Detection of QT Prolongation Through Approximation of the T Wave on Gaussian Mixture Modeling

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**Background:** To establish a simple and accurate method for the automated identification of the end of a T wave, we approximated electrocardiograph (ECG) traces using a Gaussian mixture model in conjunction with a split-and-merge expectation-maximization algorithm.

**Methods and Results:** A total of 286 ECG traces of heart beats of 50 healthy men were used as control data and ECGs from 15 subjects recorded before and after 400 mg oral moxifloxacin as positive controls. An experienced cardiologist determined the reference points by visual inspection of the original ECGs. The primary estimated point for the end of the T wave was selected as the point 2 ms before the point at which the gradient of the approximated wave was not steeper than the common threshold value. This point was then adjusted by applying modification rules proposed by an experienced cardiologist. The absolute value of the average interval between the resulting final estimated point and the manually selected reference point was 1.8±7.7 ms for the control data. After treatment with moxifloxacin, the average QT interval, corrected by Bazett’s formula, showed a 17.2±27.1 ms prolongation with a lower bound of the 95% confidence interval of 4.9 ms.

**Conclusions:** When the modification rules were applied, the accuracy of QT measurement was improved, and the present system was capable of detecting QT prolongation correctly. *(Circ J 2013; 77: 2728–2735)*

**Key Words:** Electrocardiogram; Gaussian mixture; QT interval; QT prolongation; T wave

Besides the congenital long QT syndrome, certain non-antiarrhythmic drugs, including some antibiotics, psychotropic agents, and anti-allergy agents, carry a potential risk of inducing the life-threatening arrhythmia torsades de pointes as a result of an undesirable delay in ventricular repolarization. The drug-induced prolongation of the interval between the beginning of the Q wave and the end of the T wave (QT prolongation) in electrocardiograms (ECGs) is therefore a matter of global concern in relation to the regulation of new drugs. In 2005, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which is jointly administered by the European Union, Japan, and the USA, published a technical guideline (E14) on the clinical evaluation of QT prolongation by non-antiarrhythmic drugs.

There are 2 manual methods for identifying the end of a T wave. Of these, the threshold method is the more commonly used. In this method, the T wave offset is taken as the point at which the tangent intercepts the isoelectric baseline. There is, however, a problem with this method in that it is affected by the filter bandwidth, by the threshold level, and by noise and variations in waveforms. The alternative method is the tangent method, in which a tangent is drawn at the steepest part of the downslope of the T wave, and the end of the T wave is taken as the point at which the tangent intercepts the isoelectric baseline. In both methods, the reproducibility of measurement is affected by marked inter- and intra-operator variability.

To solve these problems, a variety of automated or semi-automated QT measurement systems have been developed that use tangent intercepts, differentiated waveforms, or wavelet transformations. No accurate system, however, is currently available for automatically detecting drug-induced QT interval prolongations.

In a previous study, we developed a simple and accurate automated method for identifying the end of a T wave by using the expectation-maximization (EM) algorithm, commonly used in voice recognition, to approximate ECG traces by means of a Gaussian mixture model that contains multiple

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Gaussian functions. In the current study, we describe a system based on computer-assisted QT interval measurements to reduce inter- and intra-operator variability and provide criteria for the determination of endpoints. Furthermore, we verified the accuracy of the system in QT measurements by studying the effects of a positive control drug that has the potential to prolong the QT interval.

Methods

Subjects

As a control, three 12-lead ECGs were recorded for each of 50 healthy male subjects (mean age, 40.0±8.0 years; range, 21–57 years) in a resting state to give a total of 143 ECG traces (7 subjects recorded only 2 ECGs). The ECGs were recorded using a Kenz Cardico 1208 digital electrocardiograph (Suzukken, Nagoya, Japan).

As a positive control, the prolongation in the QT interval induced by 400mg oral moxifloxacin was examined in 15 healthy male subjects (mean age, 38.7±5.2 years; range, 30–46 years). ECGs were recorded before and 1.5–2h after oral moxifloxacin (the point of maximum plasma concentration of the drug).

In accordance with the Helsinki Declaration, all subjects gave their written informed consent and the data were recorded with unlinkable anonymization. The present study was approved by the Ethics Committee of the Research Institute of Environmental Medicine of Nagoya University.

