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## Electrocardiographic assessment of repolarization heterogeneity

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## Chapter 2

# Validation of ECG indices of ventricular repolarization heterogeneity

*A computer simulation study*

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## ABSTRACT

**Introduction.** Repolarization heterogeneity is functionally linked to dispersion in refractoriness and to arrhythmogeneity. In the current study we validate several proposed ECG indices for repolarization heterogeneity: T-wave amplitude, -area, -complexity and -symmetry ratio, QT dispersion, and the Tapex-end interval (the latter being an index of transmural dispersion of the repolarization).

**Methods and results.** We used ECGSIM, a mathematical simulation model of ECG genesis in a human thorax, and varied global repolarization heterogeneity by increasing the standard deviation (SD) of the repolarization instants from 20 (default) to 70 ms in steps of 10 ms. T-wave amplitude, -area, -symmetry and Tapex-end depended linearly on SD. T-wave amplitude increased from  $275 \pm 173$  to  $881 \pm 456$   $\mu\text{V}$ , T-wave area from  $34 \cdot 10^3 \pm 21 \cdot 10^3$  to  $141 \cdot 10^3 \pm 58 \cdot 10^3$   $\mu\text{V} \cdot \text{ms}$ , T-wave symmetry decreased from  $1.55 \pm 0.11$  to  $1.06 \pm 0.23$  and Tapex-end increased from  $84 \pm 17$  to  $171 \pm 52$  ms. T-wave complexity increased initially but saturated at  $\text{SD} = 50$  ms. QT dispersion increased modestly until  $\text{SD} = 40$  ms and more rapidly for higher values of SD. Transmural dispersion of the repolarization increased linearly with SD. Tapex-end increased linearly with transmural dispersion of the repolarization, but overestimated it.

**Conclusion.** T-wave complexity did not discriminate between differences in larger repolarization heterogeneity values. QT dispersion had low sensitivity in the transitional zone between normal and abnormal repolarization heterogeneity. In conclusion, T-wave amplitude, -area, -symmetry, and, with some limitations, Tapex-end and T-wave complexity reliably reflect changes in repolarization heterogeneity.

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# INTRODUCTION

Cardiac repolarization is more spread in time than cardiac depolarization because of regional differences in action potential duration (APD). Functionally, repolarization heterogeneity (RH) is closely related to dispersion in refractoriness, which in turn increases the vulnerability to reentrant arrhythmias.<sup>1,2</sup>

RH has been described between the apex and basal areas of the heart,<sup>3</sup> between the left and right ventricles<sup>4</sup> and between the epicardium, mid-myocardium and endocardium.<sup>5</sup> The latter type of RH has been named transmural dispersion of the repolarization (TDR).

Primary electrical disease as well as several drugs are known to exaggerate action potential differences in the heart, thus increasing RH and arrhythmia risk. A noninvasive, electrocardiographic index of RH would therefore be of great clinical value.<sup>6</sup> Several ECG indices to assess RH have been proposed, like the amplitude of the T-wave<sup>7</sup> (T<sub>amplitude</sub>), T-wave surface area<sup>8</sup> (T<sub>area</sub>), symmetry ratio of the T wave<sup>9</sup> (T<sub>symmetry</sub>), complexity of the T wave calculated by singular value decomposition<sup>10</sup> (T<sub>complexity</sub>) and QT dispersion.<sup>11</sup> The Tapex-end interval in the left precordial leads (Tapex-end) has been put forward as a measure that directly assesses the duration of TDR.<sup>12</sup>

Although clinical studies have shown that most of these ECG parameters have prognostic power,<sup>13-15</sup> it remains unknown if they really assess RH. Whole heart studies in which endo- and epicardial repolarization as well as surface ECGs are recorded are scarce. Most whole-heart biological models of ECG genesis only measure either epicardial or endocardial dispersion,<sup>16,17</sup> thus completely ignoring TDR. Tapex-end, currently the only index that assesses TDR duration, has been validated on the basis of a quasi-ECG obtained from transmural recordings of a wedge preparation of the left ventricular wall,<sup>12</sup> but not in a whole heart and torso model.

In the current study, we sought to validate the above mentioned electrocardiographic indices of RH by using a mathematical simulation model of ECG genesis of a human heart in a thorax.<sup>18</sup> Within this model, we increased the heterogeneity of the action potential durations throughout the heart and measured the consequences of these manipulations for TDR and RH, and for the ECG indices of ventricular repolarization heterogeneity.

