Newly Developed Signal-Averaged Vector-Projected 187-Channel Electrocardiogram Can Evaluate the Spatial Distribution of Repolarization Heterogeneity

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SUMMARY

The purpose of this study was to verify the spatial distribution of myocardial repolarization heterogeneity using a newly developed 187-channel signal-averaged vector-projected ECG (187-ch SAVP-ECG).

We constructed corrected recovery time (RTc) and Tpeak-end (corrected Tp-e) dispersion maps using a 187-ch SAVP-ECG based on vector-projection theory using a Mason-Likar lead system. We compared the spatial distribution and quantitative values of dispersion maps by 187-ch SAVP-ECG with those by 64-ch magnetocardiography (MCG) in 27 normal controls (control) and 16 patients (12 myocardial infarction (MI), and 4 dilated cardiomyopathy (DCM)).

The wave pattern of the 187-ch SAVP-ECG in the representative cases was similar to those in 64-ch MCG. Spatial distribution increased RTc and corrected Tp-e dispersion maps defined by 187-ch SAVP-ECG were in agreement with those by 64-ch MCG. The value of RTc dispersion in MI was higher than that in control (41 ± 21 ms in MI versus 30 ± 12 ms in control, P < 0.05). The value of corrected Tp-e dispersion in DCM was higher than that in control (58 ± 12 ms in DCM versus 30 ± 13 ms in control, P < 0.001). There was a good correlation between RTc and corrected Tp-e dispersion values determined by 187-ch SAVP-ECG and 64-ch MCG modalities (y = 0.46x + 18, r = 0.62, P = 0.02 for RTc dispersion; y = 0.52x + 15, r = 0.63, P = 0.01 for corrected Tp-e dispersion).

RTc and corrected Tp-e dispersion maps by 187-ch SAVP-ECG based on vector-projection theory can evaluate the spatial distribution of myocardial repolarization heterogeneity. (Int Heart J 2008; 49: 153-164)

Key words: Signal-averaged ECG, Body surface mapping, Vector projection, Recovery time dispersion, Repolarization heterogeneity
THERE is a growing interest in the characteristic features of ventricular repolarization that lead to lethal ventricular arrhythmia even with the use of non-antiarrhythmic drugs.\textsuperscript{1,2} Our hypothesis is that recovery time dispersion may reflect a repolarization heterogeneity leading to lethal ventricular arrhythmia. Many studies have shown that body surface potential mapping contains more diagnostic and prognostic information than can be elicited from a 12-lead ECG. Ramanathan, et al reported activation and repolarization of the normal human heart under complete physiological conditions using electrocardiograms (ECG) recorded by a body-surface 224 multielectrode vest.\textsuperscript{3,4} Aiba, et al reported the clinical usefulness of recovery time dispersion from 87-lead body surface potential mapping as a predictor of sustained ventricular tachycardia.\textsuperscript{5} Despite these advantages, body surface mapping is not routinely used as a clinical method.\textsuperscript{6} Several possible explanations are a vexatious complication and a lack of quantitative analysis of the source of excitation and repolarization heterogeneity in the heart. We have previously demonstrated the significance of 3-dimensional recovery time dispersion using 64-ch magnetocardiography (MCG) for evaluating characteristic features of ventricular repolarization.\textsuperscript{7} Recently we reported that a newly developed 187-ch signal-averaged vector-projected ECG (187-ch SAVP-ECG) could evaluate low-amplitude high-frequency potentials.\textsuperscript{8} In this study, we verified the reliability of spatial distribution and quantitative values for assessing repolarization heterogeneity using a newly developed 187-ch SAVP-ECG.

METHODS

Patient selection: The study included 27 normal volunteers (control) and 16 patients with heart disease (12 patients with myocardial infarction (MI) and 4 patients with dilated cardiomyopathy (DCM)). A summary of the baseline characteristics and values is presented in Table I. The institutional ethics committee approved the research protocols (H17-2), and all patients provided informed consent. All procedures were in accordance with institutional guidelines.

Lead electrode replacement 187-ch signal-averaged vector-projected ECG (187-ch SAVP ECG): We attached 10 electrodes to the right shoulder (R), left shoulder (L), left lower abdomen, right lower abdomen, and V\textsubscript{1} through V\textsubscript{6} (quaternary intercostal space of the left sternal border) using the Mason-Likar lead system. An electrode was connected to an input box at one end.

