Table. Clinical Characteristics and Results of Independent Component Analysis in Patients With Long-QT Syndrome

Pt No.	Age, y	Sex	Genotype	Syncope, ACA, or VT/TdP	QTc, ms	Pharmaco Therapy	No. ICs	Main Origin of ExT1†	Main Origin of ExT2†	Main Origin of ExT3†	Classification*
1	19	F	A226V	Syncope	482	BB	5	V2-V6, max-V4	V4-V6		d
2	46	F	A226V	...	478	...	5	V2-V6, max-V3	V3-V6, max-V6		d
3	15	F	D242N	...	473	...	5	V2-V6, max-V5	V3-V6		c
4	18	F	D242N	...	486	...	5	V2-V6, max-V3	V3-V6		c
5	10	M	V254M	Syncope	539	BB	5	V2-V6, max-V5	V3-V6, max-V5		d
6	15	M	V254M	Syncope, convulsion	478	BB	5	V1-V6, max-V2	V1-V6, max-V3		d
7	45	F	V254M	Convulsion	525	...	5	V1-V6, max-V2	V2-V5, max-V3		d
8	3	M	I313K	Syncope	528	BB, verap	6	V1-V4(n), V5-V6	V1(n), V5-V6	V1-V4, max-V3	a
9	13	M	I313K	Syncope	550	BB, verap	5	V2-V6, max-V4	V4-V6, max-V4		d?
10	34	F	I313K	Syncope	583	BB, mexil	6	V4-V6, max-V5	V2-V6, max-V4	V1, V3-V5	b
11	34	F	I313K	Syncope	590	BB, mexil	5	V2-V6, max-V5	V3-V6, max-V4		b
12	6	M	A341V	Syncope	580	BB	8	V1-V2, V3-V4(n)	V2, V4(n)	V2, V4	b
13	11	M	A344E	...	488	...	6	V1-V2(n), V4-V6	V2(n), V4-V6	V1-V3	d
14	20	F	L346V	...	492	BB	5	V1(n), V2-V6	V1(n), V3-V6		d
15	15	M	R366W	...	503	...	5	V1(n), V3-V6	V1(n), V5-V6		d?
16	12	M	P448R	...	428	...	6	V1-V2(n), V4-V6	V1(n), V4-V6	V1	c
17	20	F	P448R	Convulsion, TdP	543	BB	6	V1(n), V3-V6	V3-V6, max-V5	V1-V2	bifid
18	43	F	P448R	...	559	...	6	V1(n), V5-V6	V3-V6, max-V5	V1	bifid
19	17	M	R518G	Syncope	429	BB	5	V2-V5, max-V3	V3		c
20	18	M	R518G	Syncope	426	BB	5	V3-V5, max-V4	V3-V6		c
21	14	M	R555C	Syncope	508	BB	5	V1-V2(n), V5-V6	V1-V2(n), V4-V5		d
22	9	F	G643S	...	521	...	6	V2-V4(n), V6	V1-V4(n), V6	V1-V4(n), V6	bifid

ACA indicates aborted cardiac arrest; BB, β-blocker; IC, independent component; mexil, mexiletine; (n), negative wave; TdP, torsade de pointes; verap, verapamil; VT, ventricular tachycardia.

*T-wave type on original ECG according to the classification by Zhang et al[2] as follows: a indicates infantile type; b, broad-based type; bifid, bifid T wave usually observed in long-QT syndrome type 2; c, normal-appearing type; d, late-onset normal-appearing type; d?, type d is possible.

†Leads on original ECG from which each extra IC originated, with the maximum origin being presented as max.

ECG, some unavoidable noise exists, including that generated by respiratory movement and muscle contraction, in addition to extrinsic noise, such as that from electric waves. To filter these, we applied the wavelet thresholding method[9,10] to the digitized ECG before ICA to effectively reduce noises. Furthermore, inverse ICA (i-ICA), an algorithm originally developed by 1 of the authors (Y.I.),[11] was applied to the results of ICA to determine the origin of each IC extracted by the ICA that comes from the original surface. The i-ICA also was used to verify that each IC contributed significantly to the composition of the T wave and not derived from noise.

Methods

Subjects

We studied 22 patients (mean±SD age, 21.6±13.3 years) with genetically confirmed LQT1 (by *KCNQ1* gene mutation) and 30 age-matched healthy control subjects free from cardiovascular diseases. None of the subjects of the latter group were taking medications with electrophysiological effects. The study protocol was approved by the Ethics Committee of the University Hospital of Tsukuba (Ibaraki, Japan), and informed consent was obtained from each patient or parents if the patient was aged <15 years. Thirteen of the 22 patients with LQT1 had a history of syncope, convulsions, or previous demonstration of ventricular tachycardia on ECG, and 13 patients were being treated with oral β-blockers of whom 4 combined this with mexiletine or verapamil after the ECG recording (Table).

The T-wave morphology on the standard 12-lead ECG was classified according to the format proposed by Zhang et al.[2] They described 4 different T-wave morphologies characteristic for LQT1, including infantile type, broad-based type, normal-appearing type, and late-onset normal-appearing type.

Sampling of ECG Data

The ECG was recorded as time series data using an ECG amplifier (MA1000; TEAC; Tokyo, Japan). The time constant was set at 3.0 seconds. Signals were recorded from 10 channels using 20 silver-silver chloride surface electrodes. Channel 1 was set as lead I; channel 2 as lead II; channel 3 as lead III; channels 4 to 9 as bipolar leads from chest to left leg, each corresponding to C1 to C6 of conventional 12-lead ECG; and channel 10 as 4C9, representing a bipolar lead from the fourth intercostal space on the left spine border of the back to the fourth intercostal space at the left sternal border of the forechest. In each subject, the recorded data were digitized online with an A/D converter (EC-2360; Elmec; Tokyo, Japan) at a sampling rate of 1024 Hz and saved in a notebook computer as a data file for future analysis. The data of C1 to C6 were converted into V1 to V6 using the following formula to produce ECG images: $Vi=Ci+(II+III)/3$, where $i=1$ to 6.

ECG Data Analysis

The methods used for data analysis comprised the following 4 main steps: (1) noise reduction by wavelet thresholding method[9,10] (ie,

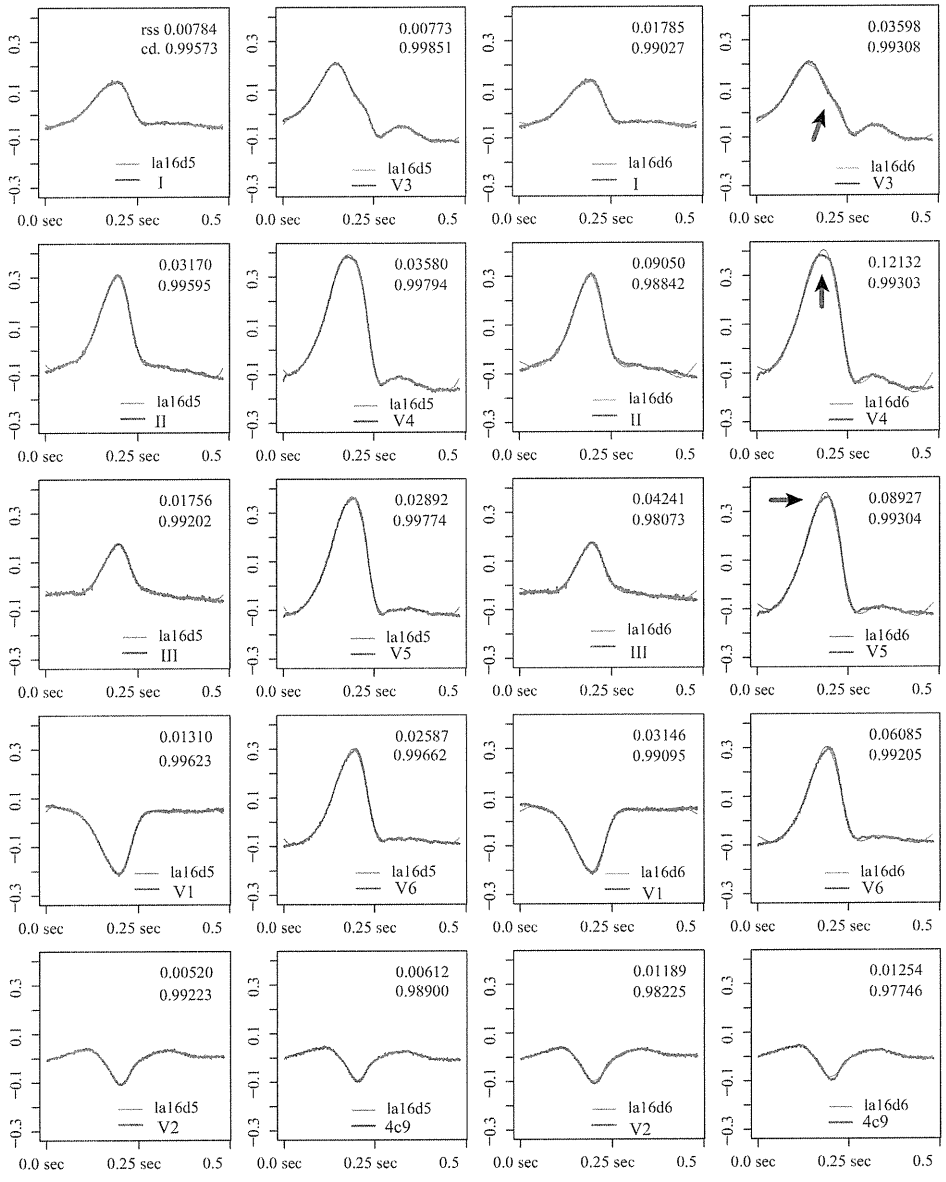

Figure 1. Noise reduction by wavelet thresholding method in a normal subject. Blue trace indicates original waveforms and red trace, approximated waveforms after noise reduction, indicating a good approximation (left 2 columns). However, when another level of wavelet was applied, there was dissociation between the peaks of the original T wave and the peaks of approximated T wave in V3 to V5 (right 2 columns, arrows), indicating inappropriate approximation. The unit for the vertical axis is mV.

approximation by wavelet), (2) radical ICA[8] with the additive random noise, (3) selection of the best model from the results of repeated ICAs, and (4) i-ICA for determination of the origin of each IC. The methods of these 4 steps used in the present study are described fully in the expanded Methods section in the online-only Data Supplement.

Noise Reduction by Wavelet Thresholding Method

To reduce noise before ICA, the hybrid threshold method (a combination of the universal threshold method and Stein unbiased risk estimate threshold method) was applied to the T-wave area (from the J point to the onset of the next P wave) of the digitized ECG. In this process, 4 types of wavelets were used, from which 1 with a maximum resolution level and best approximation to the original ECG was selected (online-only Data Supplement Figure 1). That the shape of the approximated data corresponded to the original data was confirmed by verifying each peak and flexion point of the T wave using the inverse wavelet transformation technique for each lead (Figure 1).

Radical ICA With the Additive Random Noise

The approximated data were analyzed by radical ICA. To improve the performance of ICA and, specifically, to avoid falling into the local extrema, we used the additive random noise, which was generated in multiples of the SD of the given data. The size of the additive noise had 10 values of SD, and radical ICA was repeated 16 times for each SD size, making the total times of ICA 160 for each case (online-only Data Supplement).

