Nondipolar Content of T Wave Derived from a Myocardial Source Simulation with Increased Repolarization Inhomogeneity

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Background: Several conditions with repolarization disturbances are associated with increased level of nondipolar components of the T wave. The nondipolar content has been proposed as a measure of repolarization inhomogeneity. This computer simulation study examines the link between increased nondipolar components and increased repolarization inhomogeneity in an established model.

Methods: The simulation was performed with EcgSim software that uses the equivalent double-layer source model. In the model, the shape of transmembrane potential is derived from biological recordings. Increased repolarization inhomogeneity was simulated globally by increasing the variance in action potential duration and locally by introducing changes mimicking acute myocardial infarction. We synthesized surface ECG recordings with 12, 18, and 300 leads. The T-wave residue was calculated by singular value decomposition. The study examined the effects of the number of ECG leads, changes in definition of end of T wave and random noise added to the signal.

Results: Normal myocardial source gave a low level of nondipolar content. Increased nondipolar content was observed in the two types of increased repolarization inhomogeneity. Noise gave a large increase in the nondipolar content. The sensitivity of the result to noise increased when a higher number of principal components were used in the computation.

Conclusions: The nondipolar content of the T wave was associated with repolarization inhomogeneity in the computer model. The measure was very sensitive to noise, especially when principal components of high order were included in the computations. Increased number of ECG leads resulted in an increased signal-to-noise ratio.

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principal component analysis; T wave; computer model; simulation; nondipolar components; repolarization inhomogeneity

Inhomogeneous repolarization is an important factor behind potentially serious arrhythmias¹ and great effort has been put into the search for clinically useful parameters that reflect repolarization inhomogeneity. One proposed measure is the nondipolar content of the T wave recorded at the body surface. It was originally computed from body surface map recordings.² More recently, the method has been applied to 12-lead ECG.³ The level of nondipolar components is increased in the long QT syndrome,⁴ in conduction distur-

bances,⁵ during the initial course of acute myocardial infarction,⁶ and in chronic ischemic heart disease.⁷ In the latter condition, the nondipolar content has been shown to contain prognostic information. The nondipolar components increase when repolarization is indirectly manipulated in a biological in vitro model.⁸ To our knowledge, no study has, however, investigated the association between the nondipolar content and specific changes in repolarization. The aim of this investigation was to link the concept of nondipolar content of the

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T wave to repolarization inhomogeneity. We studied repolarization changes in a computer model of the myocardial source by simulating conditions that increase global and localized repolarization inhomogeneity. After synthesizing surface ECG recordings with different lead configurations, the nondipolar content of the T wave was extracted by principal component analysis. The study examined the effects of the number of ECG leads, changes in definition of end of T wave, and random noise that was introduced into the signal.

METHODS

Synthesized ECG

Simulated multilead ECG complexes were generated with Ecgsim 1.2 (<http://www.ecgsim.org>, Dept. of Medical Physics, University of Nijmegen, The Netherlands, 2004), a model used in previous studies of repolarization inhomogeneity.^{9,10} The software employs the equivalent double layer source model (EDL), placed in a realistic torso.¹¹ The shape of the transmembrane potential is derived from biological recordings. The standard time points of maximum upstroke and maximum negative downslope in the model are calculated by an inverse procedure, based on measurements of body surface potentials. The negative resting potential and the magnitude of the upstroke are by default uniform. The operator can alter the time and amplitude characteristics at a desired position at the heart surface. The local activation time (LAT), the action potential duration (APD), and the action potential magnitude can be changed. The area affected by these modifications can be adjusted. Depolarization and repolarization can also be changed globally by manipulating the default mean and standard deviation of the timing parameters. The global manipulation does not change the relations in the parameters between different regions of the model. The software then performs a forward computation and derives a synthetic ECG at specific places on the torso surface.

ECG Leads

We investigated three different lead combinations:

- (1) Classical 12-lead ECG with the eight independent ECG leads V_1 - V_6 , I and II;

- (2) Eighteen precordial ECG leads in three rows: V_1 - V_6 , supplemented by $3V_1$ - $3V_6$ and $5V_1$ - $5V_6$, one interstitium above and below the common precordial leads; and
- (3) Body surface map with signals from 300 nodes distributed around the torso with the highest density in the left precordial area.

All simulations were performed using the default filter setting (baseline correction). Sampling was simulated at 1000 samples/sec.

T-Wave Detection

The output matrix from the ECG synthesis, consisting of one multilead ECG complex, was processed by custom developed software (Matlab, MathWorks, Natick, MA, USA). The J point was approximated as the time where the vector magnitude (derived from all leads used in the computation) dropped below 70% of the largest QRS vector magnitude. The onset of the T wave was defined as the J point + 56 ms; this definition was derived using the approximation formula $T\text{-onset} = J\text{ point} + (RR\text{ interval}/16)^{5,6}$ with RR interval fixed at 900 ms. T-offset was localized by an area-based algorithm. The T-vector magnitude integral and its successive increment were computed for consecutive sampling intervals. T-offset was defined as the first position where the area increment decreased below 0.25% of the integral.