187-ch signal-averaged vector-projected ECG (187-ch SAVP ECG): The prototype 187-ch SAVP-ECG consists of an electrode lead system, an input box, a high precision amplifier (prototype; Fukuda Denshi Co. Ltd., Tokyo), and a personal computer. The input box generates a modified X, Y, Z-lead ECG and vector-projected 187-ch synthesized ECGs from a Mason-Likar lead system. The input sig-
nal (± 550 mV) was digitized at 2 kHz by an A/D converter with a resolution of 0.076 µV. An isolation circuit recognizes the electrical separation between the input and output circuits in the form of an optical signal, thereby preventing accidental exposure of the subjects to electrical currents. The acquired ECG signals were processed by custom software (ECG manager, ICS Co. Ltd., Iwate, Japan).

We developed a vector-projected property for 187 fixed-positions on a torso surface model based on the theory reported by Frank.9,10) Representative points are shown in Figure 1. We proposed 11 parallel, equispaced transverse levels with 2-inch spacing between the levels. Level 5 coincides with the second intercostal space and level 6 coincides with the heart center. Seventeen letter designations (A through Q) indicate the intersection with each transverse level of radial lines separated by equal angles of 11.25° emanating from the longitudinal anatomic axis of the torso.

The electrical potential of the central terminal was determined by the equation CT=(R+L+F)/3. We then generated synthesized 187-ch ECGs by matrix calculation. The conceptual mathematical equation was as follows;

\[ V_p = L_p \times H = I_{pX} \times X + I_{pY} \times Y + I_{pZ} \]

where \( V_p \) represents the electrical potential at each point, \( p \), in each of the

<table>
<thead>
<tr>
<th>NO</th>
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187ch SAVP ECG indicates 187-channel signal-averaged vector projected ECG; 64-ch MCG, 64 channel magnetocardiography; OMI, old myocardial infarction; DCM, dilated cardiomyopathy; ANT, anterior; INF, inferior; POST, posterior; Lat, lateral; E, equivocal; HR, heart rate (bpm); E-QRS, QRS interval by ECG; E-QTc, QTc by ECG; E-RTc, corrected RT dispersion by ECG; E-Tp-e disp, corrected Tpeak-end dispersion by ECG; E-RTc location, location at increased RTc dispersion by ECG; M-RTc disp, RTc dispersion by MCG; M-Tp-e disp, corrected Tpeak-end dispersion by MCG; M-RTc location, location at increased RTc dispersion by MCG.
187 channels; \( L_p = (I_{p_x}, I_{p_y}, I_{p_z}) \), which is the vector projection at position \( p \); and \( H = (X, Y, Z) \), which is the cardiac electromotive force vector by the input signal from the \( X, Y, Z \)-lead ECG.

**Generation of RT dispersion and Tpeak-end dispersion by SAVP-ECG:** In general, Coulomb’s law demonstrates that electrical current is proportionate to the electrical potentials between two points, and inversely proportional to the square of distance. \(^{11} \) For generation of RT and Tpeak-end (Tp-e) dispersion maps, we calculated the relative electrical current density (ECD) from the 187-ch electrical potentials based on the theory of Coulomb’s law. The theoretical mathematical equation was as follows;

\[
F(\text{ch}_i, \text{ch}_j) = k \times \frac{(V(\text{ch}_j) - V(\text{ch}_i))}{d(\text{ch}_i, \text{ch}_j)^2}
\]

where \( F \) is the ECD \((i = 1-187, j = 1-187)\), \( k \) is a constant, \((V(\text{ch}_j) - V(\text{ch}_i))\) is an electrical potential between channel \( i \) and channel \( j \), and \( d(\text{ch}_i, \text{ch}_j) \) is the distance between channel \( i \) and channel \( j \).