ECG Recordings

ECGs were recorded at a sampling rate of 500 Hz with 0.05–100-Hz band-pass filtering and 12-bit (4.88-µV) amplitude resolution. After reducing wave drift with a 0.5-Hz high-pass filter, 3 consecutive artifact-free heart beats for the control data and 2 consecutive beats in the moxifloxacin study were extracted from the lead II ECG traces. ECG traces were digitized into 4,095 integers (range: –2,047 to +2,047) corresponding to the voltage. The unit for the output value is termed a “digit” in this study.

The Gaussian mixture model, which can readily approximate complex waveforms with relatively few parameters, consists of several Gaussian functions defined in accordance with the average (µw), standard deviation (σw), and mixing weight (w) of the mth model (m=1, ... , M), as given by equation (1):

\[
p(x_n|\Theta) = \sum_{m=1}^{M} w_m P(x_n|\mu_m,\sigma_m)
= \sum_{m=1}^{M} w_m \frac{1}{\sqrt{2\pi\sigma_m^2}} \exp \left[ -\frac{(x_n-\mu_m)^2}{2\sigma_m^2} \right]
\]

where \(x_n\) are the observed data (n=1, ..., N), \(N\) is number of data points, and \(M\) is the number of Gaussian functions. \(\Theta\) is a model parameter defined as follows:

\[\Theta = \{w_1, \ldots, w_M, \mu_1, \ldots, \mu_M, \sigma_1, \ldots, \sigma_M\}, 0 \leq w_m \leq 1, \sum_{m=1}^{M} w_m = 1.\]

In the EM algorithm, the optimized parameter \(\Theta^{(t)}\) was estimated by alternating an expectation (E) step and a maximization (M) step until variations in the Q(\(\Theta^{(t)}\)) were less than a selected value chosen as a criterion. The Q function shown in equation (2) was successively maximized as follows:

\[Q(\Theta^{(t)}) = \sum_{n=1}^{N} \sum_{m=1}^{M} \log w_m P(x_n|\mu_m,\sigma_m) \cdot P(m|x_n|\Theta^{(t)})\]

where

\[P(m|x_n|\Theta^{(t)}) = \frac{1}{\sqrt{2\pi\sigma_{m(t)}^2}} \exp \left[ -\frac{(x_n-\mu_{m(t)})^2}{2\sigma_{m(t)}^2} \right] \]

and

\[Q(\Theta^{(t)}) = \sum_{m=1}^{M} \frac{1}{\sqrt{2\pi\sigma_{m(t)}^2}} \exp \left[ -\frac{(x_n-\mu_{m(t)})^2}{2\sigma_{m(t)}^2} \right] \]

Data Preprocessing

For calculation using the EM algorithm, the input data have to be transformed to give a probability distribution or a frequency distribution. In this study, ECG traces recorded as voltage functions were transformed into (pseudo) frequency distributions. Because the Gaussian function is convex in shape, it is difficult to approximate a concave curvature by using Gaussian functions. Therefore, the area from the end of the S wave to the beginning of the Q wave in the next beat was isolated and moved vertically until the minimum digit corresponded to a value of zero (Figure 1). For the control data, 286 beats from 143 ECGs (2 consecutive beats for each ECG) were transformed. The time value at each 2-ms sampling point from the end of the S wave (taken as 0 s) was counted per digit to produce a frequency distribution.

Approximation of ECG Traces Using 1-D Gaussian Mixture Model

The Gaussian mixture model, which can readily approximate complex waveforms with relatively few parameters, consists of several Gaussian functions defined in accordance with the average (µw), standard deviation (σw), and mixing weight (wm) of the mth model (m=1, ... , M), as given by equation (1):
Identification of the End of a T wave

Having approximated the ECG traces by means of the Gaussian mixture models, we identified the end of the T wave. Initially, a reference point on the original ECG was determined by an experienced cardiologist. We calculated the gradient between the point on the approximated curve that corresponded to the reference point and the point 2 ms before it. The mean of the gradient in 286 control data was defined as a common threshold.

In practice, the end of a T wave on the approximated curve was detected using the following method. A search was conducted for the peak of the T wave on the initial half between the end of the S wave and the beginning of the Q wave of the next beat. Once the peak of the T wave had been detected, the end of the T wave (the primary estimated point) was defined as the point 2 ms before the point at which the gradient was not steeper than the threshold value (voltage difference <4.88 μV) continues for >20 ms.