Determination of Nondipolar Components

The T wave was processed by singular value decomposition. The nondipolar content is expressed by the principal components of order >3 . It has been quantified by several approaches. Some earlier publications,^{3,5-7} have defined the variables absolute and relative T-wave residue (TWRabs and TWRrel) as the sum of squares of principal components:

$$TWR_{abs} = \sum_{i=4}^n S_i^2 \quad (I)$$

$$TWR_{rel} = \frac{\sum_{i=4}^n S_i^2}{\sum_{i=1}^n S_i^2} \quad (II)$$

Figure 1. Noise and the number of used principal components. The graph illustrates the effect of noise on the nondipolar content computed from different number of components. Default model settings and ECG lead combination 2 (18 leads) were used. TWRabs (III) at the different levels of noise was computed from three sets of principal components (2, 5, and 15 nondipolar components, i.e., S₄-S₅, S₄-S₈, and S₄-S₁₈). The relation of noise level to the resulting TWRabs is shown (logarithmic scales). The curves are annotated with means of TWRabs computed from 20 generated ECG recordings. The values should be compared to those computed from the noise-free signal, 64, 83, and 91 μV² for the three sets of nondipolar components. In a noisy signal, computing the nondipolar content from a higher number of principal components led to a large, incorrect increase of TWRabs. The ratio $TWRabs_{noise}/TWRabs_{noise-free}$ can be seen as an expression of fidelity of the result, with a reasonable upper limit at 1.5. This limit was exceeded at noise levels 10, 2, and 1 μV for computations using S₄-S₅, S₄-S₈, and S₄-S₁₈, respectively.

Others⁸ use the sum of principal components:

$$TWRabs = \sum_{i=4}^n S_i \quad (III)$$

$$TWRrel = \frac{\sum_{i=4}^n S_i}{\sum_{i=1}^n S_i} \quad (IV)$$

We simultaneously derived the parameters TWRabs and TWRrel using both definitions. The calculations were based on first eight principal components (S₁-S₈). The exception was the analysis of the effect of the number of components on the result at different noise levels (Fig. 1). Here we used up to 18 components computed from lead combination 2. Finally, the S₂/S₁ ratio, a frequently used dipolar measure, was computed for comparison.

Alterations in the Myocardial Source

Global increase in repolarization dispersion was simulated by increasing the standard deviation of action potential duration from the default value 28.5 ms to 46.7 and 66.1 ms. The mean of action potential duration and the mean and standard deviation of local activation time were kept at their default values.

Localized changes were studied in the models of acute anterior and inferior myocardial infarction. The transmembrane potential on the anterior surface of the heart model was altered in a circular region with the center corresponding to the mid portion of left anterior descending coronary artery (LAD) and a diameter of 6 cm (Fig. 2). In this region, decreased resting potential, slowed conduction, and delayed repolarization were simulated. The local values of resting potential, activation time, and action potential duration were decreased

Figure 2. Schematic illustration of the LAD region. Screen-dump from EcgSim. The dots correspond to the nodes at the heart surface where the transmembrane potentials can be inspected and altered. In the simulation of acute myocardial infarction in mid-LAD region, the properties of the model were altered at the indicated node. The range of the changes is defined by the gray circle. (LAD = left anterior descending coronary artery).

by 55% and increased by 70% and 25% from the default (from -90 mV to -40 mV, from 42 ms to 71 ms, and from 238 ms to 301 ms at the center of the zone, respectively). The resulting ECG pattern was typical for the initial phase of a ST-elevation myocardial infarction (STEMI) due to occlusion of mid-LAD (Fig. 3).

A corresponding change was made in a region with a diameter of 6 cm around the mid portion of right coronary artery (RCA) in the posterior groove. The local default values of resting potential, local activation time, and action potential duration at the center were altered from -90 mV to -40 mV, from 61 ms to 104 ms, and from 214 ms to 271 ms, respectively. The resulting ECG showed a pattern of inferior STEMI, with rather discrete ST elevations in II, III, and a VF, and a reciprocal ST depression in V3 (Fig. 4).

Contribution by the Terminal Portion of the T Wave

In the three different combinations of leads, the ECG was generated with standard settings of the model. The T-wave offset was detected using

Figure 3. ECG in the model of anterior myocardial infarction. Screen-dump from EcgSim, showing the synthesized 12-lead ECG after simulating changes in the myocardial source model, mimicking acute myocardial infarction in mid-LAD region. The limited pixel resolution of the graphical output from the simulating software does not represent the precision of the simulation.