In this algorithm, the RT time interval is defined as the time difference
between the peak points of the R waves and the positive maximum peak of the first derivation of the T wave of ECD. The Tpeak-end was defined as the time difference between the peak points of the T waves and the negative maximum peak of the first derivation of the T waves of ECD. The values for the mean RT dispersion were automatically calculated for the difference between the greatest RT interval (RTmax) and the smallest RT interval (RTmin). The value of Tp-e dispersion was automatically calculated as the difference between the greatest and smallest Tp-e intervals. Corrected RT intervals and Tpeak-end intervals were calculated by Bazzet’s formula as follows\(^\text{12}\):

\[
\text{RTc dispersion} = \text{RTc max} - \text{RTc min}
\]

\[
\text{Corrected Tp-e dispersion} = \text{Tp-e max} - \text{Tp-e min}
\]

RTc and corrected Tp-e dispersion maps were displayed as a 256-color coordinated map according to time differences. In brief, time differences were scaled by color, with blue indicating < 40 ms (almost normal range of dispersion), yellow indicating 40-60 ms (slightly increased dispersion), and red indicating > 60 ms (extremely increased dispersion).

**3D RT and Tpeak-end dispersion maps by 64-ch MCG:** MCG studies were performed in the Biomagnetism Laboratory at the Memorial Heart Center of Iwate Medical University. The recordings were made in a magnetically shielded room using a 64-ch MCG (prototype; SQUID sensor, manufactured by Hitachi High-Technology Co. Ltd, Tokyo). A brief examination was performed in order to guide the probe placement. Magnetic coils were placed on precordial leads in the V1, V2, V4, and xiphoid regions.

Current signals from these magnetic coils were initially recorded at approximately 4-ms intervals, followed by a 10-minute recording for each subject in the same position. The recordings were digitized at 500 Hz, and the total frequency characteristic of this system was DC to 200 Hz.

The acquired MCG images were processed by custom software (MCG manager, ICS Co. Ltd., Iwate, Japan). The preprocessing module preprocesses the acquired MCG signals by noise filtration, elimination of bad signals, and the interpolation of missing signals. The details of our mathematical approach to MCG have been described previously.\(^\text{7,13}\) The 3D RTc dispersion, and the peak and end of the T wave (Tp-e) dispersion were determined as follows: averaged 64 MCGs were acquired in each channel. The time of the peak for the T wave was defined as the Tpeak. The 3D current density \([F_t (x,y,z)]\) was calculated from the Bz component of MCGs by applying a space filter. RT \((x,y,z)\) time intervals were determined by the time between the R wave peak and maximum dF/dt. The Tp-e was determined by the time between the T wave peaks and the max-dF/dt. The intervals of RT and Tp-e were corrected using Bazzet’s formula.\(^\text{11}\) RTc dispersion and the corrected Tp-e were calculated from the differences of RTc \mid \text{max} - \text{min} \mid
or corrected Tp-e | max - min |. The 3D RTc dispersion and corrected Tp-e dispersion maps were then displayed in color (blue, 0 ms; purple, 50 ms; red, 100 ms; linearly). The 3D RTc and corrected Tp-e dispersion maps were generated within a 3-dimensional heart polygon wall by MCG.

Statistical analysis: All results are expressed as the mean ± SD and significance was defined as \( P < 0.05 \). Analysis was performed using GraphPad PRISM (San Diego, CA, USA). The unpaired \( t \)-test was used to compare the mean values between different groups.

RESULTS

The wave pattern in the representative 187-ch SAVP-ECG in the control group was similar to the 64-ch MCG (Figure 2). RTc and corrected Tp-e dispersion maps by 187-ch SAVP-ECG indicated a homogenous color scale pattern, and 3-dimensional RTc and corrected Tp-e dispersion heart polygons by 64-ch MCG also demonstrated a homogenous color scale (Figure 2).

Figure 2. Comparison of 187-ch SAVP-ECG (A) and 64-ch MCG (B) in a representative normal control. RTc and corrected Tp-e dispersion maps with homogenous color within the heart by 187-ch SAVP-ECG (A) were in agreement with 3-dimensional (3D) RTc and corrected Tp-e dispersion maps by 64-ch MCG (B). Color scale demonstrates time differences of the RTc and corrected Tp-e dispersions (blue, 0 ms; red, 100 ms).
Table II. Summary of Relation Between 187-ch SAVP ECG and 64-ch MCG

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<th>187-ch SAVP ECG</th>
<th>64-ch MCG</th>
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<tr>
<td></td>
<td>RTc dispersion</td>
<td>c Tp-e dispersion</td>
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<tr>
<td>Control</td>
<td>30 ± 12 msec</td>
<td>30 ± 13 msec</td>
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<tr>
<td>MI</td>
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<td>DCM</td>
<td>33 ± 18 msec**</td>
<td>58 ± 12 msec**</td>
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Control indicates normal control; MI, myocardial infarction; DCM, dilated cardiomyopathy; 187-ch SAVP ECG, 187-channel signal-averaged vector projected ECG; 64-ch MCG, 64-channel magnetocardiography; RTc dispersion, corrected RT dispersion; and c Tp-e dispersion, corrected Tpeak-end dispersion.