Selection of the Best Model From the Results of Repeated ICAs

To select the best model from the 160 results of ICA in each case, 3 indices of each ICA were calculated: Amari error,[12] relative mutual information, and the fourth-order cumulants.[13] We then used the

model-based clustering function (mclust method),[14,15] which is an R (a free software environment for statistical computing and graphics) package for normal mixture modeling through expectation maximization, model-based clustering, discriminant analysis, and density estimation. The results of ICA with these 3 variables were classified into ≥2 clusters by the mclust method[14,15] to select the most appropriate model for the data (online-only Data Supplement Figure 2). The noise reduction by the wavelet thresholding method (hybrid threshold method),[9,10] the radical ICA, and the mclust method was performed with R software.

i-ICA for Determination of Origin

The i-ICA is an original method developed by 1 of the authors (Y.I.)[11] (online-only Data Supplement) and was applied to the results of ICA to investigate the origin of each T-wave component extracted by ICA (ie, the distribution of each component on the observed surface ECG). Through this analysis, we also confirmed that each IC was a significant T-wave component, not a noise, and thus, the number of ICs could be determined in each case.

Results

Noise Reduction by Wavelet Thresholding Method

Noise reduction (ie, approximation of the data) by wavelet thresholding method could be appropriately applied to all cases and was useful for the following ICA (online-only Data Supplement). Figure 1 shows a typical noise-reduction technique in a normal subject.

ICA and i-ICA in Normal Subjects

The best model was selected from 160 times ICA based on the 3 indices mentioned previously followed by the mclust method. (Details of the selection of the best model by mclust method are provided in the online-only Data Supplement.) Because the number of ICs does not theoretically exceed the number of data (ECG leads), 10 ICs at maximum were obtained by ICA in each case (Figure 2). However, in all 30 normal subjects, the T wave of the best model comprised 4 ICs. Those ICs were arbitrarily called *pre-T*, *early-T*, *middle-T*, and *late-T*, in the order of their appearance. A typical example is presented in Figure 3 and online-only Data Supplement Figure 3. In the next step, we applied i-ICA to the results of ICA in order to recognize the local distribution of each IC on the original ECG (Figure 3). Early-T became the maximum in the vicinity of V3 and V4 and formed the early phase of the T wave. Late-T was the main contributor to the V5 waveform. The middle-T occupied the area between early-T and late-T. Pre-T existed in the early phase of early-T in V3 and V4 (Figure 3, online-only Data Supplement Figure 3), although this IC was not always extracted. When absent, a small positive wave (last-T) instead of pre-T appeared after late-T in V4 to V6, making the number of ICs 4 in all normal subjects.

ICA and i-ICA in LQT1

The number of ICs of the best model that formed the T wave was ≥5 in all 22 patients with LQTS. Five ICs, 6 ICs, and 8 ICs were extracted in 14 patients, 7 patients, and 1 patient, respectively (Table). These ICs comprised the 3 previously mentioned normal ICs (ie, early-T, middle-T, and late-T) and ≥2 additional ICs. We call the latter extra ICs *ExT1*, *ExT2*, and *ExT3*. ICs extracted from the T wave in LQTS are shown

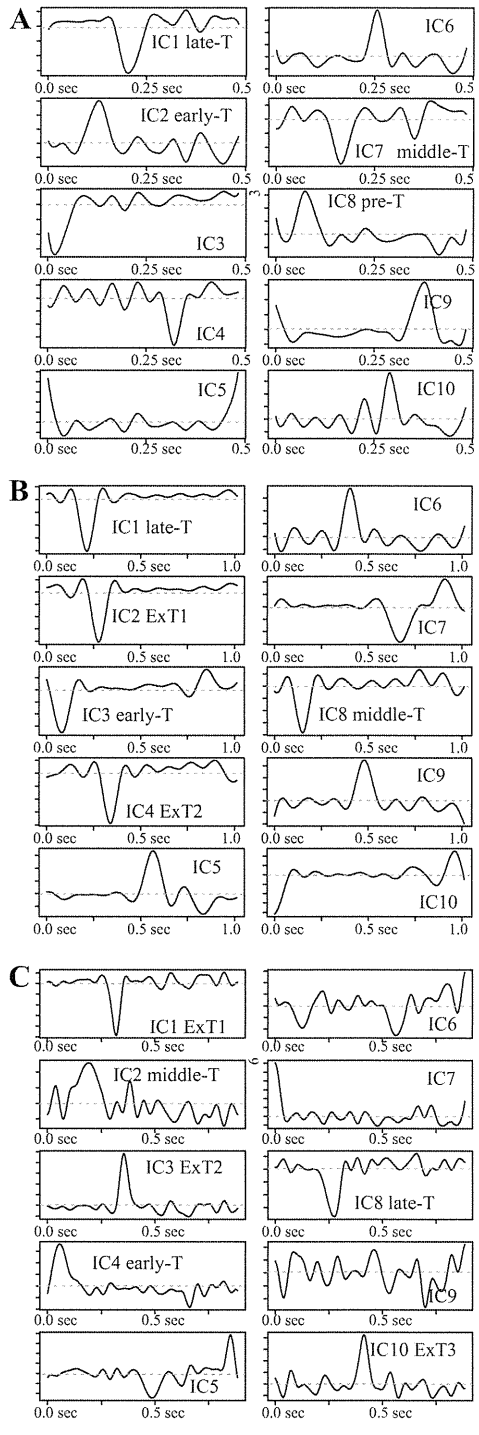

Figure 2. Ten ICs extracted by independent component analysis (ICA) in a normal subject and patients with long-QT syndrome. **A**, Ten ICs of the best model of a typical normal example. The 10 ICs were extracted by the ICA of the second time of the SD 0.7 group among 160 times ICA results. **B**, Ten ICs extracted by ICA, including 2 extra ICs, in a typical example of LQTS with 5 ICs. **C**, Ten ICs extracted by ICA, including 3 extra ICs, in a typical example of LQTS with 6 ICs. IC indicates independent component; ICx, the xth IC that appears in sequence by ICA (x=1 to 10 at maximum because the number of ICs do not exceed the number of data [ECG leads]).

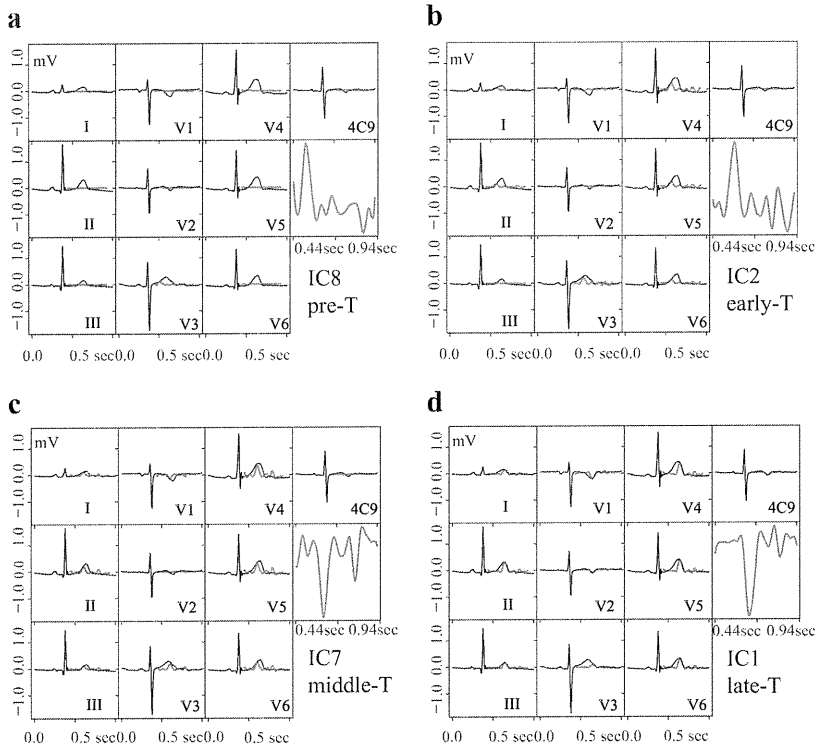

Figure 3. Results of independent component analysis (ICA) and inverse ICA in a normal subject. Four ICs constituting the normal T wave are represented in red waveforms in the second row of the fourth column of each part. Ten ICs were numbered in the order of appearance not on the T wave but in the results of the ICA. In all 30 normal subjects, the T wave included 4 ICs. Also shown are the results of inverse ICA. The blue waveforms represent the original ECG, and the red waveforms represent the distribution of each IC on the original leads, making it possible to recognize the origin of each IC on the original ECG. **a**, The waveform (red solid line) displays IC8. IC8 exists in the early phase of IC2 (early-T) in V3 and V4 (named *pre-T*). This IC was not always observed in the normal ECG. When absent, a small positive wave (last-T) appeared instead of pre-T. **b**, IC2 became the maximum in the vicinity of V3 and V4 and formed the early phase of the T wave (named *early-T*). **c**, IC7 occupied the area between IC2 (early-T) and the IC1 (late-T) (named *middle-T*). **d**, The second half of the T wave comprised IC1 (named *late-T*). IC1 is the major component of the V4 to V6 waveforms. IC indicates independent component.

in Figures 4 and 5 and online-only Data Supplement Figures 4 and 5.

The origins of the extra ICs determined by i-ICA in each patient with LQTS are listed in the Table. In most cases, the origin of ExT1 was the middle part of the T wave in V1 to V6, with the maximum origin in V2 to V5, and that of ExT2 was the late phase of the T wave mainly in V3 to V6. In cases with 3 extra ICs, the origin of ExT3 was exclusively the last part of the T wave mainly in V1 and sometimes in the left precordial leads. Among patients with the same gene mutation type (mainly family members), the constitution of the T wave was similar to one another; for example, the 3 subjects with the mutation V254M and the 2 with R518G showed similar ICs and their origins as well as the same type of T wave described by Zhang et al[2] (Table).

Even among 13 patients with LQT1 who were being treated with a β-blocker, 4 of whom also were being treated with verapamil or mexiletine, ≥5 ICs were extracted. In those with apparently normal QT intervals (patients 16, 19, and 20), extra ICs also were extracted. Patient 20 (Table) with normal QTc values under treatment with a β-blocker is presented in Figure 4 (see also online-only Data Supplement Figure 4). On the other hand, among 13 symptomatic patients, 5 ICs, 6 ICs, and 8 ICs were extracted from 9, 3, and 1, respectively, indicating that the number of extra ICs was not related to susceptibility to arrhythmias.

The classification of the types of T-wave morphology according to Zhang et al[2] are presented in the Table. Patients with the broad-based or normal-appearing T-wave morphologies tended to have 5 ICs, and those with the infantile or bifid ones tended to have 6 ICs (Table).

Discussion

The present study demonstrated for the first time, to our knowledge, that the T wave in normal subjects consists of 4 ICs, whereas those in LQTS comprised ≥5 (mostly 6) ICs, when ICA is applied to the T-wave area (ie, from the J point to the onset of the next P wave). In other words, ≥2 extra components were detected in LQTS in addition to the normal ICs present in LQTS (early-T, middle-T, and late-T). In LQTS with 5 ICs, summation of early-T, middle-T, and late-T made a distinct wave, and that of the other 2 waves (ExT1 and ExT2) provided another distinct wave. These 2 summated waves clearly divided each other. Therefore, the number of ICs of normal T waves was considered 3 instead of 4, and the other 2 waves were considered extra. Similarly, the T wave comprised 3 normal ICs and 3 extra ICs in LQTS with 6 ICs. It is noteworthy that patients with LQTS were clearly differentiated from normal subjects by the number of ICs. Furthermore, patients with LQT1 who showed normal QT intervals on the surface ECG (patients 16, 19, and 20) (Figure 4, Table) or those who were taking β-blockers also had additional ICs of the T wave (Table). However, unbiased estimates of the sensitivity and specificity of the method for the differentiation between patients with LQT1 and normal subjects should be obtained in an independent validation group with a large number of subjects.