Figure 4. ECG in the model of inferior myocardial infarction. The synthesized 12-lead ECG from simulation of acute myocardial infarction in mid-RCA region.

the algorithm outlined above. Then the nondipolar content was computed in a series of simulations where the end of the T-wave window was shifted between -150 ms and $+100$ ms from the T-offset.

The Effect of Noise

Noise was generated in six steps within the range $0.1 \mu\text{V}$ – $100 \mu\text{V}$. At each studied noise level, 20 sets of ECG data were created for the lead combinations 1 and 2 (12-lead ECG and 18-lead precordial ECG). Default model settings were used. Simulated random noise was generated as uniformly distributed random numbers between -1.0 and 1.0 . The noise signals were scaled to the required amplitude and added to the ECG signal. The resulting noisy T-wave signal was processed by singular value de-

composition and the mean values of the resulting parameters were compared to the noise level (Fig. 1).

RESULTS

Simulation of a normal myocardial source, with default model settings resulted in a normal synthesized ECG and a low level of nondipolar content (Table 1). The numerical values of the nondipolar parameters were higher for configurations using many ECG leads. In comparison, the ratio of the nondipolar content to the total power of the signal (relative T-wave residue) was rather constant for the different lead configurations. A global increase in repolarization dispersion resulted in increased nondipolar content of the T wave (Table 2).

Table 1. Values Computed from Simulation of a Normal ECG

Lead Combination		TWRabs (I)	TWRabs (III)	TWRrel (II)%	TWRrel (IV)%	$S_2/S_1\%$
1 (12-lead)	12-lead ECG	1176	51	0.0013	0.51	7.0
2 (18-lead)	18 leads in 3 rows	2685	83	0.0015	0.56	6.8
3 (300-lead)	300 leads	24,761	268	0.0017	0.63	9.0

The different measures in relation to the lead combination. Components S_1 – S_8 were used in the calculations. The model settings were at default with standard deviation of action potential duration 28.5 ms.

Table 2. TWRabs and S_2/S_1 Ratio in Increased Global Repolarization Inhomogeneity

SD APD	Lead Combination					
	1 (12-Lead)		2 (18-Lead)		3 (300-Lead)	
	TWRabs (III)	S_2/S_1	TWRabs (III)	S_2/S_1	TWRabs (III)	S_2/S_1
28.5 ms	51	7.0	83	6.8	268	9.0
46.7 ms	156	9.4	318	11.8	1170	18.0
66.1 ms	476	9.6	1201	12.7	4252	19.0

Lead combinations with 12, 18, and 300 leads are shown. SD APD = standard deviation of action potential duration.

This increase, expressed as the ratio

$$\frac{\text{TWRabs at increased repolarization dispersion}}{\text{TWRabs at default setting}},$$

was greater in recordings with higher number of ECG leads. For the dipolar measure S_2/S_1 , the increase was less prominent. See Table 2 for values of TWRabs (III) and S_2/S_1 . In both models of localized increase in repolarization dispersion (acute anterior and inferior STEMI, Table 3), the nondipolar content was elevated compared with the normal ECG (Table 1).

A widening of the analysis window was associated with an increase in the nondipolar components (Fig. 5). The introduction of noise led to a prominent increase in the nondipolar content. In computations using a high number of principal components, the relation of nondipolar content in noisy versus noiseless simulations was unfavorably high (Fig. 1).

Table 3. TWRabs Computed in Two Ways and S_2/S_1 in Simulation of an Acute Myocardial Infarction

	Lead Combination		
	1	2	3
Anterior			
TWRabs (I)	9756	31,439	279,927
TWRabs (III)	116	208	654
S_2/S_1	38.5	41.3	42.8
Inferior			
TWRabs (I)	12,795	43,404	501,619
TWRabs (III)	142	267	895
S_2/S_1	8.5	9.6	13.6

For settings of the model see text. The resulting 12-lead ECG is shown in Figures 2 and 3.

DISCUSSION

The nondipolar content of the T wave has been described as the noninvasive measure of repolarization inhomogeneity.¹² The nondipolar components are of a low magnitude and sensitive to noise. When the parameters are derived from a noisy ECG signal, their origin in repolarization inhomogeneity can be doubted; however, this association is supported by our observation of a similar pattern in the noise-free model.

In the model with random noise, the tested noise levels covered a wide range from extremely low to levels that visibly distort an ECG. Even at low noise levels, the nondipolar content was notably increased (Fig. 1). This is a known limitation of the nondipolar measures. In principal component analysis of the ST-T segments, only nondipolar content from ECG recordings with a low noise level can be used for detecting ischemia.¹³ A study on reproducibility of TWRabs (I) and TWRrel (II) shows that using just one or a few QRS-T complexes will result in an incorrectly high level of the nondipolar content.¹⁴ These authors deduce that signal averaging of 100–200 complexes is required for obtaining good reproducibility and reliability. In view of our findings, this conclusion seems reasonable.