* P < 0.05, ** P < 0.001

Figure 3. Comparison of 187-ch SAVP-ECG (A) and 64-ch MCG (B) in a representative case with anterior MI. RTc dispersion map with increased RT dispersion at the anterior lesion by 187-ch SAVP-ECG (A) was in agreement with 3D RTc dispersion maps by 64-ch MCG (B). Corrected Tp-e dispersion map by 187-ch SAVP ECG and 64-ch MCG indicated an almost homogenous pattern.

Figure 4. Comparison of 187-ch SAVP-ECG (A) and 64-ch MCG (B) in a representative case with DCM. RTc and corrected Tp-e dispersion maps by 187-ch SAVP-ECG (A) demonstrated increased dispersion at the infero-posterior lesion. These findings by 187-ch SAVP-ECG were agreement with 3D RTc and corrected Tp-e dispersion maps by 64-ch MCG.
The value of RTc dispersion in MI was higher than that in control (41 ± 21 ms in MI versus 30 ± 12 ms in control, \( P < 0.05 \)). The value of corrected Tp-e dispersion in DCM was higher than that in control (58 ± 12 ms in DCM versus 30 ± 13 ms in control, \( P < 0.001 \)), see Table II.

There was a good correlation between RTc and corrected Tp-e dispersion values determined by 187-ch SAVP-ECG and 64-ch MCG modalities (\( y = 0.46x + 18, r = 0.62, P = 0.02 \) for RTc dispersion; \( y = 0.52x + 15, r = 0.63, P = 0.01 \) for corrected Tp-e dispersion).

The wave pattern and RTc and corrected Tp-e dispersion maps by 187-ch SAVP-ECG, and 3-dimensional RTc dispersion and corrected Tp-e dispersion heart polygon by 64-ch MCG in representative cases with anterior MI, and 2 cases with DCM are shown in Figures 3, 4, and 5.

**DISCUSSION**

In this study, we constructed RTc and Tp-e dispersion maps from synthesized 187-ch SAVP-ECGs based on vector-projection theory using the Mason-Likar lead system. The spatial distribution of increased RTc and corrected Tp-e dispersion was in agreement with those in 64-ch MCG, and quantitative values of RTc and corrected Tp-e dispersion were related with those in 64-ch MCG. We reported that a newly developed 187-ch SAVP-ECG could visualize the spatial location of ventricular repolarization heterogeneity that reflects myocardial
injury within the heart.

**Signal-averaged vector projected 187-ch ECG:** Theoretically, an image surface is a geometric representation of the relationship between a fixed-position current dipole inside a volume conductor and the electric potential that is produced on the boundary of the conductor. Many factors are believed to be responsible for the distorted “electrical view” of the heart. Frank proposed that the heart-vector projection theory provided deep insight into the nature of the relationship between torso surface voltage and the internal heart generator. The image surface differs slightly from the physical torso surface. The wave pattern by 187-ch SAVP-ECG in representative cases was similar to that obtained from 64-ch MCG, although the electrical voltage potentials at the region of precordial lead V₅ were slightly smaller. In any event, this vector-projection property on the image surface is applicable for an orientation of the fixed-position heart dipole.

