Table 3 Parameters evaluated using grayscale and virtual histology intravascular ultrasound

	Elderly ($n = 72$)			Non-elderly ($n = 47$)		
	Baseline	Follow-up	p value	Baseline	Follow-up	p value
EEM volume index (mm^3/mm)	17.27 ± 5.49*	17.12 ± 5.55**	0.19	14.95 ± 4.71	14.52 ± 4.54	0.007
% change		−0.9 ± 5.1			−2.4 ± 6.3	
Plaque volume index (mm^3/mm)	9.49 ± 3.63*	9.43 ± 3.52**	0.57	8.11 ± 2.56	7.80 ± 2.40	0.007
% change		0.0 ± 9.1#			−3.1 ± 8.9	
Lumen volume index (mm^3/mm)	7.78 ± 2.53*	7.69 ± 2.63*	0.43	6.83 ± 2.63	6.72 ± 2.61	0.3
% change		−1.0 ± 12.5			−1.0 ± 10.5	
Percent atheroma volume (%)	54.5 ± 7.1	54.8 ± 7.0	0.58	54.7 ± 7.0	54.2 ± 7.0	0.35
Nominal change (%)		0.3 ± 4.5			−0.5 ± 3.6	
Fibrous volume index (mm^3/mm)	3.49 ± 2.01	3.48 ± 1.83**	0.94	3.00 ± 1.48	2.61 ± 1.17	0.0004
Change (mm^3/mm)		−0.01 ± 0.84*			−0.39 ± 0.70	
FF volume index (mm^3/mm)	1.26 ± 1.10**	0.96 ± 0.77*	0.0006	0.79 ± 0.59	0.62 ± 0.63	0.1
Change (mm^3/mm)		−0.30 ± 0.71			−0.17 ± 0.70	
NC volume index (mm^3/mm)	0.75 ± 0.54	0.87 ± 0.56	0.06	0.73 ± 0.59	0.88 ± 0.63	0.1
Change (mm^3/mm)		0.11 ± 0.50			0.15 ± 0.63	
DC volume index (mm^3/mm)	0.47 ± 0.45	0.59 ± 0.54	0.002	0.38 ± 0.36	0.49 ± 0.44	0.01
Change (mm^3/mm)		0.12 ± 0.32			0.11 ± 0.29	
Average length (mm)	25.7 ± 14.9			22.8 ± 15.0		

Data are expressed as mean ± SD

EEM external elastic membrane, *FF* fibro-fatty, *NC* necrotic-core, *DC* dense-calcium

* $p < 0.05$, ** $p < 0.01$ compared to non-elderly. # $p = 0.07$ compared to non-elderly

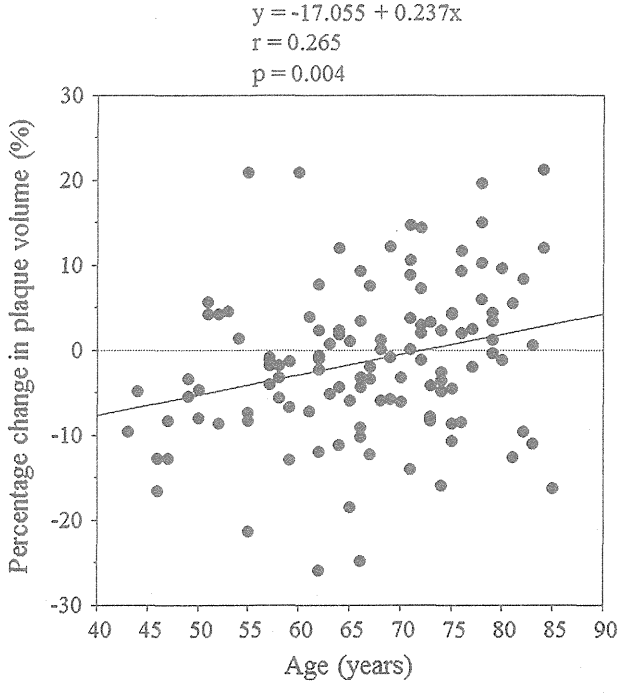

Fig. 1 Correlation between age and percentage change in plaque volume during statin therapy. Age and percentage change in plaque volume during statin therapy showed a significant positive correlation

Table 4 Predictors of percentage change in plaque volume

	Univariate		Multivariate	
	r	p value	β	p value
Age	0.265	0.004	0.223	0.02
Gender	−0.127	0.17	0.012	0.9
Coronary artery disease status	−0.066	0.48		
Hypertension	0.163	0.08	0.063	0.53
Diabetes mellitus	0.137	0.14	0.06	0.54
Smoking	0.088	0.34		
eGFR	−0.035	0.71		
Type of statin	−0.074	0.43		
Percentage change in LDL-C	−0.001	0.99		
Percentage change in sd-LDL	−0.097	0.34		
Percentage change in HDL-C	−0.114	0.22		
Percentage change in hs-CRP	0.056	0.56		
Change in EPA + DHA/AA	−0.24	0.02	−0.209	0.04

Male gender, unstable angina pectoris, hypertension, diabetes mellitus, smoking, and pitavastatin use were assigned a value of 1. Female gender, stable angina pectoris, normal blood pressure, absence of diabetes and smoking, and pravastatin use were assigned a value of 0

eGFR estimated glomerular filtration rate, *LDL-C* low-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid, *AA* arachidonic acid

the percentage change in plaque volume was different between the elderly and non-elderly patients. Furthermore, age showed a significant positive correlation with the percentage change in plaque volume and a significant predictor associated with the percentage change in plaque volume during statin therapy.

Glagov et al. [12] described vascular remodeling as a compensatory enlargement of the coronary artery in response to an increase in plaque area. In histological studies, expansion in vessel size is associated with an increase in inflammatory cells and proteolytic enzymes [13, 14]. In clinical IVUS studies, expansive remodeling is associated with plaque instability and unstable clinical presentation [15–17]. Consistent with previous findings from human autopsies [2] and IVUS [3–5, 18], our results demonstrated that coronary atherosclerosis was more advanced with expanding remodeling and greater atheroma volume in the elderly patients. Furthermore, a significant negative vessel remodeling and regression in plaque volume during statin therapy were observed only in the non-elderly patients. Thus, atherosclerosis accelerated with age [1], even in patients who received statin therapy.

According to VH-IVUS, the fibro-fatty plaque component is associated with development of acute coronary syndrome [19]. As reported in the main TRUTH trial [8], a decrease in the fibro-fatty plaque component and an increase in the calcified component were observed in both the elderly and non-elderly patients. Consistent with previous studies [20, 21], statins induced significant changes in the composition of coronary atherosclerosis without a significant regression in coronary artery plaques in the elderly patients, which illustrated the potential effects of statin against coronary events even in these high risk patients with elderly. Statin therapy reduces matrix metalloproteinase activity, apoptosis, and macrophages, and increases collagen content [22]. These changes could explain the qualitative changes observed in coronary artery plaque composition without a regression in plaque volume. However, a large amount of atheroma volume, particularly the fibro-fatty plaque component, before and during statin therapy may affect the development of coronary events in the elderly patients. As several studies have reported that statins have no effect on necrotic-core accumulation [8, 23, 24], statin therapy could not halt the progression of the necrotic-core component in this study.

Current lipid-lowering guidelines focus on LDL-C reduction as a principal target for primary and secondary prevention of cardiovascular disease [25]. Indeed, clinical trials using statins have demonstrated reductions in cardiovascular events and atheroma progression [6–8, 26]. However, not only serum LDL-C but also serum HDL-C, the LDL-C/HDL-C ratio, and other parameters are useful markers of atheroma regression and/or inhibition of progression in coronary artery plaques [27–29]. Recently, we reported that >40 % of patients receiving statin therapy continued to demonstrate atheroma progression [30]. Thus, not all patients show reductions in cardiovascular events and regression in coronary atherosclerosis under statin therapy. Bayturan et al. [31] reported that residual risk factors associated with atheroma progression in patients who achieve very low LDL-C levels (<70 mg/dl) included baseline percent atheroma volume, presence of diabetes mellitus, increase in systolic blood pressure, less increase in HDL-C, and a smaller decrease in apolipoprotein B levels. This suggests the need for intensive control of global atherosclerotic risk factors to produce regression in coronary atherosclerosis. However, although serum LDL-C, apolipoprotein B, and sd-LDL levels were significantly lower in the elderly patients, a significant regression in plaque volume was observed only in the non-elderly patients. Considering of change in the EPA + DHA/AA ratio was a significant predictor of the percentage change in plaque volume, the residual risk for cardiovascular events during statin therapy can be explained in part by n-3 to n-6 polyunsaturated fatty acids ratios [32]. More recently, Puri et al. [33] reported that greater baseline atheroma volume was associated with less disease progression while older age was a significant predictor of atheroma progression with potent statin therapy. Although coronary atherosclerosis was more advanced in the elderly patients, statin-induced regression in plaque volume and negative vessel remodeling were attenuated. This suggests that atheroma regression in older individuals in general may be more difficult to achieve.