## METHODS

### ECSIM

ECSIM, an interactive computer program conceived and realized by Van Oosterom and Oostendorp,<sup>18</sup> is a mathematical model for studying QRST waveform genesis. The model is available in the public domain at [www.ecgsim.org](http://www.ecgsim.org). It is a combination of a source model of the heart and a volume conductor model of the torso. The heart is a double layer model in which all electrical activity is represented by equivalent sources on the surface encompassing the ventricular myocardium. This surface, of which the shape has been derived from magnetic resonance imaging data, consists of 257 nodes. Each node has its own electrophysiological properties in the form of a transmembrane action potential, in which the timing of the depolarization, the timing of the maximal negative slope and the magnitude of the transmembrane potential can be changed. The default action potential (AP) onset sequence represents normal conduction of the impulse, and APD differences throughout the heart represent the natural apex-to-base and endo-to-epicardial APD heterogeneity. The heart is placed in a realistic thorax model based on magnetic resonance imaging data and includes conductance inhomogeneities like the lungs. With default parameter settings, ECSIM generates potentials on the thoracic surface that closely resemble those of a healthy subject. ECSIM allows for simulations of pathological conditions such as abnormal activation sequences or, by adjusting the magnitude of the transmembrane potential, for simulations of acute ischemia. For the current study, the default, normal settings for activation sequence and source strengths were kept throughout the simulations.

### Manipulation of repolarization heterogeneity

We adopted the standard deviation of the repolarization times of all 257 nodes ( $SD_{rep}$ ) as a measure of RH (repolarization times in the model are defined as the moments of maximum downslope of the transmembrane action potential). Different levels of  $SD_{rep}$  were obtained by increasing the standard deviation of the action potential durations ( $SD_{APD}$ ). By setting the model parameter  $SD_{APD}$  at different levels, all 257 APDs are modified without changing the mean APD. Because each node's repolarization time is calculated by adding its APD to its activation time, an increase of  $SD_{APD}$  increases  $SD_{rep}$  as well. In the current version of ECSIM the model parameter  $SD_{APD}$  can assume a number of discrete values.<sup>18</sup>  $SD_{APD}$  values were set

in such a way that  $SD_{rep}$  increased in steps of approximately 10 ms. Thus,  $SD_{rep}$  was increased from the default value of 20.8 ms to 30.7, 40.6, 51.1, 60.6, and finally to a maximum of 70.7 ms. Sinus rhythm at a rate of 60 beats per minute was maintained during all simulations.

As a control experiment, we evaluated the effects of homogeneous APD lengthening on the ECG repolarization indices in the measurable leads. The APDs of all nodes were lengthened to the same extent by increasing the mean APD from 245.1 ms at baseline to 319.0 ms and 395.0 ms, respectively.

### **Calculation of transmural dispersion of the repolarization**

In the 257 node model, 42 / 61 nodes constitute the endo / epicardium of the free left ventricular wall, 54 / 70 nodes the endo / epicardium of the right ventricular wall and 14 / 16 nodes the left / right septum. Most endocardial nodes were paired with one opposing epicardial node, and TDR was calculated as differences in repolarization time between the endo- and epicardial node. However, as there are more epicardial than endocardial nodes, some endocardial nodes had two opposing epicardial nodes. In these cases, the difference was calculated between the repolarization time of the endocardial node and the mean repolarization time of the two opposing epicardial nodes. Similarly, each left ventricular septal node was paired with one or two right ventricular septal nodes. Subsequently, all paired repolarization time differences were averaged to calculate TDR.

### **ECG analysis**

The simulated ECGs were analyzed by LEADS (Leiden ECG Analysis and Decomposition Software), our MATLAB (The MathWorks, Natick, USA) program for research oriented ECG analysis. LEADS identifies the apex and end of the T wave in each ECG lead. The end of the T wave was defined as the point where the tangent to the steepest portion of the terminal part of the T wave crosses the isoelectric line. Thereafter, the low amplitude T waves in lead V1 were excluded because these led to erroneous detection of the apex and end of the T wave.

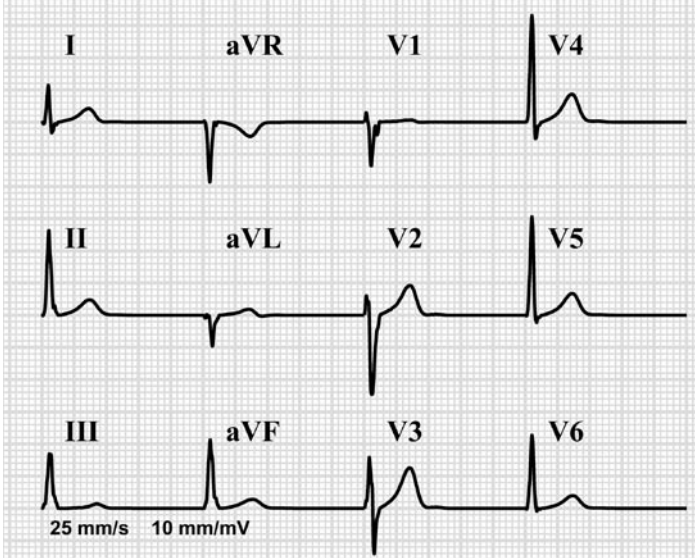
LEADS calculated  $T_{apex-end}$ ,  $T_{amplitude}$  and  $T_{area}$  in every measurable lead and in the vector magnitude signal computed from the vectorcardiogram constructed