**Figure 2.** Identification of the end of T wave by the present system. (A) The primary estimated point was defined as the point 2 ms before the point at which the gradient of the approximated wave (blue dashed line) was not steeper than that of the common threshold value (solid line, original electrocardiogram trace; vertical red solid line, primary estimated point). (B) Confirmation that the minimum voltage point (white arrow) is within the range of 60 ms before or after (vertical red dashed lines) the primary estimated point (vertical red solid line). (C) Confirmation that the beginning point (black arrow) of a flat portion (voltage difference <4.88 μV) continues for >20 ms (gray box). (D) The final estimated point is the point that satisfies criterion (B) or criterion (C) and is the nearest point to the peak of the T wave. Black arrow, beginning of a flat portion as the final estimated point; white arrow, minimal point that was not selected as the end of the T wave.

Here, \( \Theta^{(t)} \) denotes the parameters of the Gaussian functions at the \( t \)th calculation \( (w_m^{(t)}, \mu_m^{(t)}, \sigma_m^{(t)}) \).

The calculation process for the EM algorithm is as follows: (i) the initial parameters at \( t=0 \) are set randomly; (ii) in the E step, \( Q(\Theta^{(t)}|\Theta^{(t)}) \) is calculated from equation (2); and (iii) in the M step, \( t \) is replaced by \( t+1 \). Each parameter is updated and \( \Theta \) is set as \( \Theta^{(t+1)} \) so that \( Q(\Theta^{(t+1)}|\Theta^{(t)}) \) becomes maximal.

**Split-and-Merge EM Algorithm**

It is known that the convergence points of the EM algorithm are strongly dependent on the initial parameters. In a preliminary study, we selected the parameters with the highest \( Q(\Theta^{(t)}|\Theta^{(t)}) \) by changing the initial parameters 2,000 times. For the same reason as that given in our previous study, we applied the split-and-merge EM (SMEM) algorithm suggested by Ueda et al to reduce the computing time. By using the SMEM algorithm, a Gaussian function that showed a large discrepancy from the original ECG was split into 2 Gaussian functions. Simultaneously, 2 Gaussian functions that showed substantial overlapping portions were merged to obtain an optimum solution faster than would have been achieved by using the usual EM algorithm. We calculated the SMEM algorithm with 5 different initial parameters.

**Identification of the End of a T wave**

**Primary Estimated Point Obtained Using a Common Gradient Threshold** Having approximated the ECG traces by means of the Gaussian mixture models, we identified the end of the T wave. Initially, a reference point on the original ECG was determined by an experienced cardiologist. We calculated the gradient between the point on the approximated curve that corresponded to the reference point and the point 2 ms before it. The mean of the gradient in 286 control data was defined as a common threshold.

In practice, the end of a T wave on the approximated curve was detected using the following method. A search was conducted for the peak of the T wave on the initial half between the end of the S wave and the beginning of the Q wave of the next beat. Once the peak of the T wave had been detected, the end of the T wave (the primary estimated point) was defined as the point 2 ms before the point at which the gradient was not steeper than the threshold value 20 ms after the peak of the T wave; this was done to avoid false-positive recognition of any flat portion around the peak (Figure 2A).

**Identification of the Final Estimated Point Using Modification Rules** To reduce the difference between the primary estimated point (which was simply defined in terms of the gradient threshold) and the reference point chosen by the experienced cardi-
QT Prolongation Detection by ECG Approximation

Statistical Analysis
All data are expressed as mean±SD. Averages, standard deviations, 1-sided 95% confidence intervals (95% CI; 2-sided 90% CI), and determination coefficients of simple regression analysis were calculated using SPSS Statistics 17.0 software (SPSS, Chicago, IL, USA). Two-sided paired Student’s t-test was used to identify statistically significant differences in QT prolongation. Intra-class correlation coefficients (ICC) were used to evaluate the correspondence of the measured values. Mann-Whitney U-test and receiver operating characteristic (ROC) analysis were used to investigate the estimation errors. Differences of P<0.05 were considered to be significant.

Results
Definition of the End of the T Wave Using the Gradient Threshold
In our previous study, we investigated the relationships between the number of Gaussian functions used for the approximation of ECG traces, the computing time, and the average estimation error of QT intervals. As the number of Gaussian functions was increased, the computing time increased and the estimation error tended to decrease. Because the estimation error was minimal when the number of Gaussian functions was 6, we fixed the number of Gaussian functions for the current study at 6.