A meta-analysis demonstrated that effects of statin on major vascular events were similar among patients with age <65, >65 to <75, >75 years [34]. However, a large-scale, prospective, uncontrolled study performed in Japan reported that incidence of cardiovascular events during statin therapy was highest in patients aged >65 years old in the secondary prevention cohort [35]. Therefore, statin therapy may have less impact on the secondary prevention in Japanese patients with elderly.

Study limitations

The present study had several limitations. First, it is a post hoc subanalysis of the TRUTH trial. Second, although we excluded patients with angiographically apparent thrombi, an intramural thrombus might have influenced the study results. Third, IVUS examinations were performed only in the culprit vessel. Mechanical interventions might have affected the atheroma measurements because target segment of interest was located in the proximal site of culprit lesion in some patients and maximum necrotic-core area

has been often located proximal of the most severe stenosis site [36]. Finally, the small number of patients meant that the study's statistical power was insufficient to evaluate differences between the elderly and non-elderly patients. Therefore, a prospective multicenter study involving more patients is required to confirm our conclusions.

Conclusions

Coronary atherosclerosis was more advanced and vascular responses to statin therapy were attenuated in the elderly patients compared to the non-elderly patients.

Conflicts of interest None.

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スマートフォンを用いた新しい心電図伝送システムとホルター心電図法との比較

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The new ECG telemedicine system using a smart phone; Comparison of Holter ECG

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Abstract: We have developed a new wireless ECG monitoring system (ABS-1) which transmits data via a Bluetooth-equipped smartphone. The quality of ABS-1 ECG was compared against the Holter ECG's in healthy volunteers. At the lowest heart rate of each individual, ABS-1 and Holter devices recorded identical waveforms of ECG. The results suggest that this new Bluetooth wireless ECG monitoring system can become a future compact and inexpensive ECG monitoring tool for health care management at home.

Keywords: ECG, Bluetooth, smartphone

要旨

スマートフォンに標準的に装備されている Bluetooth を使った心電計（ABS-1）を開発した。この ABS-1 を使ったシステムから得られる心電図の品質を評価するために、ホルター心電計と ABS-1 を同時に装着して、その波形の比較を行った。本研究の結果、最小心拍数では両者の波形に違いは認められなかった。あたらしい心電図伝送システムは、小型で安価なシステムとして在宅医療や健康管理に活用されることが期待される。

1. はじめに

スマートフォンに標準的に装備される Bluetooth を使った通信機能をもつ小型心電計（ABS-1）を開発した。本システムの臨床的有用性を検討する基礎データとしてホルター心電図検査の波形と心拍数トレンドグラフの相違の検討を行った。また従来から普及しているホルター心電図法やイベントレコーダーと比較した特性について若干の文献的考察を行った。

2. 対象

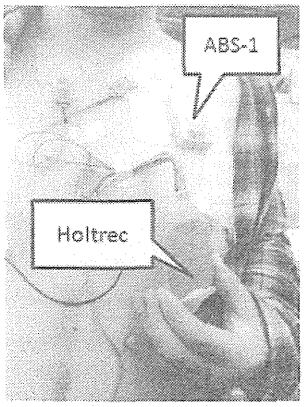
健常ボランティア 6 名（男性 3 名、女性 3 名、平均 52 ± 10 歳）

3. 方法

ホルター心電計（テルモ社製 Holtrec）と新しく開発した心電計（ABS-1）のそれぞれの特性について【表 1】に示した。ホルター心電計と ABS-1 を同時に同一被験者に装着し、約 2 時間の心電図記録を行った。ホルター心電計は 2 誘導（NASA と CM5）、ABS-1 は 1 誘導（日本光電社製ディスポ電極 T-50）を用いた【図 1】。ホルター心電計の心電図データは本体内のフラッシュメモリーに記録され、検査終了後に専用機器（有線クレドール）に

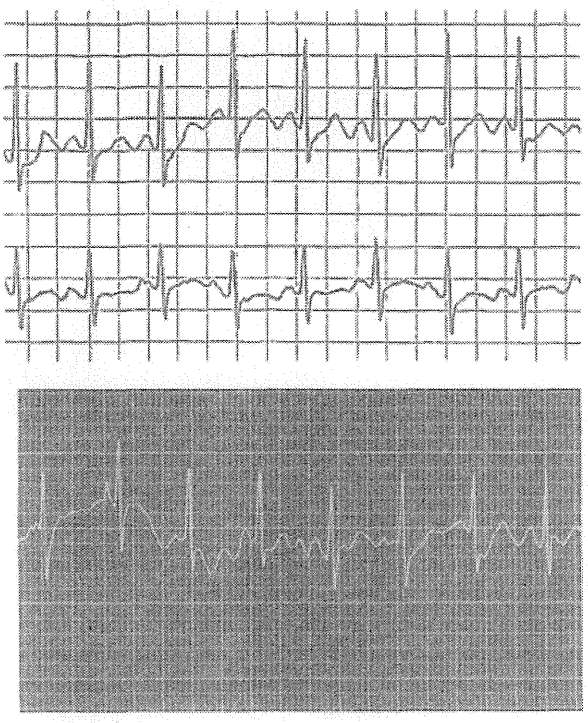
【表 1】ホルター心電計（Holtrec）と ABS-1 の性能比較

	Holtrec	ABS-1
誘導数	2 チャンネル	1 チャンネル
入力信号電圧範囲（mV）	DC ± 150, AC ± 5	DC ± 6, AC ± 6
周波数特性（Hz）	0.05 ～ 40	0 ～ 60
測定精度	10bit, 128Hz サンプリング	12bit, 200Hz サンプリング
記録媒体	32MB フラッシュメモリ	2GB フラッシュメモリ
通信方式	有線	無線（bluetooth）
記録時間	最長 25 時間	250 時間
満充電での連続稼働時間	不明（25 時間保証）	9 時間
電源	ボタン型リチウム電池（CR2032）1 個, DC3V	充電式リチウム電池　DC3.7V
サイズ，幅×高さ×厚さ mm	50 × 65 × 10	40 × 60 × 14
質量（電池含む）	30g	35g
EMC 規格適合	IEC60601-1-2:1993 年	なし



【図 1】ホルター心電計(Holtrec)とABS1の同時装着

よりコンピュータに取り込まれる。一方、ABS-1の波形は、心電計からBluetoothにより携帯電話（NTTドコモXperia acro SO-02C）に送信され、そこから無線データ通信（3G回線）を通じて、サーバーに記録される。それぞれのデータ参照方法について、ホルター心電計データは、専用解析ソフト（オフライン）にて、ABS-1のデータはタブレット端末からインターネット回線（オンライン）を通じ専用ビューワーで行った。比較するデータについて、ホルター心電図解析ソフトを使い、心拍数のトレンドグラフ、最大心拍数、最小心拍数のタイミングを抽出し、同時刻のホルター心電計とABS-1のデータを表示した【図2】。臨床経験を有する循環器専門医により、上記のタイミングのホルター心電計のデータとABS-1のそれを比較し四段階（同等以上、ほぼ同等、判断可能、判断不能）で評価した。


【図 2】ホルター心電計（Holtrec、上段）とABS-1(下段)の最高心拍数時の心電図

4. 結果

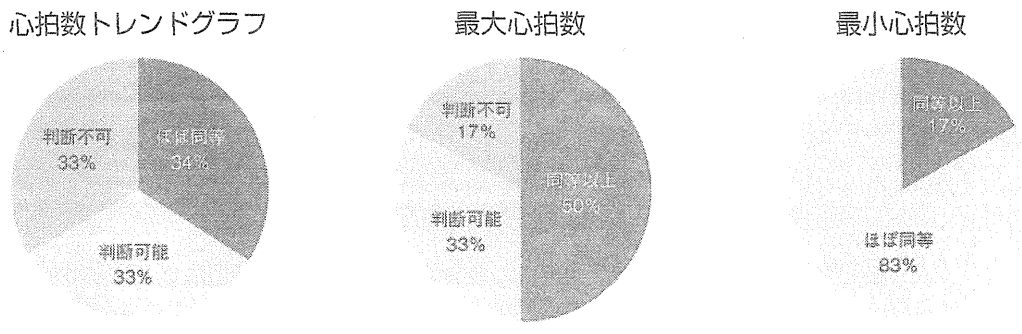
結果を【図3】に示す。心拍数トレンドについては、判断可能まで含めて67%であり、約3割で判断不能であった。最大心拍数の心電図波形については、判断可能まで含め83%、最小心拍数時の心電図波形については、すべての波形でほぼ同等以上であった。

5. 考案

発作的に起きる不整脈や虚血性心疾患などの診断には、安静時12誘導心電図法よりもホルター心電図法やイベントレコーダーと呼ばれる小型の心電計を用いた検査法が行われている[1]。イベントレコーダーの一部機種にはPHSなどの通信機器を組み込んだ製品もある。