We arbitrarily termed each T-wave component detected in the normal subjects as *pre-T*, *early-T*, *middle-T*, and *late-T*, and those observed only in patients with LQT1 as *ExT1*, *ExT2*, and *ExT3*...*ExT*n. The additional ICs were demonstrated by i-ICA to be located largely in the middle (ExT1) and late phase (ExT2 and ExT3) of repolarization, forming the second half or the last part of the T wave. The origin of ExT1

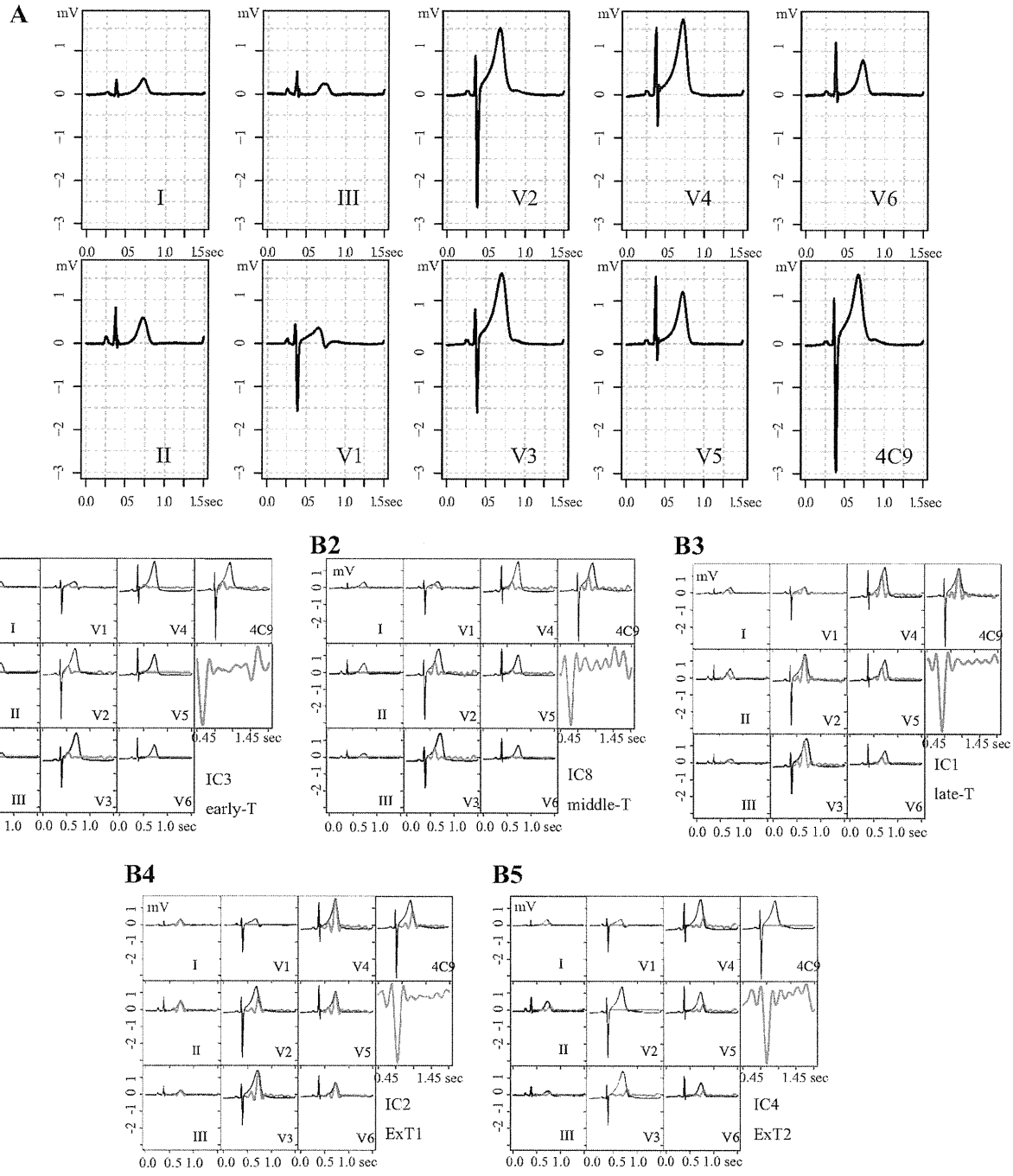

Figure 4. A typical case of LQT1 with 5 ICs (patient 20) (see Table). **A**, The 12-lead standard ECG, showing normal QTc (426 ms) and normal T-wave morphology. **B**, Results of independent component analysis (ICA) and inverse ICA. Although a β-blocker was being administered and the QT interval was normal, 5 ICs were extracted. The seventh-time ICA of the SD 0.7 group of fk22d6 was assumed to be the best model according to the rule described in the Methods section. The waveforms here are presented in the same way as in Figure 3. **B1**, IC3 was early-T, similar to that observed in normal T. **B2**, IC8 existed between IC3 (early-T) and IC1(late-T), and was named *middle-T* as in normal T. **B3**, IC1 formed the second half of the T wave in V1 to V2 and the middle part or the first half of the T wave in V3 to V6 (named *late-T*). **B4**, IC2 appeared later than IC1 (late-T) as the fourth wave in the time series, showing the maximum value at V4, and formed the latter half of left precordial leads (named *ExT1*). **B5**, IC4 appeared later than IC2 (ExT1) (named *ExT2*) as an inverted T wave with a small amplitude in V1. The maximum amplitude was observed in V4. It was confirmed to be located over V3 to V6 on the original ECG. IC indicates independent component.

was estimated to be widely distributed to V1 to V6 and those of ExT2 and ExT3 were mainly to V3 to V6, suggesting the presence of many myocardial cells that express malfunctional potassium channels due to *KCNQ1* mutation in the left ventricle. Although the origins of extra ICs could not be clearly confined to a specific area, this distribution tendency is consistent with the results of a canine model study in which after-contraction that precedes torsade de pointes arises in the left ventricle.[16]

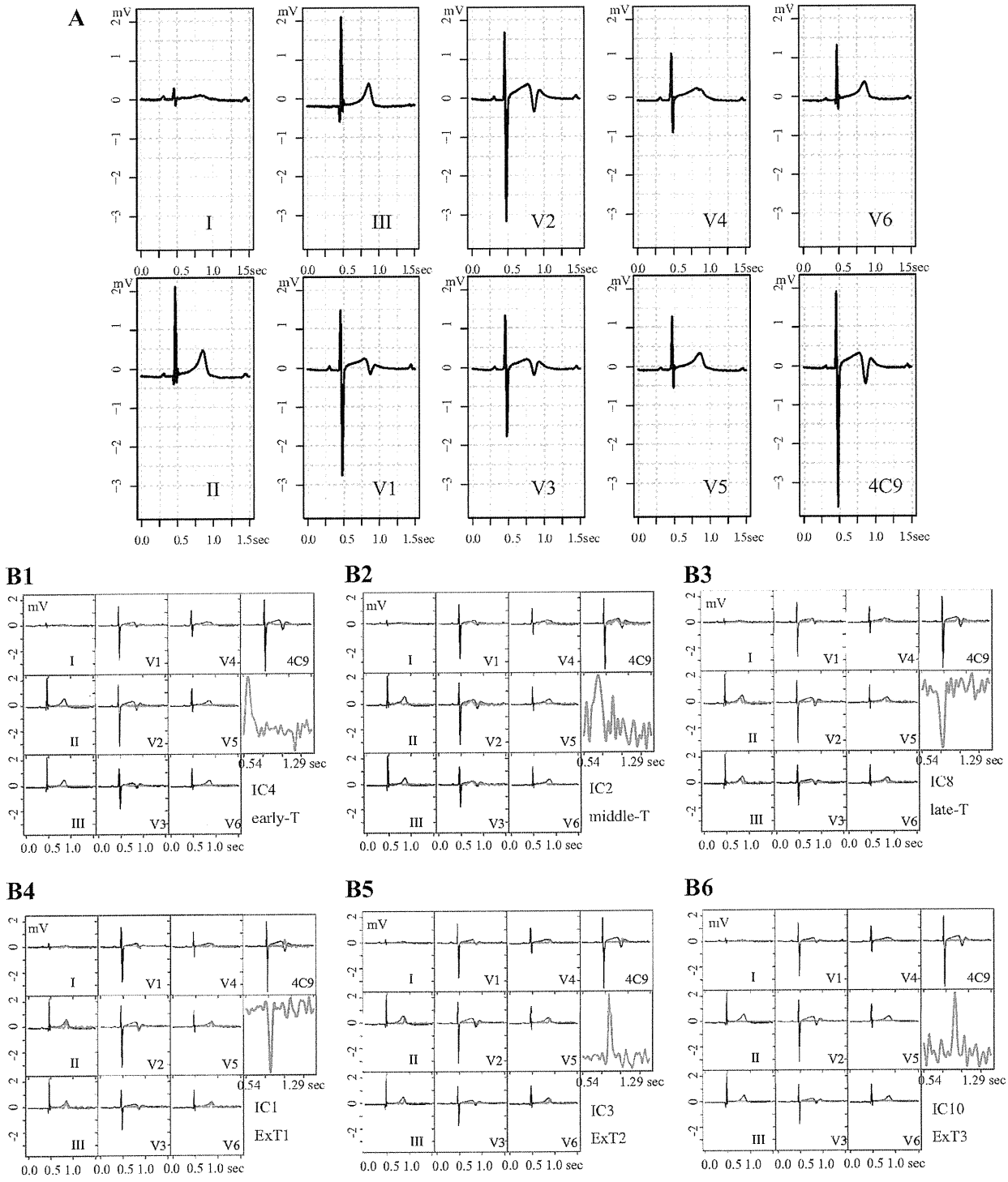

Figure 5. A typical case of LQT1 with 6 ICs (patient 13) (see Table). **A**, The 12-lead standard ECG showing prolonged QTc (488 ms). **B**, Results of independent component analysis (ICA) and inverse ICA. The seventh-time ICA of the SD 0.7 group of Ia20d5 by the mclust method was selected for the best model of this LQTS according to the rule described in the Methods section. The waveforms in each part are presented in the same way as in Figure 3. **B1**, IC4 was early-T, appearing as the first small wave in the right precordial leads similar to that observed in normal T. **B2**, IC2 was middle-T, being located at the position from the early to middle period in the right precordial leads. **B3**, IC8 appeared as the third wave, forming the latter half of the T wave in the right precordial leads (late-T). **B4**, IC1 appeared as the fourth wave and formed the inverted T wave in the right precordial leads as well as in the latter half of the T wave in the left precordial leads. This IC was ExT1 not observed in normal T waves. **B5**, IC3 appeared sequentially as the fifth wave, forming the latter half of the inverted T wave in the right precordial leads V1 to V2 as well as in the last part of T wave in the left precordial leads. This IC was ExT2 and not observed in normal T waves. **B6**, IC10 appeared as the sixth single wave, comprising the last triangle portion of the T wave in the right precordial leads. This IC was ExT3 and not observed in the normal T waves. Although the normal T wave in some healthy control subjects resembled the Aries symbol in lead V2, the last triangle existed not in normal subjects but in patients with LQTS as a single IC. IC indicate independent component.