by using the inverse Dower matrix.<sup>19,20</sup> Tsymmetry was calculated in all measurable leads as the ratio of the early T-wave area, from the J point to the apex of the T wave, to the late T wave area, from the T wave apex to the end of the T wave.<sup>9</sup> Finally, the values of Tapex-end, Tamplitude, Tarea, Tsymmetry in all measurable leads were averaged.

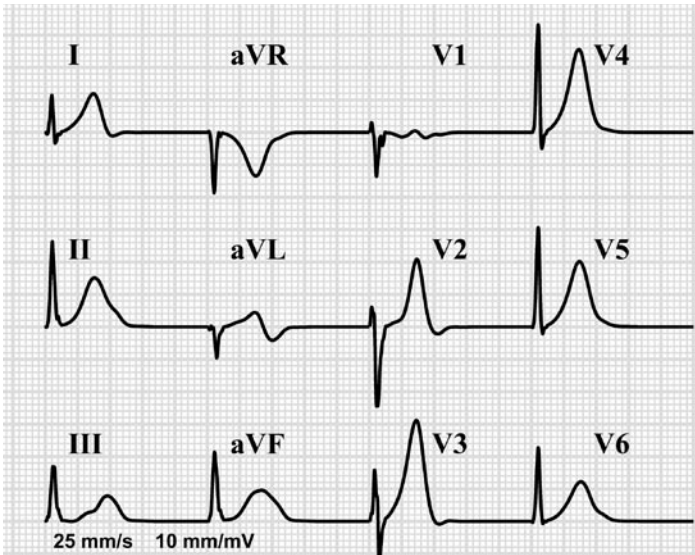
Calculation of repolarization complexity was performed by means of singular value decomposition (SVD) of the T-wave.<sup>10,21</sup> SVD was computed over an interval starting 50 ms after the J point until 50 ms after the end of the T-wave. We computed the SVD-based Tcomplexity as the square root of the summed second to eighth singular values divided by the first singular value. QT dispersion was calculated as the longest minus the shortest measurable QT interval in any of the 12 standard ECG leads.

## RESULTS

Two example ECGs generated with the default, low level of RH ( $SD_{rep} = 20.8$  ms) and with a high level of RH ( $SD_{rep} = 70.7$  ms) are depicted in Figure 1, panels A and B, respectively.



**Figure 1a.** Twelve-lead ECG as generated by ECGSIM with default, low repolarization heterogeneity (standard deviation of the repolarization times = 20.8 ms). As ECGSIM models the ventricular electrical depolarization/repolarization, no P waves are present. The signals were baseline corrected in ECGSIM and one complex is given for each lead.



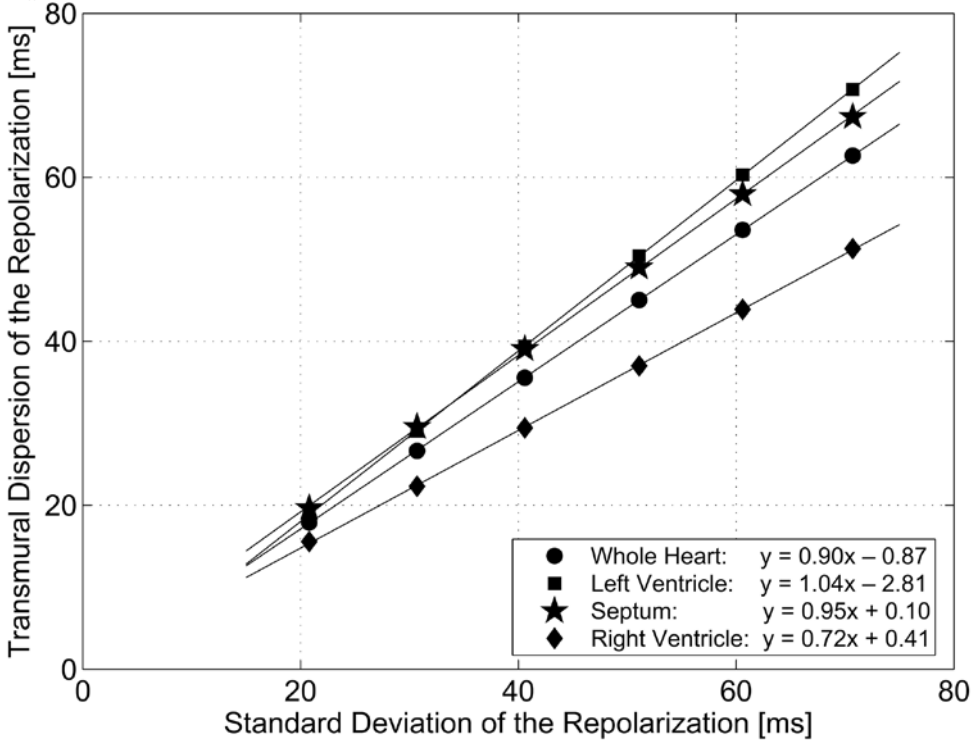
**Figure 1b.** Twelve-lead ECG generated by ECGSIM with high repolarization heterogeneity (standard deviation of the repolarization times = 70.7 ms).