3G回線やLTEなどの無線による高速インターネット環境やアプリケーションソフトを携帯電話にインストールして用いるいわゆるスマートフォンの普及により、この環境に適合した新しい心電図伝送のシステムの開発の気運が生まれてきた。実際に製品化されているものもいくつかある[2]。これらの製品は、これまでの医療機器メーカ以外で開発されているものも多く、ABS-1も携帯電話技術をつかった、いわばスピンオフ製品といえる。スマートフォンを使った心電計と従来の心電計を実際に被験者に装着しその心電図の臨床的な品質を検討した研究は我々の検索した限り無かった。本研究によりABS-1をつかって得られ最小心拍数の心電図の品質についてはホルター心電図法と比較して遜色のないことを確認できた。最大心拍数の心電図波形については、ABS-1の心電図の品質は若干劣っていると考えられた。原因としては、体動によるアーチファクトの影響と考えられ、品質向上のためにはドリフトフィルター等の画像処理の工夫が必要と考えられた。ABS-1の心拍数トレンドについては、約1/3で判断不能とホルター心電図のそれと比較するとビューワーの表示方法に改善の余地のあるものと考えられた。

従来の診断法と比べた本システムのメリットは、心電計から直接通信するのではなく、近距離（Bluetooth）の通信を用いスマートフォンを中継機器とすることで、心電計そのものを小型軽量化できることがあげられる。今回比較検討に用いた従来の製品であるHoltrecには通信機能は組み込まれておらず、機能の違いによりABS-1との重量について直接比較はできない。機能の類似した従来製品との比較について、文献上入手したカルジオフォン（日本光電社製、生産中止）というイベントレコーダーとPHSを組み合わせた製品[3]とABS-1を比較すると、従来製品のカルジオフォン120 gに対して、ABS-1の35gは明らかに軽量といえる。もう一つのABS-1のメリットとして、汎用性の高いスマートフォンやインターネット回線を



【図 3】ABS-1の心電図の評価

用いることでシステム全体のコストダウンの可能性の高いことも期待できる。一方、システムの電源について心電計本体は9時間であり、臨床で24時間連続記録するホルター心電計としての使い方は困難である。加えて中継機器となるスマートフォンの電源についても不確定な要素がある。ABS-1の一番の長所となる小型化と電池寿命はトレードオフの関係になる故にABS-1の電源効率改善は必要と考えられた。そのほかに、ABS-1はBluetoothと3G回線という2つの通信環境に依存するという不確実性[4]をもつので、臨床試験等を積み重ねる必要のあること、ABS-1から出力される心電図データについて自動的に解析するソフトウェアが存在しないため、現状ではモニタリング的な使い方しかできないことも今後の課題である。

以上の点を改良することで、すでに確立している検査法であるホルター心電図法やイベントレコーダーを補完する検査法として活用されることが期待される。また、コストの問題で進んでいない在宅医療での応用[5]も可能となると考えられた。

6. 結語

新しい心電図伝送システムで得られた心電図の品質について、ホルター心電図法と同じように十分なる臨床活用のために、さらなるシステムの改良を必要とする。

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モバイルネットワーク環境における新生児心臓病の超音波動画像遠隔診断

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Real-Time Mobile Tele-Echocardiography for Neonatal Heart Disease

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要旨

乳児死亡の原因の第1位は先天性心疾患である。出生直後に発症する心疾患の診療では、地域の小児科医と専門医チームをリアルタイムに結ぶ遠隔医療が求められる。複数の医師が、様々なネットワークと解像度の端末を用いて一つの症例検討を同時に行う場合、端末毎に最適な映像データを効率よく送信できなければならない。スケーラブル映像符号化技術(SVC)はインターネット、特にモバイルネットワークのように、不安定で狭帯域な環境であっても、伝送エラーに対する耐性に優れている。また、受信側の帯域変動に合わせた送信データの帯域調節が可能であり、多様な映像品質にも対応できる。私たちはSVCを利用した超音波動画像遠隔診断システムを構築し、新生児先天性心疾患の動画像をVPN接続した3つの回線、①高品質ネットワーク、②インターネット、③モバイルネットワークを用いて送信した。動画像の解像度は960×540、送信帯域は368kbps、768kbps、1Mbps、2Mbpsとした。モバイル接続端末としてiPad及びノートPCを用い、専門医が映像品質を主観的に評価した。その結果、送信回線、送信帯域、受信端末のすべての組み合わせにおいて高い評価が得られ、モバイルネットワーク環境とSVCの有効性が実証された。

遠隔医療において、正しい診断を行い、適切な治療方針を決定するには、超音波動画像のみならず電子カルテ上でアクセス可能な臨床情報をできるだけ多く遠隔地で共有する必要がある。私たちは、HD対応のテレビ会議システムと電子カルテをPC接続ポートを介して一体化するシステムによりこれが可能であることを示した。本システムはVPNの構築によりインターネット上でも安全に利用でき、広域医療連携とコスト削減につながる。運用にあたっては各種ガイドラインの遵守や医療機関間でのルール作りが重要である。

キーワード：乳児死亡、先天性心疾患、超音波検査、モバイルネットワーク、スケーラブル映像符号化技術

1. はじめに

新生児の心臓病は乳児死亡の原因の第1位である。医療過疎地域を含む広域医療圏において心臓病の新生児の診療を支援するための、インターネットやモバイルネットワーク環境、スケーラブル映像符号化技術を利用した遠隔医療モデルを提案する。テレビ会議システムと電子カルテを一体化することにより、電子カルテ上にある臨床情報を容易にかつ安全に遠隔地で共有できると考えている。

2. 乳児死亡と心臓病の新生児と遠隔診断

乳児死亡、新生児死亡、早期新生児死亡は、それぞれ生後1年未満、4週未満、1週未満の死亡である。乳児死亡率、新生児死亡率、早期新生児死亡率は、出生数千対のそれぞれの死亡数で表し、平成22年には2.3、1.1、0.8で、世界で最も良好な水準である。しかし、この年出生した1,071,304人のうち2,450人の赤ちゃんが1歳未満で死亡し、その約半数が生後4週未満で、約1/3が生後1週未満で死亡したのである。

乳児死亡の原因の第1位は、新生児にみられる先天性の心臓病、先天性心疾患である。先天性心疾患は新生児の約1%に発生するので、平成22年には約1万人の先天性心疾患をもった赤ちゃんが生まれたと推定される。先天性心疾患のなかで重症なタイプでは、胎児循環と呼ばれる子宮内特有の血流が生存に不可欠である。出生により胎児循環は失われ、成人と同様の循環が始まることから、この病気をもった赤ちゃんでは出生そのものが発症の引き金になり、病状は急速に進行する。早期に診断され、適切な治療が開始されなければ生後まもなく死亡する。

心臓病の新生児を診断し、治療を開始するのは地域の小児科医であり、重症例に対しては循環器小児科医や心臓外科医、麻酔科医などの専門医チームが詳細な診断に基づき、薬物治療やカテーテル治療、手術を行う。広大な岩手県は日本一小児科医が少ない医療過疎地域でもある。平成22年の15歳未満人口10万人あたりの都道府県別小児科医師数は全国平均180.2人に対し、岩手県は117.1人であり、最多の徳島県の297.9人の半数に満たない。また、東北地方は小児心臓病の専門医も少なく、全国では専門医1人当たり毎年平均約30人の新たに発生する先天性心疾患患者を診るのに対し、東北では約50人を診る計算になる。

医療過疎地域において遠隔診断が小児科医と専門医を結び、生後まもなく発症する先天性心疾患患者のトリアージ、初期治療、搬送を支援できれば、患者や家族の利益は大きく、限られた医療資源の有効利用にもつながる。岩手医大では県内の拠点病院をつなぐテレビ会議システムを用いて、新生児の心臓超音波動画像を受信し、診療支援を行ってきた。しかし、遠隔診断はテレビ会議システムを設置した環境でしか利用できず、専門医が自宅にいる場合や出張

中には遠隔診療が困難である。

複数の医師が、モバイルネットワーク環境のように、異なるネットワークと異なる解像度の端末を用いて一つの症例検討を同時に行う場合、端末毎に最適な映像データを効率よく送信できなければならない。先天性心疾患は構造が複雑で微細であり、また、新生児の心拍数は120～180/分と多いため、伝送エラーが起きやすく、モバイルネットワーク環境における動画像遠隔診断が最も困難な対象といえる。

3. スケーラブル映像符号化技術

従来の階層化されないH.264/AVCなどのデータに伝送エラーが生じた場合、フレームのすべてのデータが消失するため、フレームデータを復元できず、画像の乱れ、または直前に受信した画像を表示し続けることによる再生のかくつきが生じる。