Recent discovery of many types of mutations of genes encoding myocardial ion channels has encouraged channel-based discussion about T-wave morphology.[4] Nevertheless, the clinical usefulness of the T-wave morphology in the diagnosis of LQTS has been limited because quantitative analysis cannot be easily applied. In 1995, Moss at al[3] demonstrated for the first time the genotype-specific morphology of the T wave. In 2000, Zhang et al[2] reported more complex diversity in T-wave morphology in each type of LQTS as described earlier. Accordingly, we tried to classify the present study patients into the template. The infantile-type T wave could only be detected in 1 patient in our study who was aged <5 years. Although the other 3 types of T wave were identified, the wave morphology was rather similar to that of LQTS type 2 (hERG mutation), with a bifid T wave in 3 patients.[17] This classification was mostly qualitative and depended on the skill and experience of the investigator, and it was not necessarily easy to classify the patients convincingly. However, it is intriguing that the types of T-wave morphology described by Zhang et al[2] were associated considerably with the number of ICs in the present study. Furthermore, it is noteworthy that even in the "normal" T-wave types with normal QTc values, extra ICs were extracted (Figure 4, online-only Data Supplement Figure 4).

Among the quantitative methods of analysis, QT dispersion on the 12-lead ECG is one of the most common parameters applied to LQTS.[18] However, the value of QT dispersion remains clouded because determination of the T-wave offset is not always possible, and it is possible that some of the QT intervals measured on the different ECG leads are just different projections of a common current dipole. Assessment of monophasic action potentials at various ventricular sites is a more definitive way to evaluate the heterogeneity of ventricular repolarization,[16] but it is an invasive method using an electrode during catheterization. Recently, Kanters et al[17] applied the Hill equation to T-wave morphology analysis. Furthermore, Vaglio et al[19] reported an automatic algorithm for the quantification of T-wave morphology. Both methods could discriminate LQT1 from LQT2 and, interestingly, revealed that the repolarization process shifted to the later phase in LQT1 than LQT2. This tendency is consistent with the present results that extra ICs mainly constitute the second part of the T wave.

As a multivariate analysis of inhomogeneity of ventricular repolarization, the principal component analysis has been applied for the assessment of T-wave morphology in LQTS by some investigators,[20,21] the results of which demonstrated its usefulness in distinguishing abnormal from normal repolarization processes such that a high second/first eigenvector ratio predicts increased inhomogeneous repolarization.[20,21] Principal component analysis also was reported to be useful in prediction of cardiovascular mortality.[22] So far, ICA has not been applied for analysis of the repolarization process in LQTS. It is noteworthy that ≥2 extra ICs, which were not extracted from T waves of normal subjects, were demonstrated in all patients with LQT1, including those with normal QTc values or those taking β-blockers. Compared with the earlier methods discussed previously, ICA tends to be influenced more by the presence of noise, making it difficult to exclusively extract significant ICs. However, the wavelet thresholding technique for noise reduction combined with the sophisticated mathematical techniques for the best model selection in ICA proved to be useful for the diagnosis of LQTS. Although the complicated data analysis procedure (including waveform approximation and the best model selection in ICA) can be performed almost automatically (in the order of the flow chart presented in online-only Data Supplement Figure 1), it would be preferable in future studies to see results from an analyst who is blinded with regard to the LQTS or normal status of the study subjects and would help to further validate the usefulness of the method.

It would be intriguing to see whether the number of ICs reflects the severity of the disease; that is, those patients who experience syncope or ventricular arrhythmias tend to have ≥3 extra ICs. Although we examined only patients with LQT1 in this study to simplify interpretation of the results of the newly applied methods, further studies are needed to explore this hypothesis in a large number of subjects, including patients with other mutations of LQTS, especially LQT2 or LQT3.

Disclosures

None.

References

1. Vincent GM, Timothy KW, Leppert M, Keating M. The spectrum of symptoms and QT intervals in carriers of the gene for the long QT syndrome. *N Engl J Med.* 1992;327:846–852.
2. Zhang L, Timothy KW, Vincent GM, Lehmann MH, Fox JLC, Giuli LC, Shen J, Splawski I, Priori SG, Compton SJ, Yanowitz F, Benhorin J, Moss AJ, Schwartz PJ, Robinson JL, Wang Q, Zarebra W, Keating MT, Towbin JA, Napolitano C, Medina A. Spectrum of ST-T wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. *Circulation.* 2000;102:2849–2855.
3. Moss AJ, Zareba W, Benhorin J, Locati EH, Hall WJ, Robinson JL, Schwartz PJ, Towbin JA, Vincent GM, Lehmann MH. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. *Circulation.* 1995;92:2929–2934.
4. Antzelevitch C. Molecular genetics of arrhythmias and cardiovascular conditions associated with arrhythmias. *J Cardiovasc Electrophysiol.* 2003;14:1259–1272.
5. Cichocki A, Amari S. *Adaptive Blind Signal and Image Processing.* New York, NY: John Wiley & Sons; 2002.
6. Hyvärinen A, Karhunen J, Oja E. *Independent Component Analysis.* New York, NY: John Wiley & Sons; 2001.
7. Comon P, Jutten C. *Handbook of Blind Source Separation.* Burlington, MA: Academic Press; 2010.
8. Learned-Miller EG, Fisher JW III. ICA using spacings estimates of entropy. *J Mach Learn Res.* 2003;4:1271–1295.
9. Whitcher B. waveslim: Basic wavelet routines for one-, two- and three-dimensional signal processing. 2010; R package version 1.6.4. http://cran.r-project.org/web/packages/waveslim/index.html. Accessed April 15, 2011.
10. Gençay R, Schçuk F, Whicher B. An *Introduction to Wavelets and Other Filtering Methods in Finance and Economics.* San Diego, CA: Academic Press; 2002:112–116.
11. Yanai S, Ishikawa Y, Fuse S, Tsutsumi H. Inverse independent component analysis facilitates clarification of the accessory conductive pathway of Wolf-Parkinson-White syndrome electrocardiogram. *Pediatr Cardiol.* 2008;30:59–69.
12. Amari S, Cichocki A, Yang HH. A new learning algorithm for blind signal separation. In: Touretzky D, Mozer M, Hasselmo M. eds. *Advances in Neural Information Processing Systems 8.* Cambridge, MA: MIT Press; 1996:757–763.
13. Cardoso JF. High-order contrasts for independent component analysis. *Neural Comput.* 1999;11:157–192.

14. Fraley C, Raftery A. mclust: Model-based clustering/normal mixture modeling. 2010; R package version 3.4.8. http://cran.r-project.org/web/packages/mclust/index.html. Accessed April 15, 2011.
15. Everitt B. *An R and S-PLUS Companion to Multivariate Analysis*. London, UK: Springer-Verlag; 2007:128–134.
16. Gallacher DJ, Van de Water A, van der Linde H, Hermans AN, Lu HR, Towart R, Volders PG. In vivo mechanisms precipitating torsades de pointes in a canine model of drug-induced long-QT1 syndrome. *Cardiovasc Res*. 2007;76:247–256.
17. Kanters JK, Fanoe S, Larsen LA, Thomsen PEB, Toft E, Christiansen M. T wave morphology analysis distinguishes between KvLQT1 and HERG mutations in long QT syndrome. *Heart Rhythm*. 2004;3:285–292.
18. Surawicz B. Will QT dispersion play a role in clinical decision-making? *J Cardiovasc Electrophysiol*. 1996;7:777–784.
19. Vaglio M, Couderc JP, McNitt S, Xia X, Moss AJ, Zareba W. A quantitative assessment of T-wave morphology in LQT1, LQT2, and healthy individuals based on Holter recording technology. *Heart Rhythm*. 2008; 5:11–18.
20. Priori SG, Mortara DW, Napolitano C, Diehl L, Paganini V, Cantù F, Cantù G, Schwartz PJ. Evaluation of the spatial aspects of T-wave complexity in the long-QT syndrome. *Circulation*. 1997;96:3006–3012.
21. Extramiana F, Haggui A, Maison-Blanche P, Dubois R, Takatsuki S, Beaufils P, Leenhardt A. T-wave morphology parameters based on principal component analysis reproducibility and dependence on T-offset position. *Ann Noninvasive Electrocardiol*. 2007;12:354–363.
22. Okin PM, Devereux RB, Fabsitz RR, Lee ET, Galloway JM, Howard BV. Principal component analysis of the T wave and prediction of cardiovascular mortality in American Indians. The Strong Heart Study. *Circulation*. 2002;105:714–719.

CLINICAL PERSPECTIVE

The main ECG criteria for the diagnosis of long-QT syndrome (LQTS) include abnormal T-wave morphology as well as prolonged QT interval. We hypothesized that additional components related to the abnormally long myocardial repolarization process are included in the T wave of LQTS and investigated whether independent component analysis (ICA) can extract such abnormal repolarization components. Digital ECG data were obtained as time series in 22 patients with genetically confirmed LQTS type 1 (LQT1) and 30 normal subjects. In each case, the T-wave area was analyzed by radical ICA after noise reduction by the wavelet thresholding method. Furthermore, inverse ICA was applied to determine the origin of each independent component (IC). ICA revealed that a T wave consisted of 4 basic ICs in control subjects, whereas $\geq$5 (mostly 6) ICs were identified in all 22 patients with LQT1. The extra ICs, which were not evident in normal subjects, were assumed to contribute to the formation of abnormal T-wave morphology. The extra ICs were identified even in patients with normal QTc values and in those taking β-blockers. Inverse ICA indicated that the additional ICs originate predominantly from the late phase of the T wave of the left ventricle. These results mean that ICA is a potentially useful multivariate statistical method to differentiate patients with LQT1 from normal subjects. Further studies are needed to validate the clinical usefulness of the method in a large number of subjects, including patients with other mutations of LQTS, especially LQT2 and LQT3.

PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2012) **54**, 99–103 doi: 10.1111/j.1442-200X.2011.03487.x

Original Article

Long-term efficacy of plasma exchange treatment for refractory Kawasaki disease

Tatsunori Hokosaki, Masaaki Mori, Takashi Nishizawa, Tomoko Nakamura, Tomoyuki Imagawa, Mari Iwamoto and Shumpei Yokota

Department of Pediatrics, Yokohama City University School of Medicine, Yokohama, Japan

Abstract ***Background***: The treatment of Kawasaki disease patients who fail to respond to initial i.v. immunoglobulin (IVIG) therapy is controversial. The aim of the present study was to investigate the long-term efficacy of plasma exchange (PE) treatment for refractory Kawasaki disease.

Methods: A total of 125 Kawasaki disease patients refractory to IVIG were treated with PE. Coronary artery lesions (CAL) before PE, in the acute period, and during the late period were examined retrospectively.