$SD_{rep}$  increased linearly with the  $SD_{APD}$ , in an almost 1:1 relationship:

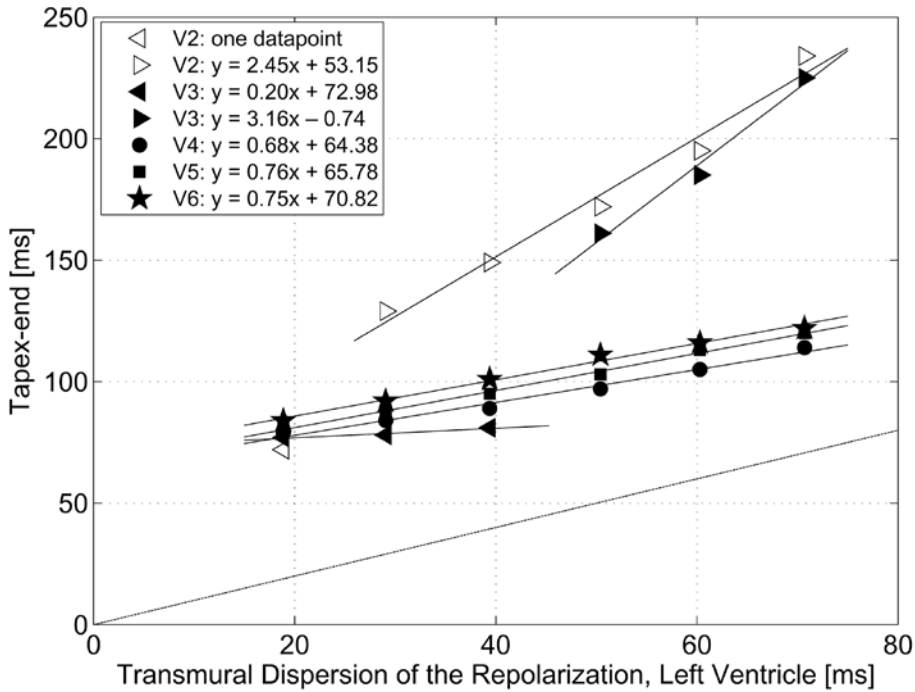
$$SD_{rep} = 0.97 \cdot SD_{APD} - 7.0 \quad (r^2 = 0.99).$$

The average absolute TDR in the left ventricle, septum, right ventricle and whole heart all related linearly to  $SD_{rep}$  (Figure 2). The slope of TDR of the right ventricle (0.72) was smaller than the slope of the left ventricle (1.04) and the septum (0.95), while the whole heart slope assumed an intermediate value (0.90). All these relationships had a correlation coefficient of 0.99.



**Figure 2.** Relation between the standard deviation of the repolarization times ( $SD_{rep}$ ) and the averaged absolute transmural dispersion of the repolarization (TDR) in the right ventricle, left ventricle, septum and whole heart.

Linear regression plots of Tapex-end in the left precordial leads as a function of TDR in the free wall of the left ventricle are depicted in Figure 3. The relationship of the Tapex-end in leads V4-6 with RH were all linear with correlations  $\geq 0.99$ . Tapex-end in leads V2 and V3 showed a discontinuity when T waves became biphasic at increasing RH levels; in lead V2 at an  $SD_{rep}$  of 30 ms and in lead V3 at an  $SD_{rep}$  of 50 ms. Tapex-end overestimated TDR in all left precordial leads.