An example of an approximation process with the usual EM algorithm is shown in Figure 3. After this process the approximated curve (blue dashed line) was close to the original ECG trace (solid line). An example of a split-and-merge operation in the SMEM algorithm is shown in Figure 4. Two Gaussian functions (orange arrows, Figure 4A) were merged into a sin-
The average heart rate for correction (calculated from the RR interval) was 64.4 ± 11.0 beats/min. The determination coefficient for simple regression analysis ($R^2$) was 0.944 and therefore the estimated and the reference QT intervals had a high degree of correlation.

### QT Prolongation by Moxifloxacin and Detection Using the Present System

The QT interval, QTcB, and QTcF for the final estimated point before moxifloxacin were 410.0 ± 23.4 ms, 417.1 ± 20.2 ms and 414.5 ± 17.8 ms, respectively. After moxifloxacin, these were prolonged to 422.7 ± 25.1 ms, 434.3 ± 23.3 ms, and 430.3 ± 21.5 ms, respectively. There was no significant difference in the heart rate before (64.2 ± 10.6 beats/min) and after (63.5 ± 9.1 beats/min) moxifloxacin treatment ($P=0.676$).

When the QT prolongation was compared with the primary estimated point, the average difference in the QT interval before and after moxifloxacin was 9.1 ± 11.5 ms ($P<0.05$), and the average difference in the QTcF interval was 12.1 ± 19.7 ms ($P<0.05$). QT and QTcF intervals therefore showed significant prolongation, whereas significant prolongation was not detected in QTcB (13.5 ± 25.2 ms, $P=0.064$).

The averaged QT intervals for the control data for a conventional tangent method, the final estimated point and the reference were 376.4±28.4 ms, 409.1±32.9 ms and 407.4±32.2 ms, respectively. When Bazett’s formula ($QTcB = QT/RR^{1/2}$) was applied, the average corrected QT interval (QTc) for the final estimated point was 420.4±24.5 ms, and when Fridericia’s formula ($QTcF = QT/RR^{1/3}$) was applied, this value was 416.3±22.6 ms. For the reference point, the value of QTcB was 418.6±23.4 ms and that of QTcF was 414.5±21.3 ms. The

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**Figure 4.** Split-and-merge expectation-maximization (SMEM) algorithm calculation (black solid line, original electrocardiogram [ECG] trace; blue dashed line, approximated ECG trace; thin red dashed lines, Gaussian functions). (A) Before the split-and-merge operation; (B) just after the split-and-merge operation; and (C) at the end of SMEM calculation. (A, B) Thick orange dashed lines, pre- and post-merged Gaussian functions; thick green chain lines, pre- and post-splitted Gaussian functions.
Discussion

We hypothesized that the ECG trace is a natural phenomenon of a type that can be approximated by means of Gaussian mixture model in conjunction with a SMEM algorithm with optimized model parameters. Approximation of an ECG trace by using Gaussian functions has also been reported by Clifford and by Lipponen et al, who modeled the PQRST wave and T wave, respectively, but did not validate the QT measurements by using real ECG data explicitly.12,13 Moreover, inter- and intra-operator variabilities persisted in their determination of criteria for the ends of T waves. The aim of the current study was to develop an accurate automated QT measurement system for detecting drug-induced prolongation of the QT interval through the addition of endpoint modification rules.

The average difference in the absolute value between the final estimated point and the reference point was 1.8±7.7 ms for the control data, and the ICC(2,2), which represents the inter-operator reliability of the measurement method, was 0.965 (almost 1). In contrast, the average difference in the absolute value between the endpoint of the tangent method and the reference point was 31.1±16.0 ms, and the ICC(2,2) was 0.718. These data indicate, therefore, that the present system of using a Gaussian mixture model with modification rules based on visual inspection has the potential to be highly accurate. Discrepancies of >10 ms from the references were observed in 15 cases (5.2% of 286 beats). Figure 6 shows magnified examples of regions around the end of the T wave in which large discrepancies were found. In Figure 6A, the discrepancy is due to incomplete fitting by the mixed Gaussian functions, whereas in Figure 6B, the discrepancy is the result of a distortion caused by a small artifact. Incomplete fitting of the type shown in Figure 6A occurred in only 5 cases, whereas artifacts near the end of the T wave, of the type shown in Figure 6B, were present in 13 cases (86.7% of 15 cases). Both types of problem were present in 3 cases. One of our most important aims is to develop a method for dealing with artifacts near the end of a T wave.