Results: Residual sequelae requiring medical treatment occurred in six cases in the late period. The outcomes of treatment tended to be better when PE was begun in the early stage. Sequelae remained in 2.8% of patients in whom PE was initiated prior to day 9 after onset, and were present in 15% of patients in whom PE was started on or after day 10. The 105 patients whose coronary arteries were normal before PE had no sequelae (residual sequelae: 0%). Dilatation was present before PE in 14 patients, but remained in only two patients in the late period (residual sequelae, 14.3%). In four of the six patients in whom aneurysms had already formed before PE, the lesions had advanced into giant aneurysms, but in the other two patients they returned to the normal range (residual sequelae, 66.6%).

Conclusions: The outcomes of PE for Kawasaki disease refractory to IVIG are favorable, and the effectiveness of this treatment is excellent, particularly if it is initiated before CAL arise.

Key words coronary artery lesion, i.v. immunoglobulin, Kawasaki disease, plasma exchange, refractory Kawasaki disease.

Through the establishment of a high-dose i.v. immunoglobulin (IVIG) protocol for Kawasaki disease, a high level of effectiveness can be achieved,[1] but between 10 and 15% of patients still fail to respond.[2]

Alternative treatments for patients refractory to IVIG have not yet been developed, and the approaches being tested vary greatly from institution to institution. Plasma exchange (PE) is a method with promising efficacy, but the number of facilities that perform it is limited, and few reports on outcomes have been published so far.[3,4] In particular, there are no large-scale studies on the effects of PE on coronary artery lesions (CAL) in the late period.

In the present study, we investigated the long-term efficacy of PE in IVIG-refractory Kawasaki disease patients.

Methods

Demographics

The subjects were 125 children with Kawasaki disease (onset: between August 1994 and March 2007) who had been treated with PE because IVIG had proven ineffective. Those patients in whom steroids other than IVIG had been given before PE had been started were excluded from the study (two patients). One patient who had been pre-treated with infliximab was also excluded. One hundred and sixteen patients received their first IVIG treatment in 19 affiliated hospitals located close to each other. When a patient was judged to be refractory to IVIG, the patient was referred to one of the two hospitals (Yokohama City University Hospital and Yokohama City University Medical Center) where PE could be performed. At the time the first IVIG treatment was started, the remaining nine patients were hospitalized in one of these two hospitals.

On the basis of the patients' treatment records, lesions in the coronary arteries before PE, in the acute period (within 1 month of onset), and in the late period (≥1 year after onset) were studied retrospectively. These lesions were defined as follows: dilatation, coronary arteries ≥3 mm in internal diameter in children <5 years of age (or ≥4 mm in diameter in children ≥5 years), or lesions 1.5-fold the diameter of the neighboring coronary artery; aneurysm, lesions >4 mm in diameter; giant aneurysm, those >8 mm in diameter. Assessment of all coronary artery branches in the acute period was carried out by measuring diameter on echocardiography.[5] In the late period, in patients in whom echocardiography was performed approximately 1 year after onset and in whom residual CAL were suspected, further coronary angiography was conducted.

Correspondence: Tatsunori Hokosaki, MD, Department of Pediatrics, Yokohama City University School of Medicine, 3-9 Fukuura, Yokohama 236-0004, Japan. Email: thokosaki@hotmail.co.jp

Received 3 November 2010; revised 14 August 2011; accepted 30 September 2011.

Indications for plasma exchange

Initial IVIG treatment was deemed ineffective if it satisfied the following conditions within 48 h of the end of treatment: (i) appearance of a fever ≥38°C at least once within 1 day; and (ii) failure to bring about improvement of at least one of three inflammation markers (leukocyte count, neutrophil count, and C-reactive protein level).[6]

A further dose of IVIG was given to patients in whom the initial IVIG administration was ineffective. If that also brought about no improvement, then PE was performed on the grounds that the patient was refractory to IVIG. There were some patients in whom abnormalities of the coronary arteries had already developed after the initial IVIG. In these patients, PE was performed promptly without a second dose of IVIG being given.

Plasma exchange method

Plasma exchange was generally conducted as a vein-to-vein procedure (although, until 2005, there was also an artery-to-vein procedure option). A 6–7 Fr double-lumen dialysis catheter was inserted into the femoral vein (or subclavian vein or internal/external jugular vein). Replacement fluid contained 5% albumin, but when anemia was present, or when younger patients were treated (<3 months of age, or <5 kg in weight), red cell concentrates and mannitol adenine phosphate (RC-MAP) were used in conjunction with treatment. The amount exchanged was approximately 1.0–1.5-fold the circulating blood plasma volume (circulating blood plasma volume [ml] was 1/13 bodyweight × [100 – hematocrit (%)]/100). Heparin was usually used as the anticoagulant, and the activated clotting time (ACT) was adjusted to remain between 180 and 250 s. While this was being done, the necessary sedation was given, and the patient was carefully secured to the bed to avoid movement. The standard duration for this procedure was 1–3 days, but if no temperature reduction or improvement in the inflammatory response was observed, the time was extended to a maximum of 5 or 6 days.

Extracorporeal circulation can be reduced to 60–90 mL, and this can be done as long as patient bodyweight is ≥5 kg. Finally, with the consent of the ethics committees of both hospitals and with the informed consent of the patients' families, PE was performed. In addition, those children who were able to understand were fully informed about the procedure.

Statistical analysis

All data are expressed as mean ± SD. Analysis was performed using Excel 2007s with the add-in software Statcel 2 (OMS, Tokyo, Japan). Fisher's exact probability test was used to analyze differences, taking $P < 0.05$ as significant.

Results

Patient characteristics

The mean age at onset was 2.6 ± 1.8 years (range, 2 months–8 years), and mean weight was 12.5 ± 3.5 kg (range, 3.9–22.5 kg). There were more boys than girls (76 boys, 49 girls), and the disease had recurred in five children (first recurrence in four, second recurrence in one). As an initial treatment to accompany IVIG, acetylsalicylic acid or flurbiprofen was also given.

Table 1 CAL versus treatment phase

	Before plasma exchange *n* (%)	Acute period *n* (%)	Late period *n* (%)
CAL(−)	105 (80.4)	84 (67.2)	119 (95.2)
CAL(+)	20 (16.0)	41 (32.8)	6 (4.8)
Dilatation	14	30	0
Aneurysm	6	6	1
Giant aneurysm	0	5	5

CAL, coronary artery lesion.

Efficacy of PE

The initial doses of IVIG were given at an average of 4.3 ± 1.5 days after onset. The mean amount of IVIG given prior to PE was 2.79 ± 1.3 g/kg. PE was started, on average, after 8.1 ± 1.9 days. The average duration of PE treatment was 3.5 ± 1.1 days. There were five patients in whom PE was started without IVIG retreatment because of changes noted in the coronary artery. Patients were initially treated with IVIG on days 4, 5, 7, 8, and 13. All patients experienced symptomatic improvement, laboratory data normalized following PE, and they needed no further treatment.

The coronary arteries before starting PE were within normal limits in 105 patients, but dilatation was seen in 14 and aneurysms in six, making a total of 20 with CAL (16.0%). These lesions numbered 41 (32.8%) in the acute period (enlarged lesions including transient dilatation totaled 30, and there were six aneurysms and five giant aneurysms). Even 1 year after onset, coronary sequelae requiring systemic drug treatment were found in six patients (4.8%; one aneurysm, five giant aneurysms; Table 1).

The relationship between the timing of the first IVIG treatment and CAL is shown in Figure 1(a). In patients with sequelae, these sequelae arose on days 4–6 after onset, and were not the result of a delay in IVIG.

Figure 1(b) shows the relationship between the day on which PE was started and CAL. Of the 105 patients in whom PE was started on or before day 9 after onset, sequelae remained in 2.8%, and were present in 15% of the 20 patients in whom PE commenced from day 10 after onset or later. Although the outcome of treatment tended to be better when PE was begun in the early stage, this difference was not statistically significant ($P = 0.052$).

Figure 1(c) shows the relationship between the duration of PE treatment and CAL. Coronary prognosis was poor only in patients treated with PE for 5 days, but treatment for 4 or 6 days resulted in good coronary outcome.

The differences in the percentages of patients with coronary sequelae, versus presence of CAL before PE, are shown in Figure 2. Although lesions were seen in the acute period in 21 of the 105 patients whose coronary arteries were normal before PE (dilatation in 19, aneurysms in two), all of them returned to within the normal range (i.e. 0% residual sequelae; Fig. 2a). Among the 14 patients in whom dilatation was present before PE, progression to aneurysm occurred in two patients and to a giant aneurysm in one in the acute period, but in the late period,

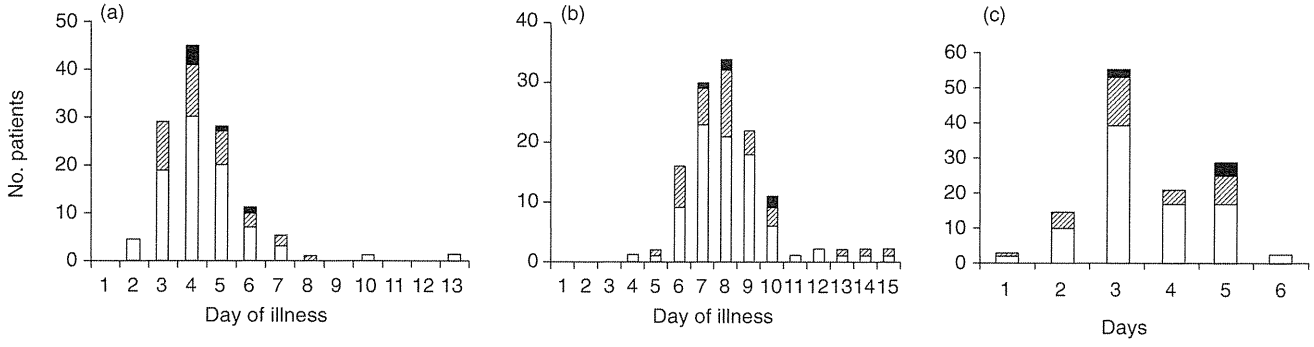

Fig. 1 (a) Timing of initial i.v. immunoglobulin (IVIG); (b) day on which plasma exchange (PE) was started; (c) duration of PE treatment, versus development of coronary artery lesions (CAL). (■) CAL(+) remaining in late period; (▨), CAL(+) only at acute period; (□), CAL(–).

regression of the lesions took place in 11 patients, including one of the aneurysms (residual sequelae, 14.3%; Fig. 2b). Four of the six patients in whom aneurysms had formed before PE in the acute period underwent progression to giant aneurysms, which remained in the late period, but the lesions of the other two, which did not progress beyond aneurysms, regressed (residual sequelae, 66.6%; Fig. 2c).

Table 2 lists details of the six patients in whom sequelae remained. All patients already had CAL before PE. Patient 2 was found to have a right coronary artery occlusion on angiography performed 8 years after onset. In patient 3, complete occlusion of the left anterior descending coronary artery was discovered 4 years after onset. Both of these patients, however, were asymptomatic because of collateral coronary artery enlargement. For the four followed-up patients, at the time of writing, although they are receiving medical treatment and their exercise is restricted, their everyday lives appear relatively normal.

Complications of PE

Two cases of complications (one of hypotensive shock and one of pneumothorax) were encountered. Hypotensive shock arose in a 4-year-old boy. Soon after PE was started in this patient, tachycardia, hypotension, and respiratory impairment were noted, but the patient improved under artificial respiratory management and catecholamine, and underwent PE for a 5 day period without any further problems. The pneumothorax occurred in a 3-month-old boy during catheterization of the internal jugular vein. It was seen on chest radiography but there was no impairment in respiration, and the patient's condition was monitored. He recovered the next day when the problem resolved.