**Figure 3.** Relation between the transmural dispersion of the repolarization (TDR) in the left ventricular free wall and the Tapex-end in the left precordial leads. Discontinuities in the V2 and V3 data are caused by a transition from a monophasic to a biphasic T wave. (dashed line = line of identity)

### Tapex-end, Tamplitude, Tarea and Tsymmetry

The relationships of Tapex-end, Tamplitude, Tarea and Tsymmetry with RH were close to perfectly linear (Tables 1a and b). Table 1a lists values that were averaged over the ECG leads in which the respective RH index could be measured (lead V1 had to be excluded because of a low amplitude T wave). The RH indices were also measured in the vector magnitude signal (Table 1b). All linear regressions had correlations of at least 0.98. Regressions with the vector magnitude derived indices had generally steeper slopes than those with the average of the ECG leads. All RH indices but Tsymmetry had a positive relation with RH.

Averaged over ECG leads	slope	intercept	$r^2$	Value at baseline RH $SD_{rep} = 20.8$	Value at maximal RH $SD_{rep} = 70.7$
Tapex-end (ms)	1.7	48	0.99	$84 \pm 17$	$171 \pm 52$
Tamplitude ( $\mu V$ )	12.1	48	0.99	$275 \pm 173$	$881 \pm 456$
Tarea ( $\mu V \cdot ms$ )	$2.1 \cdot 10^3$	$-11 \cdot 10^3$	0.99	$34 \cdot 10^3 \pm 21 \cdot 10^3$	$141 \cdot 10^3 \pm 58 \cdot 10^3$
Tsymmetry	-0.01	1.72	0.98	$1.55 \pm 0.11$	$1.06 \pm 0.23$

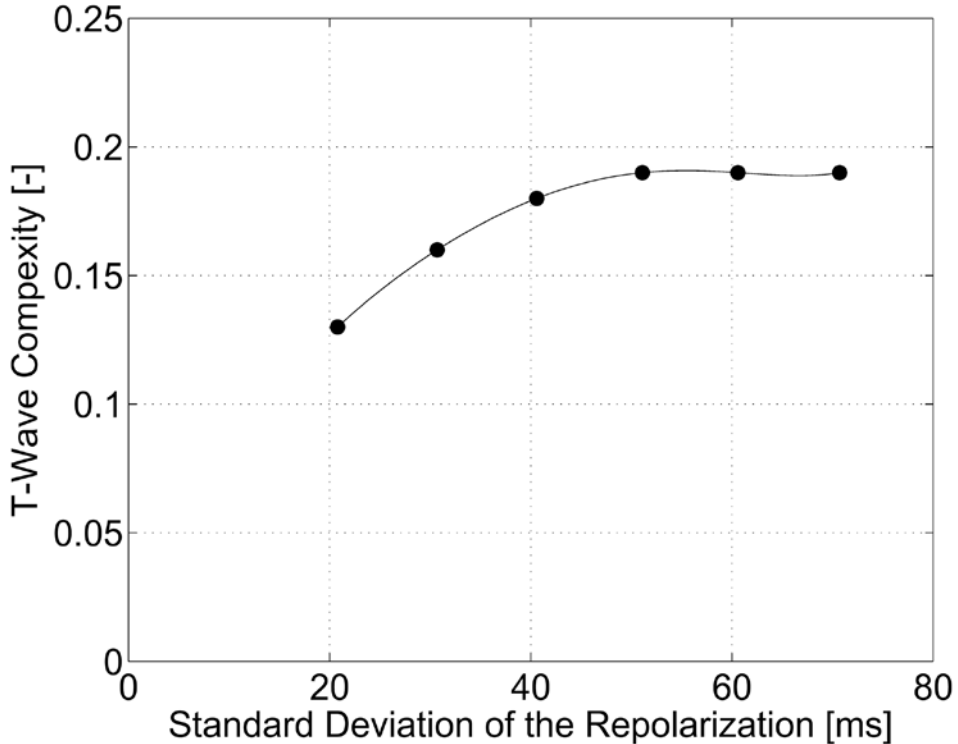
**Table 1a.** Slope, intercept and correlation ( $r^2$ ) of the linear regressions of Tapex-end, Tamplitude, Tarea and Tsymmetry on repolarization heterogeneity (RH) and the value of these RH indices at minimal and maximal RH.