We also investigated the relationship between the amount of adjustment between primary and final estimated points and the discrepancy between the final estimated points and the reference point. The average difference in the absolute value between the final estimated point and the reference point was 1.8±7.7 ms for the control data, and the ICC(2,2), which represents the inter-operator reliability of the measurement method, was 0.965 (almost 1). In contrast, the average difference in the absolute value between the endpoint of the tangent method and the reference point was 31.1±16.0 ms, and the ICC(2,2) was 0.718. These data indicate, therefore, that the present system of using a Gaussian mixture model with modification rules based on visual inspection has the potential to be highly accurate. Discrepancies of >10 ms from the references were observed in 15 cases (5.2% of 286 beats). Figure 6 shows magnified examples of regions around the end of the T wave in which large discrepancies were found. In Figure 6A, the discrepancy is due to incomplete fitting by the mixed Gaussian functions, whereas in Figure 6B, the discrepancy is the result of a distortion caused by a small artifact. Incomplete fitting of the type shown in Figure 6A occurred in only 5 cases, whereas artifacts near the end of the T wave, of the type shown in Figure 6B, were present in 13 cases (86.7% of 15 cases). Both types of problem were present in 3 cases. One of our most important aims is to develop a method for dealing with artifacts near the end of a T wave.

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whereas when the average difference was \(\geq 14.0\) ms, the average discrepancy between the final estimated points and the reference points was 4.4 ms. When the difference between the primary and final estimated points is large, and it can be estimated that the point derived by visual inspection by an experienced cardiologist. When the difference between the primary and final estimated points was \(<10\) ms, the average discrepancy between the final estimated points and the reference points was 4.4±14.0 ms, whereas when the average difference was \(\geq 10\) ms, the average discrepancy was 32.8±16.2 ms. There was a significant difference (\(P<0.01\)) between these discrepancies on Mann-Whitney U-test. When a large difference exists between the primary and final estimated points, the discrepancy between the final estimated points and the reference points increases.

We performed an ROC analysis using the difference between the primary and final estimated points as a predictor variable and the discrepancy between the final estimated points and the reference point obtained by visual inspection as an outcome variable. The group where the discrepancy was \(<10\) ms was 0 (negative), and the group with a discrepancy \(\geq 10\) ms was 1 (positive).

The resulting ROC curve is shown in Figure 7. The area under the curve was 0.902, the lower bound of the 95% CI was 0.788, and the upper bound was 1.0. The cut-off for the modification to the primary estimated points was 21 ms when the Youden index, expressed as sensitivity-(1-specificity), was maximal (0.767). The classification results for the control data are listed in Table. When measuring QT intervals, this system is able to show a warning message when the difference between the primary and final estimated points is large, and it can also indicate some candidate points that lie on a local minimum or the beginning of a flat portion that continues for \(<20\) ms. Modification rules for visual inspection can be arranged in advance and reflected in the system. Application of these rules could support the selection of an appropriate endpoint for a T wave, and could improve intra- and inter-operator reproducibility.

The average discrepancy between the final estimated points and the visually observed points selected by the experienced cardiologist was 1.8±7.7 ms (absolute value) for the control data, and the upper bound of the 1-sided 95% CI was 2.6 ms. These results indicate that this system has a sufficient precision to detect relatively small effects (approximately 5 ms), as required in the ICH-E14 guideline.

In another study on moxifloxacin by Démolis et al, which involved an exercise test on a bicycle ergometer, the QT interval (RR=1,000 ms, 379±24 ms) before treatment with a placebo was approximately 40 ms shorter than the present corrected QT interval (QTcB; the reference point in the control data, 419±23 ms). This variation could be caused by differences in age and race, by the presence or absence of QT interval correction, or by the choice of the criterion for the identification of the end of the T wave, among other factors. In the present study, QTcB (the final estimated point) after 400 mg moxifloxacin was 17.2±27.1 ms, which is a significant prolongation (\(P<0.05\)). This prolongation was similar to that found by Démolis et al (a 15-ms prolongation from the placebo group to the group receiving 400 mg moxifloxacin; RR=1,000 ms). The lower bound of the 1-sided 95% CI was 4.9 ms. The average difference in QTcF intervals, corrected by Fridericia’s method, was 17.2±21.5 ms (\(P<0.05\)), lower bound of 1-sided 95% CI: 5.9 ms). Positive-control drug criteria for the Through QT Study in ICH-E14 are as follows: the effect on the mean QTcF interval is \(>5\) ms, and the lower bound of the 1-sided 95% CI is \(>0\) ms. Moxifloxacin has been widely used as a positive control drug that produces QT prolongation. The present system detected QT prolongation significantly beyond the ICH-E14 criteria. This means that it has sufficient accuracy to detect QT prolongation correctly. In contrast, for the primary estimated point, which was simply defined by the common gradient threshold in this study, there was no significant difference in the QTcF interval after use of moxifloxacin. Given that significant prolongation was found in the QT interval (9.1±11.5 ms; \(P<0.05\)) and in the QTcF interval (12.1±19.7 ms; \(P<0.05\)), the primary estimated points have a certain degree of confidence. When the modification rules based on visual inspection were applied, however, the accuracy of QT measurement was improved, supporting the reproducibility of visual inspection. In addition, future investigation for contamination by artifacts could help to improve the precision of the present system.

