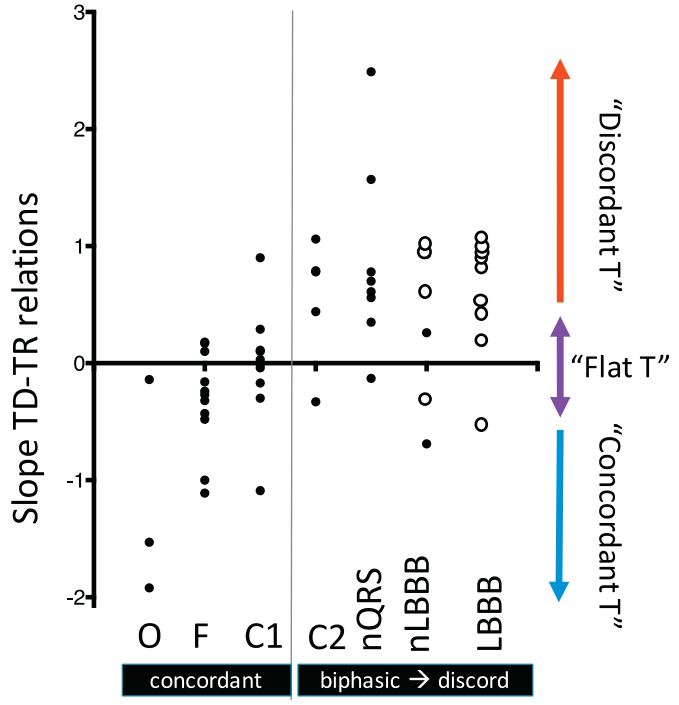


Fig. 4. Individual values of the slope of the relation between depolarization and repolarization times in previous studies and in the present one. O = Opthof et al. [1,2], F is Franz et al., [18], C1 and C2 are the CABG and aortic stenosis patients, respectively of the Cowan study [4]. All data refer to LV measurements, except in the non-LBBB and LBBB patients, where values from the combined measurements were used. The latter choice was made in order to create the most positive scenario fort the match between the slope and T-wave polarity. The open symbols represent discordant T-waves.

in later than in earlier activated regions. Therefore, our results provide an important extension of the understanding of repolarization in failing hearts that is complementary to the in vitro data.

The present data may also be used to improve computer models of electrophysiology in failing hearts. In failing hearts, abnormal expression of at least a dozen ion channels has been described, which has resulted in various models for "failing myocytes" (reviewed by Gomez, Cardona, and Trenor [31]). Combined with posttranslational changes in these channels and with changes in gap junctions and the extracellular matrix, the resultant changes in repolarization are hard to predict. The results from the present study may provide useful data for fine-tuning these computer models.

5. Limitations

The present study was performed in patients with heart failure. The invasiveness of these investigations precluded inclusion of a large number of subjects, as these mapping procedures were only performed in patients with clinical indication of such a study.

Frequently, T-wave abnormalities are linked to arrhythmia. While we investigated the T-wave and repolarization, we had no data on arrhythmia and therefore, no conclusions can be drawn in this regard.

This study employed the moment of maximum derivatives of unipolar electrograms, which can be used when measuring local electrograms with clinical mapping equipment. Early studies of human ventricular repolarization (e.g. [4,18]) used monophasic action potential (MAP) recordings, which may approach true local APD best, but the dV/dt of unipolar electrograms are validated surrogates for APD [32] although unipolar electrograms are susceptible to far-field potentials.

In the present study the majority of the data was derived from the endocardial surface of the ventricles. Useful information may be derived from epicardial mapping, which may be easiest obtained using the ECG-imaging technique [33].

6. Conclusions

In patients with heart failure and reduced ejection fraction the pattern of repolarization follows that of depolarization, albeit with generally smaller dispersion. A special feature was discovered in hearts with LBBB, where there is almost no intraventricular dispersion of repolarization in the LV, despite the considerable dispersion of depolarization there. There is a large inter-patient variation in the slopes of the TD-TR relations despite similar T-wave morphologies, indicating that T-wave morphology is likely determined by more factors than the TD-TR relation alone.

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Disclosures

The authors report that there is no conflict of interest with any of the sponsors regarding the content of this research.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.02.056.

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