Discussion

We previously reported the effectiveness of PE in patients refractory to IVIG.[7,8] A comparison of the outcomes in the 46 children given PE treatment with those of the 59 who did not receive it indicated that PE significantly reduced the frequency of onset of acute-phase coronary lesions by 17.4% versus 40.7% ($P = 0.0012$). In the present study, we increased the number of patients, and followed the course of longer term coronary lesions (i.e. >1 year). Although there were differences in the IVIG schedules in early stage treatment; additional treatment; and the day after onset on which PE was started, provided that PE could be started before coronary artery expansion began, the outcomes were surprising in that there were no sequelae (0/105). In those patients in whom dilatation had already begun before the start of PE treatment, the proportion of patients in whom sequelae remained was 30% (6/20). This difference was statistically significant ($P = 0.001$). In four of the five patients in whom sequelae in the form of giant aneurysms remained, the process of development of these aneurysms was clearly evident before PE (the

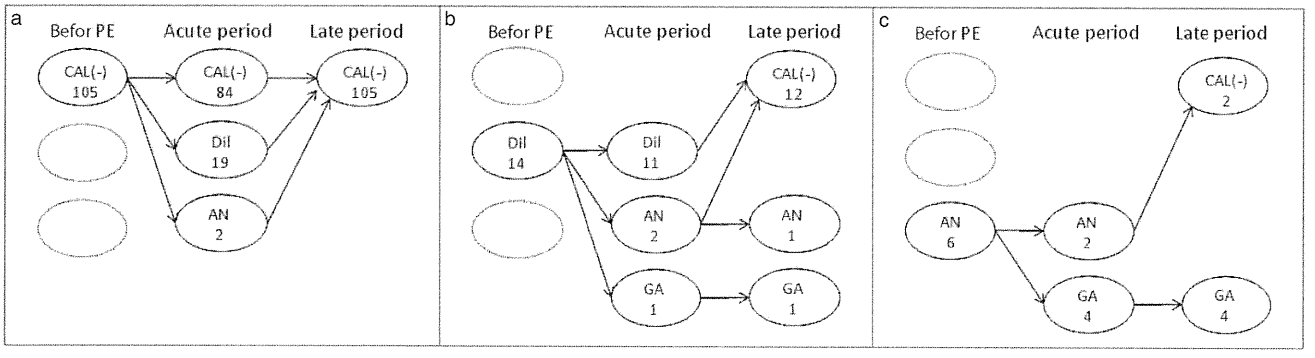

Fig. 2 Outcome versus presence of coronary artery lesions (CAL) before plasma exchange (PE): (a) 105 patients without CAL before PE; (b) 14 patients with dilatation (Dil) before PE; (c) six patients with aneurysm (AN) before PE. GA, giant aneurysm.

Table 2 Patients with coronary artery lesions at late phase

Patient	Gender	Age at onset (years)	Start of IVIG (day)	Total dose of IVIG (g/kg)	Start of PE (day)	Duration for PE (days)	Maximum coronary artery size (mm)			Comments
							Before PE	Acute period	Late period	
1	M	6.0	6	2.4	14	3	5.7	8.0	8.4	
2	M	1.8	4	2.0	7	5	3.3	8.6	11	Occlusion of RCA after 8 years
3	M	0.4	4	3.5	10	3	4.8	9.5	9.7	Occlusion of LAD after 4 years Follow up at other institution
4	F	4.8	5	2.5	8	5	3.3	6.8	7.0	
5	M	3.7	4	3.0	8	5	7.1	9.8	8<	Follow up at other institution
6	M	0.5	4	4.0	10	5	4.0	9.0	9.9	

CAL, coronary artery lesion; IVIG, i.v. immunoglobulin; LAD, left anterior descending artery; PE, plasma exchange; RCA, right coronary artery.

one remaining patient had only an enlarged lesion). It is therefore proposed that even treatments supplementary to PE could not have prevented these sequelae.

Treatments additional to PE were selected for patients unresponsive to IVIG. The usefulness of the steroids used in many institutions, which are easy and cheap to use, is not yet clear. There are many reports related to their benefits,[9,10] but other reports indicate that they are not effective in suppressing coronary lesions.[11–16] In addition, sufficient grounds for excluding the risk of rupture of an arterial aneurysm are not yet available. In particular, steroids are unlikely to be effective when the formation of an aneurysm has already commenced.

In the acute stage of Kawasaki disease, the levels of different inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-2, and IL-6, are high.[17,18] In particular, TNF-α has a harmful effect on blood vessels, and contributes greatly to the formation of CAL in Kawasaki disease.[19,20] PE directly removes the inflammatory cytokines from the blood circulation, but there is speculation about the mechanism involved in the resolution of the inflammation.

More recently, the anti-TNF-α antibody infliximab has also been used to treat Kawasaki disease,[21–23] but its validity remains unclear.

Compared to infliximab or steroids, PE has some advantages. PE can be performed despite concomitant infection. Infliximab is contraindicated for patients with cardiac failure, but slow PE is a feasible option for such patients. The safe use of infliximab for infants is also unclear, but PE has no age limit.

Plasma exchange is disadvantageous in comparison with other treatments in terms of medical costs and some side-effects. Advanced medical equipment such as a dialyzer is needed. Patients should be treated in the intensive care unit during PE in most institutions. Side-effects associated with PE, such as hypotension, electrolyte abnormality, bleeding, allergy, and infection, have been reported.[24] In the present study, serious complications occurred in two patients (1.6%) but there were no deaths, and continued treatment was possible in both cases. PE can be performed safely even in children.

We therefore conclude that PE is one of the most effective therapies for patients refractory to IVIG. When other additional therapies are not effective, PE should be considered. In this context, it is important that the efficacy of other additional therapies be considered and that PE be started as soon as possible in order to meet the goal of reducing residual sequelae.

In conclusion, the outcomes of PE for Kawasaki disease refractory to IVIG are favorable, although not statistically significant, and the present study was not a controlled clinical trial. If this therapy can be initiated before any CAL arise, good effectiveness can be expected. PE should be considered in refractory Kawasaki disease patients for whom other options (steroids and infliximab) have failed.

Limitations

The present study was not a controlled clinical trial, and we did not compare additional therapies, for example, steroids and infliximab. There were some cases that did not fit our standard

protocol for deciding when PE was started, because the patients' initial treatment had taken place at other hospitals. The initial IVIG doses and timings differed from those in other hospitals.

Acknowledgments

We express our deep gratitude to the following hospitals and departmental staff for their generous cooperation in undertaking treatment and survey procedures: Kanagawa Prefectural Ashigarakami Hospital, Odawara Municipal Hospital, Fujisawa City Hospital, Saiseikai Yokohamashi Nanbu Hospital, Yokohama Minami Kyousai Hospital, Yokohama City Minato Red Cross Hospital, National Hospital Organization Yokohama Medical Center, Yokohama Sakae Kyosai Hospital, Yokohama Rosai Hospital, and Miura City Hospital. We would also like to thank Mr C. W. P. Reynolds for assistance with the manuscript.

References

1 Newburger JW, Takahashi M, Gerber MA *et al.* Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Diagnosis, treatment, and long-term management of Kawasaki disease: A statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 2004; **114**: 1708–33.
2 Burns JC, Capparelli EV, Brown JA, Newburger JW, Glode MP. Intravenous gamma-globulin treatment and retreatment in Kawasaki disease. US/Canadian Kawasaki Syndrome Study Group. *Pediatr. Infect. Dis. J.* 1998; **17**: 1144–8.
3 Villain E, Kachaner J, Sidi D, Blaysat G, Piéchaud JF, Pedroni E. Trial of prevention of coronary aneurysm in Kawasaki's disease using plasma exchange or infusion of immunoglobulins. *Arch. Fr. Pediatr.* 1987; **44**: 79–83.
4 Takagi N, Kihara M, Yamaguchi S *et al.* Plasma exchange in Kawasaki disease. *Lancet* 1995; **346**: 1307.
5 Research Committee on Kawasaki Disease, Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease. Japanese Ministry of Health and Welfare, Tokyo, Japan, 1984.
6 Mori M, Imagawa T, Yasui K, Kanaya A, Yokota S. Predictors of coronary artery lesions after intravenous gamma-globulin treatment in Kawasaki disease. *J. Pediatr.* 2000; **137**: 177–80.
7 Mori M, Imagawa T, Katakura S *et al.* Efficacy of plasma exchange therapy for Kawasaki disease intractable to intravenous gamma-globulin. *Mod. Rheumatol.* 2004; **14**: 43–7.
8 Imagawa T, Mori M, Miyamae T *et al.* Plasma exchange for refractory Kawasaki disease. *Eur. J. Pediatr.* 2004; **163**: 263–4.
9 Wright DA, Newburger JW, Baker A, Sundel RP. Treatment of immune globulin-resistant Kawasaki disease with pulsed doses of corticosteroids. *J. Pediatr.* 1996; **128**: 146–9.
10 Miura M, Ohki H, Yoshiba S *et al.* Adverse effects of methylprednisolone pulse therapy in refractory Kawasaki disease. *Arch. Dis. Child.* 2005; **90**: 1096–7.
11 Shulman ST. Is there a role for corticosteroids in Kawasaki disease? *J. Pediatr.* 2003; **142**: 601–3.
12 Lang BA, Yeung RS, Oen KG *et al.* Corticosteroid treatment of refractory Kawasaki disease. *J. Rheumatol.* 2006; **33**: 803–9.
13 Jibiki T, Terai M, Kurosaki T *et al.* Efficacy of intravenous immune globulin therapy combined with dexamethasone for the initial treatment of acute Kawasaki disease. *Eur. J. Pediatr.* 2004; **163**: 229–33.
14 Furukawa T, Kishiro M, Akimoto K, Nagata S, Shimizu T, Yamashiro Y. Effects of steroid pulse therapy on immunoglobulin-resistant Kawasaki disease. *Arch. Dis. Child.* 2008; **93**: 142–6.
15 Ogino K. Frequency of coronary artery lesions in cases treated with steroids in the acute period. *Pediatr. Cardiol. Cardiac. Surg.* 2008; **24**: 304.
16 Suzuki H. Analysis of coronary artery lesions in cases treated with steroids in the acute period. *Pediatr. Cardiol. Cardiac. Surg.* 2008; **24**: 304.
17 Matsubara T, Furukawa S, Yabuta K. Serum levels of tumor necrosis factor, interleukin 2 receptor, and interferon-gamma in Kawasaki disease involved coronary-artery lesions. *Clin. Immunol. Immunopathol.* 1990; **56**: 29–36.
18 Leung DY, Cotran RS, Kurt-Jones E, Burns JC, Newburger JW, Pober JS. Endothelial cell activation and high interleukin-1 secretion in the pathogenesis of acute Kawasaki disease. *Lancet* 1989; **2**: 1298–302.
19 Maury CP, Salo E, Pelkonen P. Elevated circulating tumor necrosis factor-alpha in patients with Kawasaki disease. *J. Lab. Clin. Med.* 1989; **113**: 651–4.
20 Furukawa S, Matsubara T, Umezawa Y, Okumura K, Yabuta K. Serum levels of p60 soluble tumor necrosis factor receptor during acute Kawasaki disease. *J. Pediatr.* 1994; **124**: 721–5.
21 Weiss JE, Eberhard BA, Chowdhury D, Gottlieb BS. Infliximab as a novel therapy for refractory Kawasaki disease. *J. Rheumatol.* 2004; **31**: 808–10.
22 Burns JC, Mason WH, Hauger SB *et al.* Infliximab treatment for refractory Kawasaki syndrome. *J. Pediatr.* 2005; **146**: 662–7.
23 Burns JC, Best BM, Mejias A *et al.* Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease. *J. Pediatr.* 2008; **153**: 833–8.
24 Shemin D, Briggs D, Greenan M. Complications of therapeutic plasma exchange: A prospective study of 1,727 procedures. *J. Clin. Apher.* 2007; **22**: 270–76.