In vector magnitude signal	slope	intercept	$r^2$	Value at baseline RH $SD_{rep} = 20.8$	Value at maximal RH $SD_{rep} = 70.7$
Tapex-end (ms)	2.7	60	0.99	116	252
Tamplitude ( $\mu V$ )	16.7	86	0.99	403	1253
Tarea ( $\mu V \cdot ms$ )	$3.4 \cdot 10^3$	$-19 \cdot 10^3$	0.99	$52 \cdot 10^3$	$221 \cdot 10^3$
Tsymmetry	-0.012	1.60	0.99	1.39	0.78

**Table 1b.** Slope, intercept and  $r^2$  of the linear relations of Tapex-end, Tamplitude, Tarea and Tsymmetry with RH and the value of these indices at minimal and maximal values of RH.

### Tcomplexity

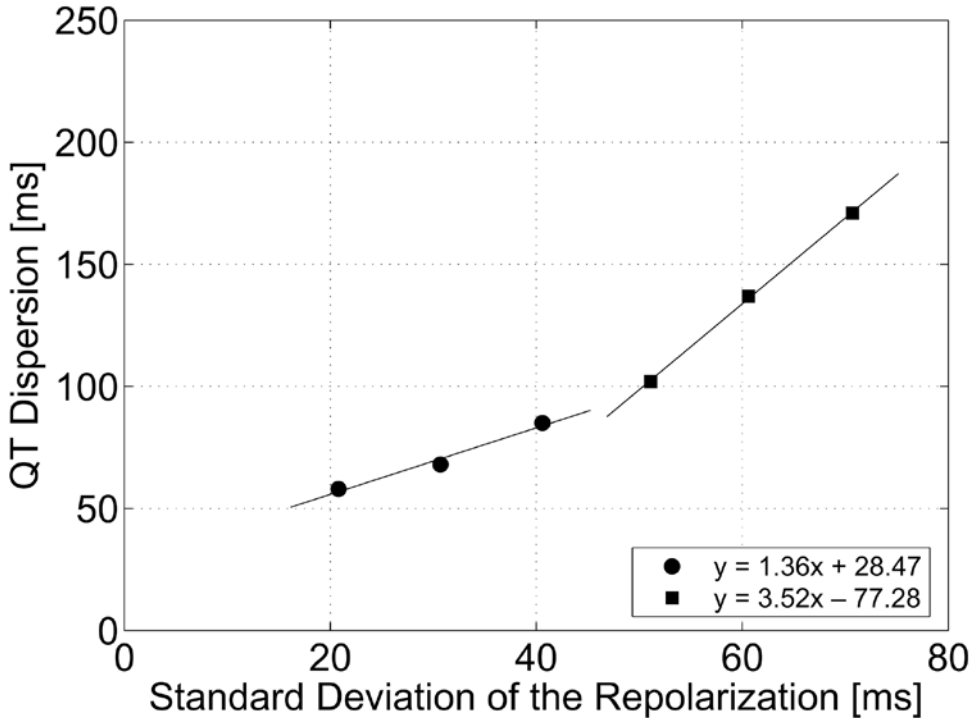
Tcomplexity increased initially and saturated at about  $SD_{rep} \geq 40$  ms, see Figure 4. Tcomplexity increased from 0.13 at default to 0.18 at an  $SD_{rep}$  of 40 ms and remained 0.19 while  $SD_{rep}$  increased from 50 to 70 ms.



**Figure 4.** Relation between the standard deviation of the repolarization times ( $SD_{rep}$ ) and the T-wave complexity as expressed by the ratio of the 2nd-8th components to the first component in the vectorcardiogram. For visual support we fitted a line through the six data points by a 5th order polynomial. The figure shows that the sensitivity to changes in repolarization heterogeneity decreases at higher heterogeneity values.

### QT dispersion

QT dispersion increased modestly at low and intermediate levels of RH and more rapidly at higher levels of RH, see Figure 5. QT dispersion increased from 58 ms at default to 68 and 85 ms at  $SD_{rep} = 30$  and  $SD_{rep} = 40$  ms, respectively. Thereafter, QT dispersion increased more rapidly to 102, 137 and 171 ms. The slope of the regression line for  $SD_{rep} \leq 40$  ms was 1.4 and the slope of the regression line for  $SD_{rep} \geq 50$  ms was 3.5.



**Figure 5.** Relation between the standard deviation of the repolarization times ( $SD_{rep}$ ) and QT dispersion. QT dispersion is sensitive to changes in the repolarization heterogeneity in the very pathological zone (slope 3.5), but has a lower sensitivity in the transitional zone between normal and abnormal (slope 1.4). Therefore this parameter is not well suited to discriminate between normal and abnormal repolarization heterogeneity.