**Study Limitations**

This study was performed in a limited number of healthy subjects. Thus, only the normal T waves were approximated and analyzed. QT measurement of abnormal morphologic T waves such as biphasic, notched, inverted T waves and TU complexes

| Discrepancy in the final estimated point | \(>10\) ms | \(\leq 10\) ms |
|----------------------------------------|-----------|-------------|
| Difference between the primary and the final estimated points | >21 ms | 13 | 27 |
|                                           | \(\leq 21\) ms | 2 | 244 |
remains to be evaluated. Inverted T waves could be measured using vertical mirror image.

Conclusions
The present system is capable of measuring QT intervals correctly, and might satisfy the E14 guidelines.

Disclosures
No grants.

References
1. JCS Joint Working Group. Guidelines for risks and prevention of sudden cardiac death (JCS 2010): Digest version. Circ J 2012; 76: 489–507.
2. Takigawa M, Kawamura M, Noda T, Yamada Y, Miyamoto K, Okamura H, et al. Seasonal and circadian distributions of cardiac events in genotyped patients with congenital long QT syndrome. Circ J 2012; 76: 2112–2118.
3. Haverkamp W, Breithardt G, Camm AJ, Janse MJ, Rosen MR, Antzelevitch C, et al. The potential for QT prolongation and proarhythmia by non-antiarrhythmic drugs: Clinical and regulatory implications. Report on a Policy Conference of the European Society of Cardiology. Eur Heart J 2000; 21: 1216–1231.
4. Alexandrou AJ, Duncan RS, Sullivan A, Hancox JC, Leishman DJ, Witchel HJ, et al. Mechanism of hERG K+ channel blockade by the fluoroquinolone antibiotic moxifloxacin. Br J Pharmacol 2006; 147: 905–916.
5. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf (accessed December 4, 2012).
6. McLaughlin NB, Campbell RWF, Murray A. Comparison of automatic QT measurement techniques in the normal 12 lead electrocardiogram. Br Heart J 1995; 74: 84–89.
7. Hibino S, Nakatochi M, Ueda N, Horiba M, Yasui K, Kagamihara Y, et al. Approximation of ECG T wave by using Gaussian mixtures and automatic measurement of QT interval. Seizure J 2010; 48: 359–368 (in Japanese).
8. Dempster AP, Laird NM, Rubin DB. Maximum likelihood from incomplete data via the EM algorithm. J R Stat Soc Series B Stat Methodol 1977; 39: 1–38.
9. McLachlan GJ, Basford KE. Mixture models: Inference and applications to clustering. New York: Marcel Dekker, 1988.
10. Ueda N, Nakano R, Ghahramani Z, Hinton GE. SMEM algorithm for mixture models. Neural Comput 2000; 12: 2109–2128.
11. Turner D. An intuitive approach to receiver operating characteristic curve analysis. J Nucl Med 1978; 19: 213–220.
12. Clifford GD. A novel framework for signal representation and source separation: applications to filtering and segmentation of biosignals. J Biol Syst 2006; 14: 169–183.
13. Lipponen JA, Tarvainen MP, Lyyra-Laitinen T, Lahtinen T, Karjalainen PA. Estimation of T-wave morphology using Gaussian functions. IFMBE Proc 2010; 25: 895–897.
14. Perkins NJ, Schisterman EF. The inconsistency of “optimal” cutpoints obtained using two criteria based on the receiver operating characteristic curve. Am J Epidemiol 2006; 163: 670–675.
15. Démolis JL, Kubista D, Tenenèz L, Funck-Brentano C. Effect of a single oral dose of moxifloxacin (400mg and 800mg) on ventricular repolarization in healthy subjects. Clin Pharmacol Ther 2000; 68: 658–666.