これに対して、映像データに基本階層と拡張階層の階層構造を与えるスケーラブル映像符号化技術（SVC）は、データの拡張階層に伝送エラーが生じても、正常に受信した基本階層のデータを利用して画像の乱れを防止する。LTE等により使用可能な帯域が今後増加しても、帯域が保証されていないインターネット、特に通信が不安定なモバイルネットワーク環境では、常に帯域は変動し、混雑によりエラーが発生することは避けられない。SVCはこのエラーへの耐性が強い。また、様々なモバイル端末が増加する環境のなかで、SVCは、送信するデータの帯域を受信側の帯域の変動に合わせて調節することや、フルHDからQVGA等の低画質まで、異なる品質に対応することができる。さらにSVCは従来のシステムに比し、遅延が軽減できる、会議1拠点あたりのコストやネットワークインフラのコストが低廉であるなどの特徴を有している。

4. モバイルネットワーク環境における超音波動画像遠隔診断の実証実験

私たちは、新生児の心臓超音波動画像を符号化パラメータを変化させてSVCで符号化し、ローカル環境、広域ネットワーク環境、モバイルネットワーク環境の3つの環境で映像再生端末に配信し、画質を評価する、「心臓超音波画像配信・評価システム」を構築してきた。画質評価は、ITU-T P.910で規定された一重刺激法に従い、学会所属の専門医が、その画像で診断できるか否か、0（不可）から1（優）まで、連続的に評価する主観評価で行い、PSNRによる客観評価も合わせて行った。その結果、1Mbps未満の帯域制限がある場合、解像度640×448の最上位階層の圧縮率を上げるよりも、解像度320×224の階層に下げる方が、高い画質評価が得られることが明らかになった。

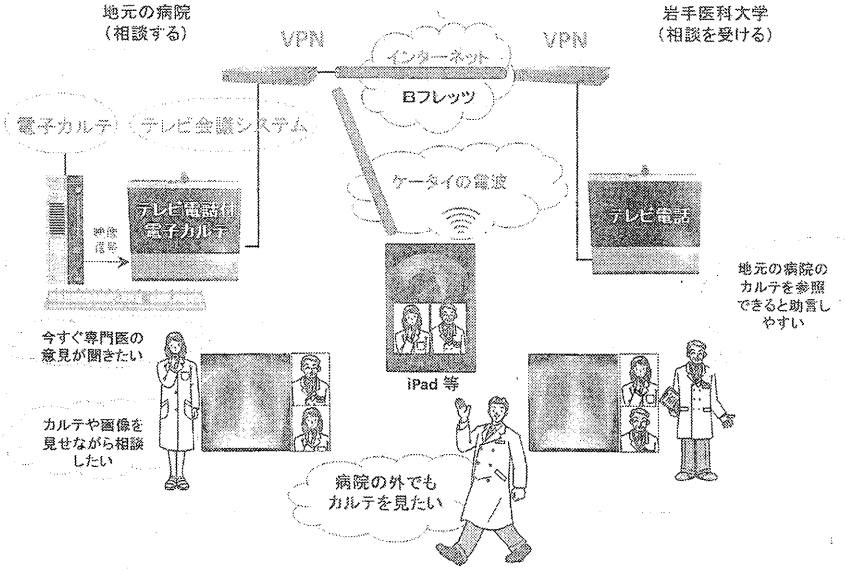
今回の研究では、岩手医大倫理員会の承認を得て、SVCを実装したテレビ会議システムを用いた映像配信装置を構築した。映像を配信する回線として、①高品質ネットワーク、②通常のネットワーク（インターネット）、③モバイルネットワーク（インターネット）の3種類を構築した。全ての回線でVPN接続による実験環境を構築し、モバイル接続端末としてiPad及びノートPCを用いた。新生児の心臓超音波動画像を青森県八戸市の医療機関から送信し、岩手医大で受信して、専門医による主観評価を行った。解像度は960×540とし、送信帯域は、368kbps、768kbps、1Mbps、2Mbpsとした。

その結果、専門医の評価値は0.6～0.8であり、受信された動画像は全ての組み合わせにおいて診断可能であると判断された。また、3種類のネットワークでの評価に差がみられなかったことから、配信ネットワークとしてモバイルネットワークが有効利用できると考えられた。SVCがモバイルネットワークという比較的不安定で狭帯域なネットワーク環境において有効であることが実証された。

5. 岩手医大が提案するテレビ会議システムと電子カルテの一体化による医療連携

遠隔診断には、超音波動画像だけではなく、心電図やレントゲン、CT、MRI、PET、シンチ等の画像、血液検査結果等の検体検査、サマリーや処方内容等、患者の病態を正しく把握できる情報を複数参照できることが望ましい。電子カルテ上でアクセス可能な臨床情報をできるだけ多く遠隔地で共有することが、正しい診断と適切な治療方針の決定にとって重要である。

私たちは、HD対応のテレビ会議システムと電子カルテをPC接続ポートを介して一体化することで、それが比較的容易に可能になると考えている【図1】。同意を得た患者さんについて岩手医大などの連携先と相談するとき、診



【図1】院内外の複数の医師間で患者さんの相談をしたい

察室で使っている電子カルテの端末がそのままテレビ会議システムの端末になる。テレビ会議システムは広域ネットワーク環境のみならずインターネット上でも利用できる。VPN の構築により、セキュリティが確保される。インターネットの利用は、岩手県に限定されない、より広域での医療連携につながり、ランニングコスト上も優れている。SVC の技術を用いることで、モバイルネットワーク環境での利用も可能である。なお、テレビ会議の内容は会議の開始とともに録画によって保存することが可能である。これらの運用にあたっては、厚生労働省「医療情報システムの安全管理に関するガイドライン」等を遵守し、医療機関間で連携のルールを明確にしておくことが重要である。

6. おわりに

遠隔医療は、医療や介護、健康増進に、ICT を役立てることである。それは手段であって、目的ではない。目的はあくまでも住民一人一人が健康に生きることである。手段は多種多様であり、インターネットやモバイルネットワークの利用はその一例にすぎない。現場で最も大切なのは、手段となるものは使い易くなければならないということである。どんなに優れた技術であっても、使いにくいものは結局使われずに廃れていく。遠隔医療が必ずしも広く普及しない理由のひとつは、手段であるはずのものが使いにくく、実際に利用しようとすると、送信者、受信者である医療従事者の負担が大きいことにあるのではないだろうか。私たちはできるだけ使い易い、人にやさしい遠隔医療を目指していきたい。

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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Genetic Background of Catecholaminergic Polymorphic Ventricular Tachycardia in Japan

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Background: The genetic background of catecholaminergic polymorphic ventricular tachycardia (CPVT) has been extensively investigated for the last decade in Western countries, but it remains unstudied in the Asian population.

Methods and Results: In 50 Japanese probands from unrelated families who satisfied clinical criteria for CPVT, genetic testing was conducted in all exons on 3 CPVT-related genes: *cardiac ryanodine receptor 2* (*RYR2*), *calsequestrin 2* (*CASQ2*) and *inward rectifier potassium channel 2* (*KCNJ2*), and the clinical features between *RYR2*-genotyped and -non-genotyped patient groups were compared. Genetic and clinical evaluation was also done in 46 family members. In the genetic screening, 28 (18 novel) *RYR2* (56.0%), 1 compound heterozygous *CASQ2* (2.0%) and 1 *KCNJ2* (2.0%) mutation carriers were identified. In the *RYR2* mutation-positive group, the frequency of bidirectional ventricular tachycardia and the use of β-blockers were significantly higher than in the mutation-negative group. In contrast, there was no significant difference in supraventricular arrhythmias between the 2 groups. With regard to disease penetrance, the number of family members of *RYR2*-genotyped probands with a clinical diagnosis of CPVT was high.