**RT and Tpeak-end dispersion maps:** Measurement of the dynamics and spatial characteristics of ventricular repolarization is of interest in assessing patients with ischemic heart disease at risk of ventricular arrhythmias, or determination of the efficacy of drugs intended to alter repolarization. The QT interval has been used as an index of choice for assessing repolarization abnormalities. However, it lacks the power to assess the spatial aspects of repolarization and the ability to detect localized shortening in the setting of global prolongation. For direct cardiac surface measurement, QRST integrals and activation recovery intervals (ARIs) have been used to assess repolarization and its disparity. Activation recovery time (ART) from unipolar electrograms is a good estimate of end-of-repolarization time measured from a monophasic action potential (MAP), suggesting the usefulness in evaluation of global sequence and dispersion of ventricular repolarization. We speculated that the value of the RTc interval and RTc dispersion might be reflecting a physiological property of ARI. Furthermore, recent advances in electrophysiology have shown that the M cell may contribute to transmural dispersion heterogeneity and its role in the development of QT dispersion and lethal cardiac arrhythmias. Fish, et al demonstrated that the Tpeak-end dispersion in ECG provides repolarization abnormalities of the transmural dispersion of repolarization (TDR). They reported that epicardial activation augments TDR because the epicardial action potential repolarized earlier and the M cells with the longest action potential duration located in the deep subendocardium repolarized later compared with endocardial activation of the ventricular wall. Therefore, evaluating a global sequence and dispersion of ventricular repolarization and transmural dispersion heterogeneity in various diseases is important for assessing the risk stratification. However, it is difficult for identifying the reference points of the end of T waves automatically in multichannel body surface mapping. In this study, we have determined the RT and Tp-e intervals of
the ECD automatically using a computer as described above. Our algorithm of this 187-ch SAVP ECG was able to measure the RTc dispersion and corrected Tp-e dispersion in cases with simple T-wave inversion. However, we have frequently experienced several cases in which it was difficult to identify the peak and terminal end of T waves. In such cases, we obtained the quantitative values of RTc and corrected Tp-e dispersion after the identification of reference points by visual observation.

At the same time, we obtained a correlation between RTc and corrected Tp-e dispersion values determined by 187-ch SAVP-EKG and 64-ch MCG modalities, although there was a discrepancy in these values in several cases. In essence, 64-ch MCG could detect 3-dimensional electrical current density by magnetic fields, while 187-ch SAVP-EKG would represent calculated 2-dimensional electrical current density. In this respect, the measurement accuracy by 64-ch MCG seems to be superior compared with that by 187-ch SAVP-EKG. In addition, the value of corrected Tp-e dispersion by SAVP 187-ch ECG in DCM was higher than that in MI. Unfortunately, there was no obvious evidence to explain this phenomenon. In an early report by Medina-Ravell, LV epicardial pacing and biventricular pacing led to significant QT prolongation and enhanced TDR, defined as the interval between the peak and the end of the T wave (Tpeak-end). These findings suggest that a local existence of myocardial injury may contribute to an increased Tp-e dispersion. In the present study, a spatial location of increased repolarization heterogeneity on RTc and corrected Tp-e dispersion maps by SAVP 187-ch ECG was in agreement with those by 64-ch MCG in patients with MI and DCM. This indicates that RTc and corrected Tp-e dispersion by SAVP 187-ch ECG might easily visualize the spatial location of repolarization heterogeneity of the heart.

**Future clinical application:** The ability of certain drugs to prolong QT needs to be characterized. Regulatory concerns on the ability of an ever-increasing number of noncardiovascular drugs to prolong the corrected QT (QTc) interval and induce potentially lethal ventricular tachyarrhythmia have culminated in initiatives to harmonize internationally regulatory guidance on strategies by which new drugs are evaluated for their potential. The International Conference on Harmonization (ICH) has released consensus texts for clinical (ICH topic E14) and nonclinical (ICH topic S7B) strategies as regulatory drafts for wider consultation. The principal recommendation of ICH E14 is that every drug should be assessed for its effect on cardiac repolarization. However, QT measurements vary among electrocardiographs and analysis software. Kligfield, et al postulated that technically based differences in automated QT and QTc measurements must be considered when these intervals are used as markers of heart disease, prognosis, or arrhythmogenic risk. In this study, we derived an automatic measurement and functional dispersion maps for RTc and corrected Tp-e intervals. Future
research will evaluate the significance of our algorithm for the evaluation of repolarization heterogeneity caused by various drugs.

**Study limitation:** Since our sample size is small, further study with a larger sample size and comparisons with body surface mapping and electrophysiological studies will be needed to verify the clinical usefulness of this novel 187-ch SAVP-ECG.

**ACKNOWLEDGMENTS**

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**REFERENCES**