### Homogeneous APD lengthening

Homogeneous APD lengthening resulted in no apparent morphological T-wave changes, only the ST segment lengthened. Changes in  $T_{apex-end}$ ,  $T_{amplitude}$ ,  $T_{area}$  and QT dispersion due to homogeneous APD lengthening were less than 3 % of the changes due to  $SD_{rep}$  increase. Only  $T_{symmetry}$  and  $T_{complexity}$  decreased considerably, 19 % and 47 % of the changes due  $SD_{rep}$  increase, respectively. These changes were in opposite direction to the changes induced by increasing  $SD_{rep}$ .

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## DISCUSSION

In this modeling study, we evaluated the effects of repolarization heterogeneity on electrocardiographic indices proposed to assess repolarization heterogeneity. The observed changes in the ECG indices were not caused by APD lengthening per se, as homogeneous APD lengthening caused only minor changes in most ECG indices, and counteracted rather than contributed to the changes in the other ECG indices due to RH increase.

### **Tapex-Tend interval**

Tapex-end is the only measure that potentially estimates the time window during which repolarization is heterogeneous. Tapex-end is believed to represent TDR, the interval from the end of the epicardial APDs to the end of the (sub)endocardial APDs.<sup>12</sup> In left ventricular wedge preparations, the apex of the T-wave concurs with the end of the epicardial AP because the end of the epicardial AP is very steep.<sup>12,22,23</sup> This steep descent of the epicardial AP caused the largest differences in amplitude with the (sub)endocardial AP. However, when other AP morphologies are present, a different phase of the AP could coincide with the apex of the T wave. For example, a steep descent at the start of phase 3 with a more slowly diminishing tail at the end of the AP could cause the apex of the T wave to coincide with the start of phase 3 of the epicardial AP. In that case, Tapex-end would overestimate TDR.

In our study, overall Tapex-end had a good linear relation with RH (Tables 1a and b). However, Tapex-end in the left precordial leads overestimated TDR by several tens of milliseconds, this bias having the same order of magnitude as TDR itself (Figure 3). The abrupt increase in Tapex-end in leads V2 and V3 when biphasic T-waves evolve due to increased RH illustrates an additional problem: the difficult localization of the end of the T wave.

The 1:1 relation between the duration of Tapex-end and TDR as found in the wedge preparation did not hold in a three dimensional structure as ECGSIM. The differences between the transmural quasi-ECG in the wedge preparation and the surface ECG may be explained by different AP morphologies and also by the fact that the wedge is but part of a heart. Therefore, the floating endocardial electrode in the wedge

preparation is not the analogue of the Wilson central terminal in electrocardiography. Moreover, in the regular electrocardiogram other structures in the heart than the left ventricular free wall additionally contribute to the cardiac vector. Amongst others, this causes a considerable amount of cancellation, a phenomenon not occurring in the wedge preparation.

### **T-wave complexity by singular value decomposition**

Singular value decomposition is a method to quantify the complexity of the repolarization. A smooth simple T wave is usually associated with a normal repolarization process, while a notched, irregular morphology is seen with disturbed repolarization processes.<sup>24</sup> SVD-calculated complexity is higher in Long-QT patients and can be used to distinguish these patients from healthy subjects.<sup>10</sup> In patients with arrhythmogenic right ventricular dysplasia, higher repolarization complexity, measured in body surface maps as a decreased contribution of the first, most simple SVD component, was associated with arrhythmias.<sup>25</sup> In U.S. veterans with cardiovascular disease, repolarization complexity calculated with SVD conferred independent prognostic information.<sup>15</sup> Van Oosterom mathematically proved that a higher RH leads to increased T-complexity.<sup>26</sup> Our results in ECGSIM suggest that T-wave complexity reacts to small increases in RH, but fails to increase further with higher levels of RH. SVD may therefore be useful to detect increases of RH, but is unlikely to discriminate between smaller and larger RH values.

### **QT dispersion**

QT dispersion, defined as the longest minus the shortest QT interval in any of the 12 ECG leads, was initially believed to represent local repolarization differences.<sup>11</sup> According to current insight this concept is incorrect; QT-interval differences in ECG leads depends on projections of the (global) heart vector on the different lead vectors and can therefore not represent local repolarization differences.<sup>27</sup> Another problem of manual measurement of QT dispersion is the low reproducibility, for example due to the subjectivity involved in exclusion of low-amplitude T waves and the difficult measurement of the end of T waves in noisy ECGs. Nevertheless, QT dispersion may have a weak relation with repolarization disturbances<sup>28</sup> and was associated with arrhythmias in some studies.<sup>29,30</sup>

We measured QT dispersion values up to 171 ms. Although most previous studies

reported smaller values, similar values have been reported in patients shortly before an episode of Torsade de Pointes<sup>31</sup> and in Long QT patients who remained symptomatic despite beta-blocker therapy.<sup>32</sup> We measured the QT dispersion value of 171 ms at the maximum simulated RH ( $SD_{rep} = 70$  ms), a situation that is likely to be highly arrhythmogenic in reality.