Conclusions: Thirty gene mutation carriers were found for 3 genes in 50 probands clinically diagnosed as having CPVT. The penetrance of CPVT phenotype was significantly higher in *RYR2* mutation carriers, thus *RYR2* gene screening in CPVT patients would be indispensable to prevent unexpected cardiac sudden death of young family members. (*Circ J* 2013; **77:** 1705–1713)

Key Words: Beta-blockers; Calsequestrin; Catecholaminergic polymorphic ventricular tachycardia; Flecainide; Ryanodine receptor

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a form of inherited cardiac arrhythmia, characterized by polymorphic or bidirectional ventricular tachyarrhythmia (pVT or bVT) induced by physical exercise, emotional stress or catecholamine use.[1–3] CPVT patients have autosomal dominant or recessive traits. The QTc interval is generally within the normal range, but sinus bradycardia and atrial arrhythmias have been associated with CPVT.[3–5]

Editorial p1684

The first gene locus mapped to chromosome 1q42–43[1] was an autosomal dominant form of CPVT (CPVT1), and muta-

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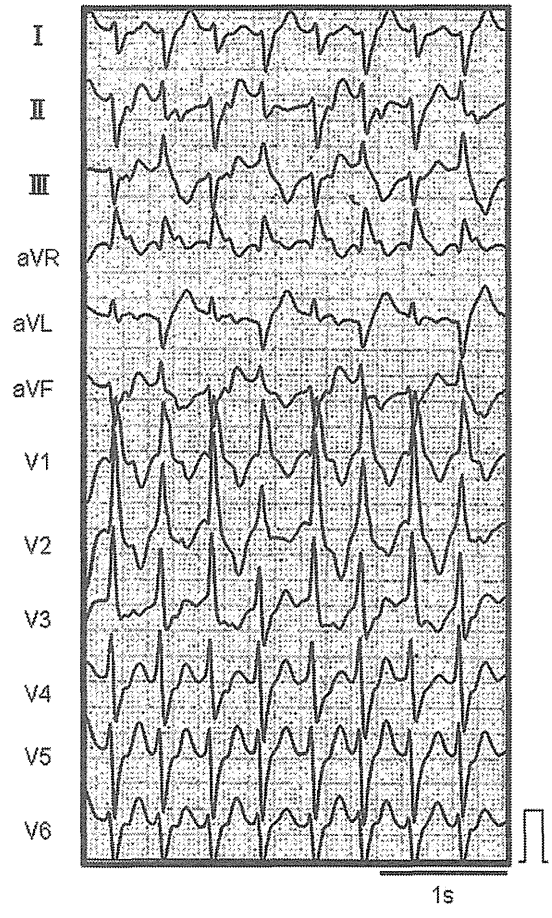

Figure 1. Representative 12-lead electrocardiogram showing exercise-induced bidirectional ventricular tachyarrhythmia recorded in a patient (30p; **Table 1**) carrying *inward rectifier potassium channel 2* (*KCNJ2*) mutation, p.G144D.

tions were identified in a gene encoding a cardiac ryanodine receptor (*RYR2*; MIM 180902).[4,6–10] Homozygous or compound heterozygous mutations in calsequestrin 2 (*CASQ2*; MIM 114251) were then reported to cause the second variant of CPVT (CPVT2).[2,11–13] *CASQ2* encodes a Ca-binding protein in the sarcoplasmic reticulum and plays a key role in maintaining cytosolic Ca^{2+} concentration, in collaboration with *RYR2*. In 2009, the third variant of CPVT was reported to result from a mutation in *KCNJ2* (MIM 600681), which encodes Kir2.1, a subunit for inward-rectifier potassium channels.[14] The *KCNJ2* mutation (p.V227F) produced no functional defects on Kir2.1 channels at rest but an unusual latent loss of function regarding the cAMP-dependent protein kinase A (PKA)-dependent phosphorylation of Kir2.1 channel proteins.[14] This in turn leads to the loss of response in Kir2.1 function to β-adrenergic stimulation. More recently, Bhuiyan et al reported a new malignant variant of CPVT in an inbred family with autosomal recessive inheritance. They have mapped this recessive CPVT locus to chromosome 7p14–p22.[15] Roux-Buisson et al identified *triadin* (*TRDN*) as a new gene responsible for an autosomal recessive form of CPVT.[16]

To date, there are a substantial number of reports on the genetic background in CPVT cohorts from Western countries,[2,4,6–9,11–13,17,18] but few in Asian populations.[19–21] In the present study, we therefore conducted genetic testing on 3 CPVT-related candidate genes – *RYR2*, *CASQ2*, and *KCNJ2* – in 50 CPVT probands from unrelated Japanese families and their 46 family members and examined their correlation with clinical phenotypes.

Methods

Subjects

Fifty clinically diagnosed CPVT probands and their 46 family members (total, 96) were included in genetic analysis. The entry criteria were the presence of the following arrhythmias documented on exercise stress testing and/or Holter monitoring electrocardiogram (ECG) in the absence of structural heart abnormalities: bVT (**Figure 1**); pVT; or ventricular fibrillation (VF). The characteristic QRS morphology of bVT or pVT is a change in QRS axis every other beat, with 2 or more types of patterns, during more than 4 consecutive beats. We also included a 2-year-old boy without typical arrhythmias but whose father was symptomatic and genetically diagnosed as CPVT and who died suddenly in his 30 s (**Table 1**; 13-p). We excluded patients who suffered bVT or pVT due to prominent electrolyte imbalance, drug treatment, or organic heart disease such as cardiomyopathy, ischemic heart disease, or congenital heart disease. Primary electrical diseases such as long QT syndrome (LQTS) were also excluded. Bradycardia was defined as follows: in children aged <16 years, heart rate below the second percentile of established age- and sex-appropriate norms;[22] in adults, <60 beats/min on resting ECG without intake of β-blocker.

Mutation Analysis

The protocol for genetic analysis was approved by the Institutional Ethics Committee and was performed under its guidance. All subjects gave written informed consent before genetic analysis. Genomic DNA was isolated from peripheral white blood cells. Intronic primers amplifying the *RYR2, CASQ2* and *KCNJ2* coding regions were used for polymerase chain reaction (PCR) amplifications as previously reported.[6,7,9,17,23] PCR products were analyzed on direct sequencing. The cDNA sequences of *RYR2*, *CASQ2* and *KCNJ2* were based on the GenBank reference sequence NM_001035.2, NM_001232.3 and NM_000891.2, respectively. Regarding RyR2 mutation-negative probands, we also searched for large genomic rearrangements affecting exon 3 and 97, as reported previously.[4] In addition to these 3 genes, we examined the entire coding sequence for *KCNQ1*, *KCNH2*, *SCN5A*, and *KCNE1–5* to exclude an unexpected presence of compound mutations related to primary electrical diseases.

All novel putative pathogenic variants were examined and confirmed to be absent in 400 chromosomes from 200 Japanese controls.

Statistical Analysis

All continuous variables are reported as mean±SD. Differences between continuous variables were evaluated using unpaired Student's t-test, and categorical variables using chi-squared analysis. Statistical significance was set at $P<0.05$.

Results

Genetic Analysis

***RYR2* (CPVT1)** The genetic analysis for *RYR2* identified 26 different missense heterozygous mutation carriers and 2 carriers with large DNA deletions including exon 3 in 50 pro-

Table 1. Characteristics of Genetic Mutation Carriers in CPVT Patients

Family number	Proband or family	Sex	Age at onset (years)	Exercise-related syncope	Required CPR	Cardiac manifestations							β-blockers	Dosage of BBL, mg (mg/kg)
						HR at rest (beats/min)	QTc (ms)	bVT	pVT	VF	Atrial tachyar-rhythmia	Other arrhythmia		
1	p	F	16	+	+	47	424	+	–	–	–	SSS	Bisoprolol	5
	f1	F	–	–	–	44	384	–	–	–	–	SSS	Bisoprolol, Flecainide	NA
	f2	F	–	–	–	85	380	–	–	–	AF	–	–	–
	f3	F	–	–	–	39	381	–	–	–	–	Sinus bradycardia	–	–
	f4	F	–	–	–	81	476	–	–	–	–	–	–	–
	f5	M	–	–	–	78	419	–	–	–	–	–	–	–
2	p	F	1	+	–	53	420	–	+	–	–	C-AVB	Carvedilol	NA
	f	F	–	–	–	52	470	–	–	–	–	–	–	–
3	p	F	19	+	–	41	NA	–	+	–	–	–	Propranolol	90
4	p	M	11	+	–	44	393	+	+	–	–	–	Atenolol	100 (2.22)
5	p	F	7	+	+	76	441	–	–	+	–	–	Propranolol	75 (2.01)
	f	F	–	+	–	NA	NA	–	–	–	–	–	–	–
6	p	M	8	+	+	48	419	–	+	+	–	–	Propranolol	120 (3.20)
7	p	M	13	+	+	84	438	–	–	+	–	–	Atenolol	37.5
	f1	F	–	–	–	52	410	–	–	–	–	–	–	–
	f2	M	–	–	–	75	400	–	–	–	–	–	–	–
8	p	F	12	+	–	56	444	–	+	–	–	–	Atenolol	NA
9	p	M	10	+	–	81	446	+	–	–	–	–	Bisoprolol	2.5
10	p	M	10	+	+	52	440	+	+	+	–	–	Atenolol	50 (0.97)
11	p	F	10	+	–	72	429	+	–	–	AF	–	Atenolol	100 (3.23)
12	p	M	–	–	–	50	394	–	+	–	–	–	Metoprolol	60
13	p	M	–	–	–	84	420	–	–	–	–	–	–	–
14	p	F	14	+	+	56	423	–	+	+	–	–	Atenolol	12.5
15	p	F	8	+	–	58	479	–	+	–	–	–	Propranolol	75
16	p	M	4	+	+	89	400	+	–	+	–	–	Atenolol	50 (2.5)
17	p	F	6	+	–	55	440	+	–	–	–	–	Nadolol	60 (1.51)
18	p	F	6	+	–	67	424	+	+	–	AT	–	Propranolol	120 (5.00)
19	p	M	3	+	–	77	434	+	+	–	–	–	Carteolol	3 (0.20)
	f1	F	–	–	–	NA	NA	–	–	–	–	–	–	–
	f2	M	–	–	–	86	407	–	–	–	–	–	–	–
20	p	M	14	+	+	58	417	–	+	+	–	–	Propranolol	90
21	p	F	7	+	–	56	420	–	+	–	–	–	Propranolol	30 (1.00)
22	p	M	2	+	–	50	423	+	–	–	–	–	Propranolol	NA
23	p	F	15	+	–	60	414	+	+	–	–	–	Metoprolol	120 (2.36)
	f	M	10	+	–	64	428	–	–	–	–	–	Metoprolol	40 (1.03)
24	p	F	2	–	–	47	440	–	+	–	AT	–	Atenolol	NA
25	p	F	6	+	–	86	409	+	+	–	AFl	–	Atenolol	75 (0.88)
26	p	F	9	–	–	NA	NA	–	+	–	–	–	Propranolol	60
	f1	F	–	–	–	NA	NA	–	–	–	–	–	Propranolol	NA
	f2	F	–	–	–	NA	NA	–	–	–	–	–	Propranolol	60
27	p	M	4	+	+	40	396	+	+	+	–	–	Propranolol	60
28	p	F	6	+	–	NA	NA	–	+	–	–	–	Propranolol	NA
29	p	M	4	+	+	75	494	–	+	+	–	–	Propranolol	40 (2.00)
	f1	M	–	–	–	53	372	–	–	–	–	–	–	–
	f2	F	–	–	–	66	408	–	–	–	–	–	–	–
	f3	M	–	–	–	94	385	–	–	–	AT	–	–	–
30	p	F	6	+	–	63	380	+	+	–	–	–	Bisoprolol	NA