Pediatr Cardiol
DOI 10.1007/s00246-011-0065-y

CASE REPORT

Intrapericardial and Retrocardial Implantation of Implantable Cardioverter-Defibrillator Lead in a Child with Type 3 Long QT Syndrome

Yasuhiro Ichikawa · Mari Iwamoto · Sadamitsu Yanagi · Munetaka Masuda

Received: 13 May 2011 / Accepted: 9 July 2011

Abstract A 6-year-old girl with type 3 long QT syndrome was safely and successfully implanted with an implantable cardioverter-defibrillator (ICD) system. Prior to implantation, she had experienced uncontrollable life-threatening arrhythmia in spite of high-dose administration of mexiletine. An ICD coil lead for transvenous use was placed in the intrapericardial and retrocardial space and was connected to a generator placed in front of the posterior sheath of the right abdominal rectal muscle. Administration of a beta-blocker in addition to atrial pacing almost completely eliminated the patient's life-threatening arrhythmia attacks. Intrapericardial and retrocardial implantation of ICD coil leads might be useful for children.

Keywords Implantable cardioverter-defibrillator · LQT3 · Beta-blocker · Mexiletine · Intrapericardial and retrocardial approach Child

Y. Ichikawa · M. Iwamoto (✉)
Department of Pediatric Cardiology, Yokohama City University, 3-9 Fukuura, Kanazawa-ku, Yokohama City, Kanagawa 236-0004, Japan
e-mail: miwamoto@yokohama-cu.ac.jp

S. Yanagi
Department of Pediatric Cardiology, Kanagawa Children's Medical Center, 4-138-2 Mutsukawa, Minami-ku, Yokohama City, Kanagawa 232-8555, Japan

M. Masuda
Department of Cardiac Surgery, Yokohama City University, 3-9 Fukuura, Kanazawa-ku, Yokohama City, Kanagawa 236-0004, Japan

Published online: 05 August 2011

Introduction

The frequency with which implantable cardioverter-defibrillators (ICDs) are used to prevent cardiac death due to life-threatening arrhythmia has increased over the last few years, even in pediatric patients. Patients with congenital long QT syndrome (LQTS) who have episodes of torsades de pointes (TdP) and ventricular fibrillation (Vf) despite treatment with antiarrhythmic drugs are among the major candidates for ICD implantation. Yet the use of the transvenous ICD lead system is limited in younger children because of their small body size, potential for somatic growth, and high risk of venous obstruction. Several ICD lead implantation techniques have been adapted for pediatric use, including the transvenous approach [5], the intrapericardial approach [6], and the subcutaneous approach [1, 3, 7]. The epicardial ICD patch placement [11] was also reported. However, none of them have satisfactory long-term results. Here, we present a case in which a child suffering from type 3 long QT syndrome (LQT3) with episodes of Vf in spite of high-dose administration of mexiletine was successfully implanted with an ICD system.

Case Report

A 6-year-old Japanese girl with LQT3 was referred to our institution for ICD implantation. When she was in utero, ventricular tachycardia (VT) was documented by echocardiography. After birth, an electrocardiogram (ECG) (Fig. 1) showed a prolonged QT interval of 500 ms associated with polymorphic premature ventricular contraction (PVC), VT, and TdP. A novel SCN5A missense mutation (R1623Q) was discovered in the proband, although she had

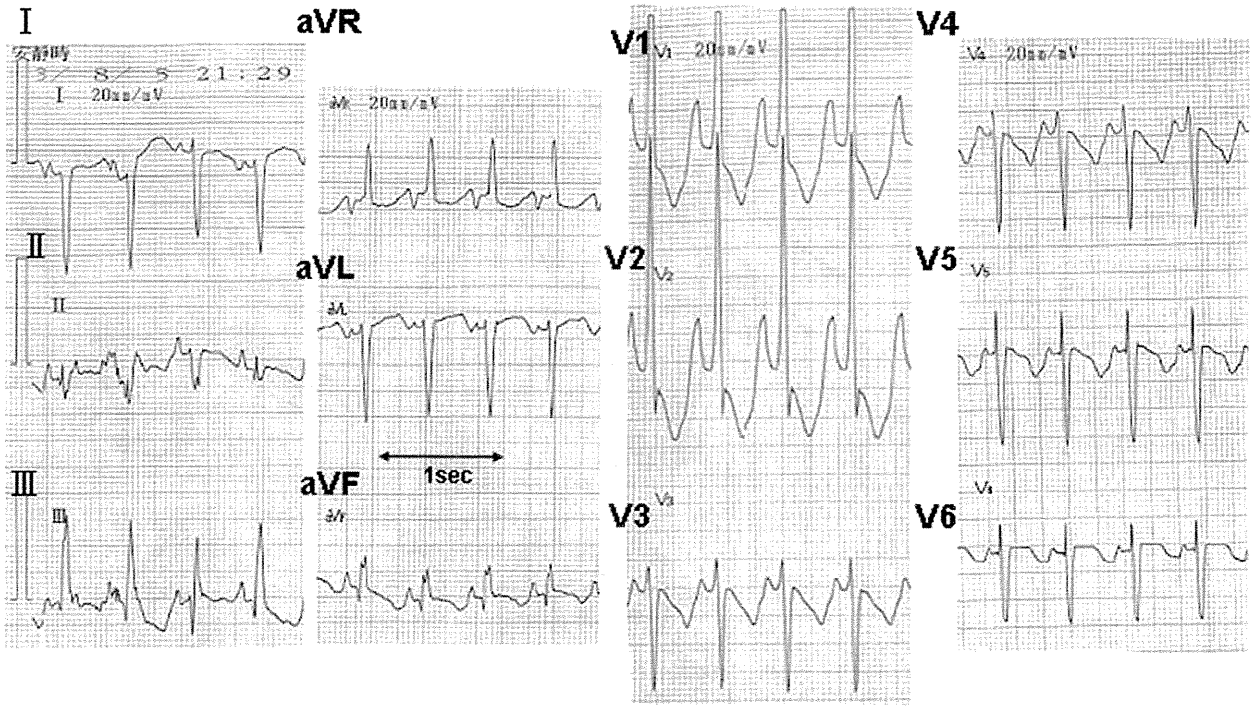

Fig. 1 ECG on the day of birth showed QT interval prolongation (HR = 125 bpm, QT = 0.38 s, QTc = 0.50 s [Fridericia's formula)]. No antiarrhythmic drug therapy had been administered prior to this recording

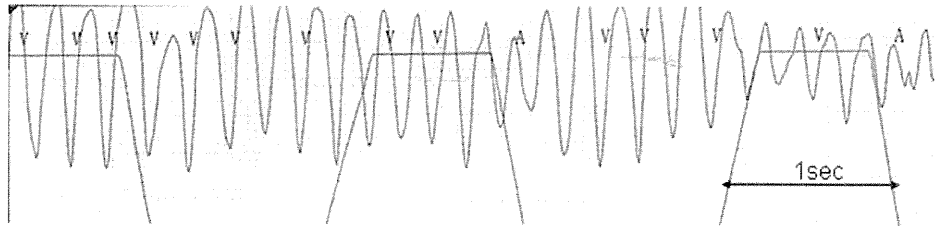

Fig. 2 Monitoring ECG showed Vf with a duration of about 1 min, associated with an episode of syncope

no family history of arrhythmia syndromes. Her parents had normal ECG results and did not undergo genetic testing. Intravenous injection followed by continuous infusion of mexiletine successfully abolished TdP. She was discharged from the hospital on oral mexiletine intake. As she had episodes of syncope and convulsion once a month after discharge, she was diagnosed with epilepsy, based on electroencephalogram recordings showing spikes combined with of the absence of VT in her ECG recordings. When she was 5 years old, a 24-h Holter ECG recording showed episodes of TdP and Vf (Fig. 2). High-dose mexiletine therapy (20 mg/kg/day) was administrated, but frequent episodes of self-limited Vf were subsequently documented in ECG. An ICD implantation was indicated and she was referred to our hospital.

On admission, the patient was 118 cm in height and had a body weight of 21.6 kg; physical examination revealed no abnormal findings. ECG showed a bifid T-wave in leads V3, V4, V5, and V6. QT interval was normal according to Fridericia's formula (QTc = 0.42 s) due to the administration of high doses of mexiletine. An exercise ECG showed shortening of the QT interval (QT = 0.26 s, QTc = 0.35 s) associated with RR interval shortening. A 24-h Holter monitoring ECG revealed three episodes of ventricular tachycardia [maximum heart rate (HR) = 179 bpm] and bradycardia (minimum HR = 58 bpm) during sleep.

An ICD system was implanted under general anesthesia. With the patient in a supine position, a partial median sternotomy was made. An ICD coil lead (SPRINT QUATTRO SECURE S®; Medtronic Inc., Minneapolis, MN, USA) was placed according to the following method (Fig. 3). After the pericardial space was opened, dissection was performed between the right pulmonary artery and the right upper pulmonary vein to allow access to the retrocardial space. The tip of the ICD coil lead was fixed by