Increasing the number of principal components used in the calculation led to an unfavorable response (Fig. 1). This is due to the properties of random noise and the nondipolar parameters being measures of variance. Random noise will result in increased variance and an unfavorable signal-to-noise ratio in the principal components of higher order.

A shift of the end of the computation window had a gradual and predictable effect. This finding agrees with a previous study that found that a small shift of the T-offset in both directions has only marginal effect on the computed values.¹⁵

Figure 5. Effect of changes in definition of the end of the analysis window. Zero point on the x-axis corresponds to the offset of the T wave as detected by the algorithm. A left shift resulted in a truncation of the T wave and a decrease of the nondipolar content. A right shift beyond the visible offset of the T wave was associated with a further increase in the nondipolar content of the derived ECG. This is related to the local properties of the myocardial source model. In the region with latest repolarization (posteriorbasally), the membrane potential does not return to -90 mV until over 30 ms after the end of the T wave.

TWRabs computed according to (I) from 12-lead ECG in the myocardial infarction model was smaller, but in the same range as clinical values obtained during the first 24 hours of STEMI⁶ (Table 3, 10,000–13,000 units in the two models, compared with a median of 25,000 units in clinical cases). The size of the modeled lesion was comparable to that in clinical STEMI. A circular lesion with a diameter of 6 cm and a wall thickness of 1 cm will result in 28 g affected myocardium, an amount comparable to the mean infarct mass of 34 g measured by magnetic resonance in STEMI patients.¹⁶ The degree of the introduced localized conduction slowing and repolarization delay, however, was not based on biological measurements. Therefore, the absolute level of the nondipolar components in the STEMI model must be cautiously interpreted.

In the model of inferior STEMI, smaller changes in surface ECG were observed (and the dipolar measure S_2/S_1 was not increased), although the size of the affected myocardium was similar to that in the anterior STEMI model. The nondipolar components, however, were in the same range as in anterior STEMI.

The absolute values describing the nondipolar content differ greatly between the methods (1) and

(3). Approach (3) seems more relevant. In (1), a squaring of the principal components inflates any differences between the groups as well as the noise. In any comparisons, the internal rank of the computed values will, however, be the same for (1) and (3). If rank-based statistical methods are used, groupwise comparisons will be equally valid. The relative measure TWRrel (III) has been proposed as a more appropriate quantification of the nondipolar content. It is a dimensionless ratio normalized with respect to the total power of the T wave. This may also be a disadvantage since it will be affected by changes in the total power of the T wave.^{5,8}

The concept of nondipolar content is not obvious and its physiological relevance has been questioned.¹⁷ The nondipolar components of the T wave quantify the small discrepancy between the actual electrical field generated at the body surface and the field from a pointwise source in the center of a large conducting sphere (i.e., the dipolar model). This mismatch can be given a physiological interpretation. The heart is rather large compared to the torso. Myocardium with small arrhythmogenic propensity, however, repolarizes in a highly coordinated fashion with small regional differences. It is reasonable that this synchronization should

result in a field pattern similar to that generated from a pointlike source. In a heart with increased arrhythmogenic potential, a less coordinated repolarization would give rise to a pattern that differs more from the dipolar model, that is, a pattern with larger nondipolar content. Therefore, the nondipolar content should reflect local differences in repolarization.

In comparison with nondipolar parameters, dipolar measures are much larger and less vulnerable to errors. By definition, they describe properties of a single global repolarization vector. They will therefore only reflect local repolarization inhomogeneity indirectly through changes in the global vector. This may explain the unchanged dipolar measure S_2/S_1 together with a substantial increase in the nondipolar content in our model of inferior myocardial infarction.

Limitations

Our results depend on the simulation model. The global as well as the localized changes introduced in the model are simplistic compared to the biological complexities of diffuse repolarization abnormality and acute myocardial infarction. The generated random noise is not equivalent to the real situation where correlation will exist between the noise patterns in adjacent ECG leads. Analysis of surface ECG is limited by the fact that the inverse problem has no unique solution (Helmholtz, 1853).¹⁸ Therefore, one ECG picture can be the result of multiple different patterns of myocardial repolarization. Nevertheless, when a relevant simulation of changes in the modeled myocardial source is associated with changes in the generated ECG, it seems reasonable to assume that similar changes detected in real ECG recordings are associated with changes in the myocardium of the same kind as those in the model.

CONCLUSION

In the present computer model, the nondipolar content of the T wave was a more general marker of repolarization inhomogeneity than a commonly used dipolar measure. The former was robust with respect to the delimitation of the T wave, but very sensitive to random noise, especially when principal components of high order were included in the computations.

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