(Table 1 continued the next page.)

Other medicine	ICD	Mutation					Exercise stress test	Pharmacologic stress test	Family history	
		Gene	Exon	Nucleotide change	Protein change	Previous report			Sudden death	Diagnosed CPVT
–	+	*RYR2*[a]	3	Deletion	exon3 deletion	Bhuiyan et al[4]	Multifocal couplets PVC	–	+	+
–	+	*RYR2*	3	Deletion	exon3 deletion	Bhuiyan et al[4]	Bifocal couplets PVC	–	+	+
Verapamil	–	*RYR2*	3	Deletion	exon3 deletion	Bhuiyan et al[4]	Isolated intermittent PVC	–	–	–
–	PM	*RYR2*	3	Deletion	exon3 deletion	Bhuiyan et al[4]	NA	–	–	–
–	–	*RYR2*	3	Deletion	exon3 deletion	Bhuiyan et al[4]	NA	–	–	–
–	–	*RYR2*	3	Deletion	exon3 deletion	Bhuiyan et al[4]	NA	–	–	–
–	PM	*RYR2*	3	Deletion	exon3 deletion	Bhuiyan et al[4]	Multifocal couplets PVC	–	+	+
–	–	*RYR2*	3	Deletion	exon3 deletion	Bhuiyan et al[4]	NA	–	+	+
–	–	*RYR2*	8	g506a	R169Q	Hsueh et al[21]	pVT	–	+	–
Flecainide	+	*RYR2*	14	a1221t	R407S	Novel	bVT	–	–	–
–	–	*RYR2*	14	g1259a	R420Q	Medeiros-Domingo et al[18]	VF	–	–	+
–	–	*RYR2*	14	g1259a	R420Q	Medeiros-Domingo et al[18]	Unifocal bigeminal PVC	–	–	–
Verapamil, Flecainide	–	*RYR2*	35	a4652g	N1551S	Novel	pVT	–	+	+
–	–	*RYR2*	43	a6574t	M2192L	Novel	NA	PVC by epinephrine	–	–
–	–	*RYR2*	43	a6574t	M2192L	Novel	NA	–	–	+
–	–	*RYR2*	43	a6574t	M2192L	Novel	Multifocal couplets PVC	–	–	+
–	–	*RYR2*	44	c6737t	S2246L	Priori et al[8]	pVT	–	+	+
–	–	*RYR2*	47	c7160t	A2387V	Novel	Unifocal bigeminal PVC	–	–	+
Flecainide	–	*RYR2*	47	g7199t	G2400T	Novel	pVT	–	–	–
Verapamil, Flecainide	+	*RYR2*	49	a7420g	R2474G	Novel	NA	–	–	–
–	–	*RYR2*	52	g7883a	G2628E	Novel	Multifocal couplets PVC	–	+	–
–	–	*RYR2*	77	a10913	D3638A	Novel	NA	–	+	+
–	–	*RYR2*	86	g11583c	Q3861H	Novel	NA	–	–	–
–	–	*RYR2*	86	g11583t	Q3861H	Novel	pVT	–	–	–
Verapamil	–	*RYR2*	86	c11628g	D3876E	Novel	NA	–	–	–
–	–	*RYR2*	88	g11836a	G3946S	Priori et al[8]	pVT	–	–	–
–	–	*RYR2*	88	g11836a	G3946S	Priori et al[8]	pVT	–	–	–
Flecainide	–	*RYR2*	90	g12006a, c13175g	M4002I, K4392R	Novel	NA	–	–	–
–	–	*RYR2*	90	c13175g	K4392R	Novel	NA	–	+	+
–	–	*RYR2*	90	c13175g	K4392R	Novel	NA	–	+	+
–	–	*RYR2*	90	c12313t	L4105F	Hasdemir et al[10]	NA	–	–	–
–	–	*RYR2*	90	c12372a	S4124R	Novel	pVT	–	–	–
–	–	*RYR2*	90	a12533g	N4178S	Medeiros-Domingo et al[18]	bVT	–	–	–
Flecainide	+	*RYR2*	94	a13759g	I4587V	Novel	bVT	–	–	+
–	–	*RYR2*	94	a13759g	I4587V	Novel	Multifocal couplets PVC	–	–	+
–	–	*RYR2*	99	a14174g	Y4725C	Novel	NA	pVT by ISP	–	–
Verapamil	–	*RYR2*	99	a14251c	K4750Q	Novel	AFl	–	–	–
Verapamil	–	*RYR2*	100	g14311a	V4771I	Priori et al[8]	bVT	–	–	+
–	–	*RYR2*	100	g14311a	V4771I	Priori et al[8]	pVT	–	–	+
–	–	*RYR2*	100	g14311a	V4771I	Priori et al[8]	pVT	–	–	+
Flecainide	–	*RYR2*	102	c14593g	L4865V	Novel	pVT	–	–	–
Verapamil	+	*RYR2*	103	t14756c	L4919S	Novel	pVT	–	–	–
–	–	*CASQ2*[b]	2, 11	a259t, g1083a	K87X, W361X	Novel	NA	–	–	–
–	–	*CASQ2*	2	a259t	K87X	Novel	NA	–	–	+
–	–	*CASQ2*	11	g1083a	W361X	Novel	NA	–	–	+
–	–	*CASQ2*	11	g1083a	W361X	Novel	NA	–	–	+
Verapamil, Flecainide	–	*KCNJ2*[c]	1	g431a	G144D	Novel	Multifocal couplets PVC	–	–	–

Age at onset, age at which patients experienced the first symptomatic arrhythmic attack or were recorded as having physical stress-induced ventricular tachycardia. [a]NM_001035.2; [b]NM_001232.3; [c]NM_000891.2. AF, atrial fibrillation; AFl, atrial flutter; AT, atrial tachycardia; bVT, bidirectional ventricular tachyarrhythmia; CASQ2, calsequestrin 2; CPR, cardiopulmonary resuscitation; CPVT, catecholaminergic polymorphic ventricular tachycardia; HR, heart rate; ICD, implantable cardioverter-defibrillator; KCNJ2, inward rectifier potassium channel 2; NA, not available; PM, pacemaker; PVC, premature ventricular contraction; pVT, polymorphic ventricular tachyarrhythmia; QTc, corrected QT interval; RYR2, cardiac ryanodine receptor; VF, ventricular fibrillation.