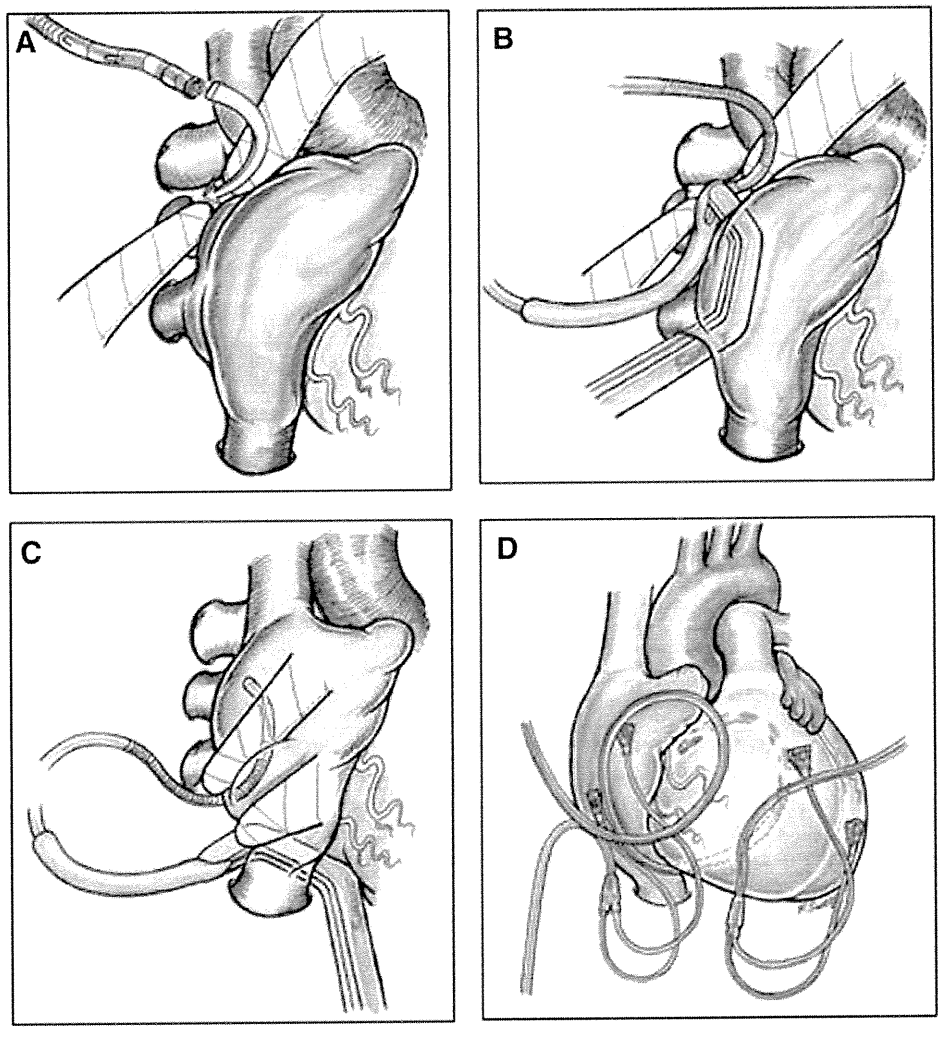

Fig. 3 Our intrapericardial and retrocardial ICD implantation technique. **a** After dissection between the right pulmonary artery and the right upper pulmonary vein, the tip of the ICD coil lead was fixed by being screwed to the pericardium behind the right upper pulmonary vein. **b, c** The other tip of the ICD coil lead was passed behind the heart, guided by a Nelaton catheter. **d** Atrial epicardial leads were fixed at the right atrium. The ventricular epicardial leads were placed at both ventricles to allow biventricular pacing

being screwed to the pericardium behind the right upper pulmonary vein. The ICD coil lead was passed behind the heart, and the middle part of the lead was fixed to the front part of the diaphragm to prevent dislocation of the lead. This fixation was kept quite loose, however, allowing the lead's position to adapt to the patient's somatic growth. An ICD generator (VITALITY®; Guidant Inc., Indianapolis, IN, USA) was implanted in a pocket created in front of the posterior sheath of the right abdominal rectal muscle. Atrial and ventricular epicardial leads (Episure®, Medtronic Inc.) were placed at the right atrium and at both ventricles and then connected to the generator (Fig. 4). The defibrillation threshold (DFT) was 5 J in the operation room and was kept at this value for 10 days after ICD implantation. To prevent bradycardia-induced TdP, the dual chamber pacing, dual chamber sensing and inhibited response (DDI) mode was chosen, with a basic rate of 75 bpm and an AV delay of 200 ms. Ventricular tachyarrhythmia detection was set to occur at 220 bpm for VT and 250 bpm for Vf.

Ventricular tachycardia was further controlled by pacing, and total ventricular arrhythmia episodes decreased from 139 to 0 episodes per day in 24-h Holter recordings. There were no perioperative complications, and the patient was discharged from our institution 21 days after ICD implantation.

After discharge, the patient experienced episodes of arrhythmia, which were corrected by appropriate discharge of the ICD, once a month. Intracardiac ECG recordings made by the generator over the course of 1 month revealed three to five episodes of short-run polymorphic VT and one episode of VT that lasted longer than 20 s. The addition of a beta-blocker (initially 1 mg/kg/day propranolol, then switched to 5 mg/kg/day acebutolol to prevent bronchial asthma attacks) fully suppressed ventricular arrhythmias. In the end, combination therapy consisting of atrial overpacing and oral intake of mexiletine and acebutolol has effectively suppressed the incidence of TdP. ICD discharge has accordingly been abolished.

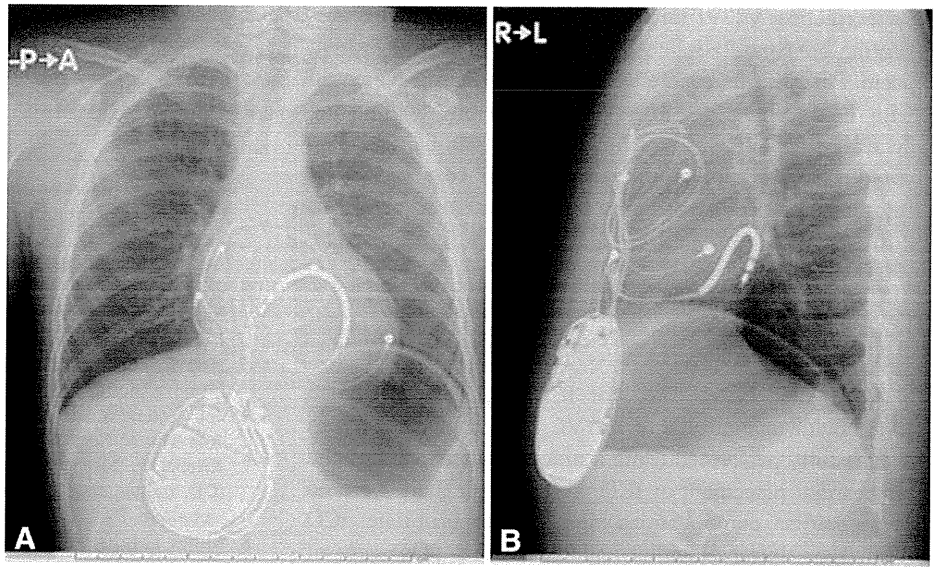

Fig. 4 **a** Anteroposterior and **b** lateral chest X-ray film after the ICD implantation procedure. The ICD coil lead is located behind the heart

Discussion

Implantable cardioverter-defibrillator implantation can save patients who have life-threatening arrhythmia from cardiac death. Because there have been so few cases of ICD implantation in children, however, ICD therapy has not been standardized and remains a medically challenging mode of treatment. Children's somatic growth potential and the fact that they will require device therapy throughout their lives may increase their risk of device-related complications.

Our case fulfilled the indication criteria for ICD implantation, because the patient had the SCN5A gene mutation, had experienced episodes of VT/Vf, and had been unsuccessfully treated with antiarrhythmic therapy [4].

Techniques for ICD lead implantation have previously been reported: the transvenous approach [5], the intrapericardial approach [6], and the subcutaneous approach [1, 3, 7]. In the adult patient, the ICD coil lead is usually implanted through the transvenous approach, as it is less invasive and requires a lower DFT. In children, however, the transvenous approach is frequently associated with device-related complications such as venous occlusion, tricuspid regurgitation, and lead fracture [5, 6, 10].

Epicardial ICD patch placement is associated with a risk of constrictive pericarditis, which can result in cardiac dysfunction due to loss of ventricular compliance [6, 11].

In the subcutaneous coil lead approach [3, 7], the lead tip is placed through a subcutaneous tunnel, sometimes in the chest wall. This method is less likely to impair cardiac function, but it is associated with some complications such as lead fracture, dislocation of coil lead, and high DFT [7].

Placing the coil lead by the intrapericardial approach [6] offers the advantage of reducing the DFT because the coil lead is located close to the heart. The risks of lead fracture and dislocation are considered to be lower with this method than with the others. Although the intrapericardial approach may be associated with a risk of adhesive pericarditis, Hsia et al. [6] have reported the successful placement of ICD coils in seven children with no inappropriate discharges, no perioperative complications, and no increases in DFT. In adapting their technique, we did not use fluoroscopic guidance through a small pericardial window, as they did; rather, we performed a partial sternotomy with a small incision, which allowed us to view the placement procedure directly, in order to avoid damaging the organs behind the heart such as the esophagus and to ensure that we placed the ventricular lead on both ventricles to avoid univentricular pacing.

In LQTS patients, preventing Vf, TdP, and prolongation of the QT interval during the placement procedure is very important to reduce the risk of perioperative complications [2]. For this reason, we selected anesthetic medications that do not prolong the QT interval, such as fentanyl, rocuronium, and propofol.

Proper placement of the ICD is essential not only to ensure that the ICD will function properly and thereby save the patient's life but also to avoid mental strain due to inappropriate discharge occurring while the patient is conscious. In our case, because short self-limited episodes of Vf (5–10 s) had been frequently observed in ECG monitoring and the patient was conscious for up to 15 s after the onset of Vf, the VT detection time was set at 25 s.

In patients with bradycardia-induced VT/Vf such as LQT3 and LQT2, ICD implantation will be useful not only

for correcting VT/Vf through discharges but also for preventing bradycardia-induced arrhythmia through overdrive pacing. In a similar case, PVC and VT have been decreased with DDI pacing [9]. High-dose mexiletine and pacing decreased VT/Vf episodes but could not abolish syncope completely. In another malignant LQT3 case (R1623Q) [8], the combined use of a beta-blocker and mexiletine was effective at controlling TdP.

Conclusion

The patient was indicated for ICD implantation due to LQT3 with uncontrollable VT/Vf. ICD implantation was successfully performed using a unique intrapericardial and retrocardial placement of ICD coil system. There were no perioperative complications and no inappropriate ICD discharges. Intrapericardial and retrocardial placement of the ICD coil lead is a useful method for young children.

References

1. Berul CI, Triedman J, Forbess J et al (2001) Minimally invasive cardioverter defibrillator implantation for children: an animal model and pediatric case report. PACE 24:1789–1794
2. Booker PD, Whyte SD, Ladusans EJ et al (2003) Long QT syndrome and anaesthesia. Br J Anaesth 90:349–366
3. Drago F, Fazio G, Silvetti MS et al (2007) A successfully novel ICD implantation and medical treatment in a child with LQT syndrome and self-limiting ventricular fibrillation. Int J Cardiol 118:e108–e112
4. Epstein AE, DiMarco JP, Ellenbogen KA et al (2008) ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). Circulation 117:2820–2840
5. Gasparini M, Regoni F, Galimberti P et al (2005) Endocardial implantation of a cardioverter defibrillator in early childhood. J Cardiovasc Electrophysiol 16:1381–1383
6. Hsia TY, Bradley SM, LaPage MJ et al (2009) Novel minimally invasive, intrapericardial implantable cardioverter defibrillator coil system: a useful approach to arrhythmia therapy in children. Ann Thorac Surg 87:1234–1239
7. Kriebel T, Ruschewski W, Gonzalez y Gonzalez M et al (2006) ICD implantation in infants and small children: the extracardiac technique. PACE 29:1319–1325
8. Miller TM, Estrella E, Myerburg RJ et al (2004) Recurrent third-trimester fetal loss and maternal mosaicism for long-QT syndrome. Circulation 109:3029–3034
9. Mönnig G, Köbe J, Löher A et al (2005) Implantable cardioverter-defibrillator therapy in patients with congenital long-QT syndrome: A long-term follow-up. Heart Rhythm 2:497–504
10. Sherrid MV, Daubert JP (2008) Risks and challenges of implantable cardioverter-defibrillators in young adults. Prog Cardiovasc Dis 51:237–263
11. Stephenson EA, Betra AS, Knilans TK et al (2006) A multicenter experience with novel implantable cardioverter defibrillator configurations in the pediatric and congenital heart disease population. J Cardiovasc Electrophysiol 17:41–46