In our simulations, QT dispersion increased relatively little with initial RH increases, but it increased more at higher levels of  $SD_{rep}$ . QT dispersion is sensitive for changes of RH in the very pathological zone, but has little sensitivity in the transitional zone between normal and abnormal. Therefore, this parameter is not well suited to discriminate between normal and abnormal. The above mentioned theoretical and practical objections in combination with the insensitivity for small increases in RH render QT dispersion unsuitable as an index of RH.

### **T-wave amplitude**

Tamplitude reflects the net maximal voltage gradients in the whole heart after cancellation. The repolarization gradients in ECGSIM are caused by the voltage difference of opposing endo- and epicardial APs. By increasing RH the already long endocardial APDs were further lengthened and the already short epicardial APDs were further shortened, mainly achieved by a change in the duration of the plateau phase. This caused the endo- and epicardial APs to shift further out of phase such that endocardial APs still had a high amplitude and are less opposed by the already diminished epicardial AP amplitude. Our simulated T waves mimic the high amplitude T waves found in long-QT syndrome type 1.<sup>33</sup> In wedge preparations mimicking the long-QT 1 syndrome, application of an  $I_{Ks}$  current blocker in combination with isoproterenol caused a relatively longer APD of the mid-myocardium (sub-endocardium) compared to the epicardial APD. This caused an increased voltage gradient directed toward the epicardium and therefore, high amplitude T-waves on the transmural quasi ECG.<sup>23</sup> The mathematical background of the dependence of Tamplitude on RH in the equivalent surface source model was worked out by Van Oosterom.<sup>34</sup> For inter-individual comparison, the main disadvantage of the Tamplitude is its individual variability, due to differences in thorax and heart size. For example, athletes will have a higher Tamplitude<sup>35</sup> mostly on the basis of a higher cardiac mass and not necessarily caused by an increased RH. This problem may be dissolved by recording a reference ECG, for example before the start of potentially



arrhythmogenic medication.

### **T-wave surface area**

Several studies showed a relation between RH, assessed from a limited number of action potential recordings, and Tarea. Tarea correlated with increased RH in rabbit hearts in which epicardial monophasic action potentials were recorded simultaneously with a surface ECG.<sup>8</sup> In dogs, T-wave<sup>36</sup> and QRST<sup>37</sup> surface area was related to RH and a lowered threshold for ventricular fibrillation.<sup>38</sup> Drugs that lengthen the APDs of specific cell layers, for example  $I_{Kr}$  blockers that foremost cause a lengthened midmyocardial APD, cause an increased Tarea in left ventricular wedge experiments.<sup>22</sup> In our simulations, Tarea showed large increases at increasing RH. Tarea has the practical advantage of a low sensitivity to noise. Tarea may be the most comprehensive measure of RH, as it not only represents the maximum of the summed voltage gradients, like the T-amplitude, but also encompasses the time window during which the repolarization differences exist.

### **T-wave symmetry ratio**

The T symmetry ratio was brought under attention by di Bernardo and Murray.<sup>9</sup> They found that the T wave became more symmetrical with increased apico-basal and transmural dispersion. A normal symmetry ratio is 1.5 and with an increased RH this symmetry ratio approaches 1.0. Ischemia is known to induce high peaked symmetrical T waves, increased RH<sup>39</sup> and vulnerability to arrhythmias.<sup>40</sup> An advantage of this morphological parameter is that, in contrast to the high individual variability of Tamplitude, Tsymmetry seems to be more stable with different positions of the heart in the thorax.<sup>9</sup> In our study, we also found that increased RH is reflected in a decreased Tsymmetry.

### **Limitations**

As with all electrocardiographic studies, this simulation study addresses the forward problem and not the inverse problem, *i.e.*, the changes in RH cause changes in the repolarization indices in the simulated surface ECG, but such ECG changes could theoretically also be caused by phenomena other than increased RH.

### **Conclusions**

The well-established concept of RH is likely to play a major role in arrhythmo-

genesis. In a realistic three dimensional computer model we simulated a number of situations with increased RH. It appeared that transmural dispersion of the repolarization increased linearly with global RH. QT dispersion has a low sensitivity in the transitional zone between normal and abnormal RH and has a weak theoretical basis as an index of RH. Tapex-end in the left precordial leads overestimated TDR. Tcomplexity did not discriminate between higher values of RH. In conclusion, Tsymmetry, Tamplitude, Tarea, and, with some limitations, Tapex-end and Tcomplexity reliably reflect changes in repolarization heterogeneity.

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