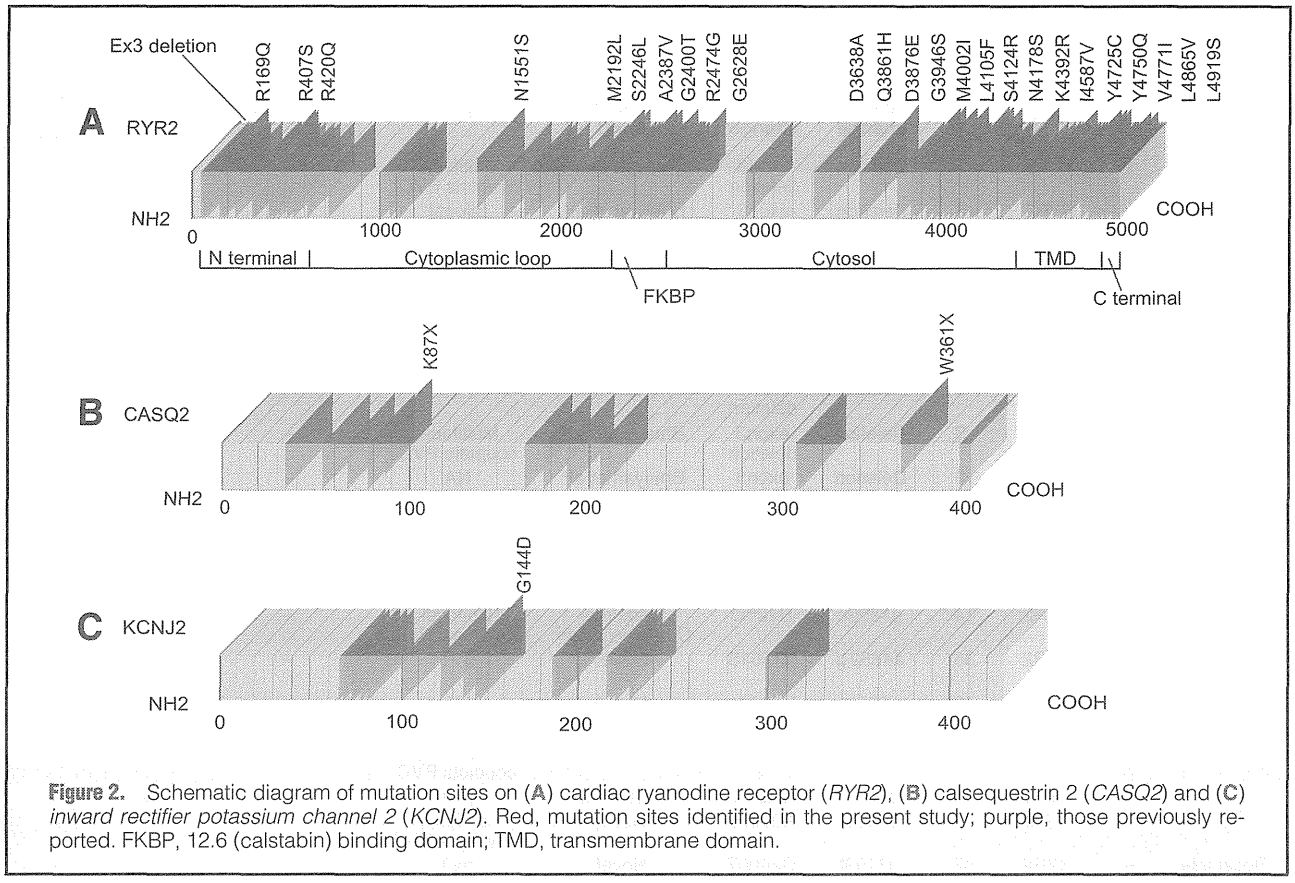

Figure 2. Schematic diagram of mutation sites on (**A**) cardiac ryanodine receptor (*RYR2*), (**B**) calsequestrin 2 (*CASQ2*) and (**C**) *inward rectifier potassium channel 2* (*KCNJ2*). Red, mutation sites identified in the present study; purple, those previously reported. FKBP, 12.6 (calstabin) binding domain; TMD, transmembrane domain.

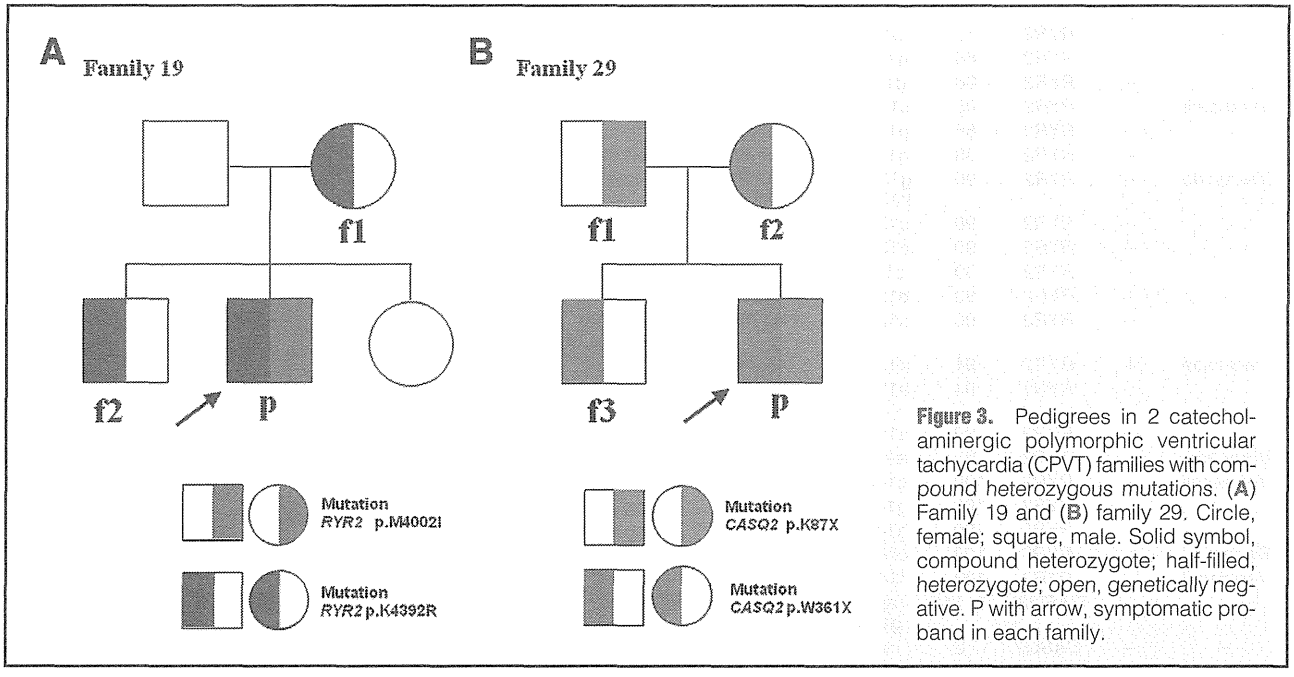

Figure 3. Pedigrees in 2 catecholaminergic polymorphic ventricular tachycardia (CPVT) families with compound heterozygous mutations. (**A**) Family 19 and (**B**) family 29. Circle, female; square, male. Solid symbol, compound heterozygote; half-filled, heterozygote; open, genetically negative. P with arrow, symptomatic proband in each family.

bands (incidence: 56.0%): exon3 deletion, p.R169Q, p.R407S, p.R420Q, p.N1551S, p.M2192L, p.S2246L, p.A2387V, p.G2400T, p.R2474G, p.G2628E, p.D3638A, p.Q3861H, p.D3876E, p.G3946S, p.M4002I, p.K4392R, p.L4105F, p.S4124R, pN4178S, p.I4587V, p.Y4725C, p.K4750Q, p.V4771I, p.L4865V and p.L4919S (**Table 1**; **Figure 2A**). All patients were heterozygous and 18 of the mutations were novel. **Table 1** lists genetic and clinical data of all the individuals who carried genetic mutations, including the family members. We examined 46 relatives of 28 probands with *RYR2* muta-

Table 2. Clinical Characteristics of CPVT Probands and Comparison of *RyR2* Mutation Positive and Negative Groups

	Total (n=47)	*RYR2*-positive CPVT (n=27)	*RYR2*-negative CPVT (n=20)	P-value
Male	19 (40.4)	11 (40.7)	8 (40.0)	NS
Mean age at onset (years)	10.2±7.3	8.6±4.7	12.6±9.9	NS
Family history of sudden death	7 (14.9)	6 (22.2)	1 (5.0)	NS
Clinically diagnosed CPVT family members	10 (21.3)	9 (33.3)	1 (5.0)	0.018
Mean HR (beats/min)	62±14	59±14	67±13	NS
Mean QTc (ms)	424±28	426±21	420±39	NS
More severe symptom				
Life-threatening arrhythmias	17 (36.1)	9 (33.3)	8 (40.0)	NS
Exercise-induced syncope	37 (78.7)	23 (85.2)	14 (70.0)	NS
Ventricular arrythmia				
bVT	17 (36.2)	13 (48.1)	4 (20.0)	0.043
pVT	31 (66.0)	19 (70.4)	12 (60.0)	NS
VF	16 (34.0)	8 (29.6)	8 (40.0)	NS
Atrial arrhythmia	6 (12.8)	4 (14.8)	2 (10.0)	NS
AF	1 (2.1)	1 (3.7)	0	NS
Afl	1 (2.1)	1 (3.7)	0	NS
AT	2 (4.3)	2 (7.4)	0	NS
PSVT	2 (4.3)	0	2 (10.0)	NS
Sinus bradycardia	22 (46.8)	18 (66.7)	4 (20.0)	0.014
Exercise-stress test	31 (64.8)			
Positive	30 (63.8)	19 (70.3)	11 (55.0)	NS
Negative	1 (2.1)	0	1 (5.0)	NS

Data given as mean±SD or n (%). Mean age at onset, mean age at which patients experienced the first symptomatic arrhythmic attack or were recorded as having physical stress-induced ventricular tachycardia. Exercise stress test was considered positive for bigeminal PVCs, PVC couplets, bVT, pVT, or VF. PSVT, paroxysmal supraventricular tachycardia. Other abbreviations as in Table 1.

tions and identified 14 mutation carriers (29.2%). Two of the family members with *RYR2* mutations experienced exercise-induced syncope (5-f,23-f; Table 1). To confirm whether the *RYR2* mutations were inherited from the parents or not, we conducted genetic screening of the parents in 14 probands with *RYR2* mutations, and found that 8 probands were considered to carry de novo *RYR2* mutations (57.1%). In 1 patient (19-p, Table 1; arrow, Figure 3A), we identified compound heterozygous *RYR2* mutations: p.M4002I and p.K4392R. This patient was a 3-year-old boy who lost consciousness while taking a bath. His parents and siblings were all asymptomatic, and his father and sister were negative on genetic analysis. In contrast, the boy's mother (19-f1) and brother (19-f2) carried p.K4392R. Concerning p.K4392R, we identified this variant in 1 control sample from 200 normal controls. Therefore, p.M4002I was considered to be a de novo mutation and the cause of CPVT in this patient.

***CASQ2* (CPVT2)** In one of 50 probands, we identified the compound heterozygous *CASQ2* mutations p.K87X and p.W361X (Figure 2B). Both were nonsense mutations. The index patient (29-p; Table 1; Figure 3B) was a 4-year-old boy (arrow, Figure 3B) who lost consciousness at his nursery school while playing with other children and was found to have pulseless pVT in the emergency room. His parents (29-f 1 and 29-f 2) and elder brother (29-f 3) were all asymptomatic although they carried either of these 2 *CASQ2* mutations in a heterozygous trait (Figure 3B).

***KCNJ2* (CPVT3)** We also identified a heterozygous missense *KCNJ2* mutation, p.G144D (Figure 2C) in one of the present probands. The proband (30-p; Table 1) was a 31-year-old woman who had exercise-induced syncope since the age of 6. Her ECG at rest showed considerably frequent premature ventricular contractions (PVCs), which hindered the accurate measurement of U-wave. Exercise tolerance test induced bVT (Figure 1). She and her family members had neither periodic paralysis nor dysmorphic features. This patient then underwent catheter ablation therapy for PVCs and received bisoprolol fumarate (5 mg/day). The drug was not effective and was replaced with verapamil (240 mg/day). After treatment the PVCs were suppressed, and ECG showed prolonged QU intervals with prominent U-waves in the right precordial leads, suggesting phenotypic similarity with Andersen-Tawil syndrome.[24]

Proband Clinical Characteristics

Of 50 probands consecutively referred for genetic tests under the clinical diagnosis of CPVT, we excluded an asymptomatic 2-year-old proband (13-p; Table 1) and 2 with *CASQ2* and *KCNJ2* mutations. All the remaining probands were symptomatic and complained of syncope or palpitation on exercise (Table 2). Their mean age at symptom onset was 10.2±7.3 years (range, 0–39 years). Seventeen of them experienced life-threatening ventricular arrhythmias that required resuscitation, and 37 experienced repetitive exercise-induced syncope. Baseline ECG showed a normal sinus rhythm with normal QTc interval (except for 15-p in Table 1; mean QTc, 424 ms). Proband 15 had a relatively longer QTc (479 ms). We excluded this proband from the analysis of QTc interval because we suspected an additional gene mutation to cause LQTS although we failed to identify it. Regarding the dysrhythmias, bVT

Table 3. Comparison of the Treatment Between *RYR2* Mutation Positive and Negative Probands

	Total (n=47)	*RYR2*-positive CPVT (n=27)	*RYR2*-negative CPVT (n=20)	P-value
β-blockers	43 (91.5)	27 (100.0)	16 (80.0)	0.027
β-blockers only	27 (57.4)	16 (59.3)	11 (55.0)	NS
Flecainide	8 (17.0)	6 (22.2)	2 (10.0)	NS
Verapamil	9 (19.1)	6 (22.2)	3 (15.0)	NS
Verapamil only	1 (2.2)	0 (0)	1 (5.0)	NS
Amiodarone	1 (2.2)	0 (0)	1 (5.0)	NS
Combination				
β-blockers+verapamil	4 (8.5)	3 (11.1)	1 (5.0)	NS
β-blockers+ICD	3 (6.4)	1 (3.7)	2 (10.0)	NS
β-blockers+flecainide	2 (4.3)	2 (7.4)	0 (0)	NS
β-blockers+verapamil+ICD	1 (2.2)	1 (3.7)	0 (0)	NS
β-blockers+flecainide+ICD	3 (6.4)	2 (7.4)	1 (5.0)	NS
β-blockers+verapamil+flecainide	2 (4.3)	1 (3.7)	1 (5.0)	NS
β-blockers+verapamil+flecainide+ICD	1 (2.2)	1 (3.7)	0 (0)	NS
ICD	8 (17.0)	5 (18.5)	3 (15.0)	NS
No medication	2 (4.2)	0 (0)	2 (10.0)	NS

Data given as n (%). CPVT, catecholaminergic polymorphic ventricular tachycardia. Other abbreviations as in Table 1.

(Figure 1) was documented in 17 cases (36.2%), pVT in 31 (66.0%) and VF in 16 (34.0%) on ECG in the absence of medication. Atrial fibrillation was noted in 1 proband (2.1%), atrial flutter in 1 (2.1%), atrial tachycardia in 2 (4.3%) and supraventricular tachycardia in 2 (4.3%). All types of arrhythmias were paroxysmal and induced by exercise.

Clinical Characteristics of *RYR2* Mutation-Positive vs. -Negative CPVT

In order to characterize the clinical features of CPVT patients, we divided them into 2 groups (Table 2): *RYR2* mutation positive (n=27) and negative (n=20). Among 27 *RYR2* mutation carriers, there were only 11 male carriers (40.7%). The number of probands whose family members were clinically diagnosed as having CPVT was significantly larger in the *RYR2* mutation-positive group (P=0.018). Exercise-induced bVT (P=0.043) and sinus bradycardia (P=0.021) were significantly more frequent in the *RYR2* mutation-positive patients. In contrast, atrial arrhythmias were detected at a similar frequency in both groups (P=0.261).

Exercise Stress Test

Thirty-one probands of 47 underwent exercise stress tests. The remaining 16 subjects were not examined because of cerebral palsy, hypoxic brain damage at the first attack or diagnosis on other examinations such as Holter monitoring ECG. Thirty probands of 31 developed various arrhythmias during exercise stress test and were judged as positive probands; 19 of them were found to carry *RYR2* mutations (Table 1). The prevalence of positive stress test was not statistically different between the mutation-positive and -negative groups (Table 2).

Treatment

There were 47 symptomatic probands, and 45 of them received medical treatment (Table 3). Two probands who were not genotyped had no medication. Beta-blockers were prescribed in 43 patients (91.5%); 27 of them (57.4%) were treated with β-blockers alone, and the other 16 probands took them in combination with other medication and/or implantable cardioverter-defibrillator (ICD) implantation. Beta-blocker treatment was significantly more prevalent (P=0.027) in the *RYR2* mutation-positive probands (Table 3), and there was a tendency for more of them to receive combination therapy with β-blockers and verapamil or flecainide or ICD. ICD was used in 5 *RYR2*-positive and 3 mutation-negative probands, and all received β-blockers simultaneously, which appeared to partially protect against subsequent ICD shock delivery (mean follow-up period, 63 months). Two of them (1-p, 23-p; Table 1) received appropriate ICD therapy. Flecainide was prescribed in 6 *RYR2* mutation-positive patients, which was frequently more prescribed in the *RYR2* mutation-positive than negative group and in all cases it suppressed ventricular tachycardia or ventricular extrasystoles on exercise test.

Among *RYR2*-positive probands first treated with β-blockers alone, 5 (19%) were refractory to β-blockers with recurrent syncope (mean follow-up, 48 months), and additional flecainide therapy was then introduced, which was successful in all cases. The detailed clinical outcome is reported elsewhere.[25]

Discussion

In the present study, we first screened for gene mutations in a considerable number of Japanese CPVT patients and summarized the clinical data. The major findings are as follows: (1) in 50 clinically diagnosed CPVT probands, we identified 26 different *RYR2* mutations in 28 probands (CPVT1; incidence, 56.0%); (2) we identified probands with compound heterozygous *RYR2* mutations, compound heterozygous *CASQ2* mutations and heterozygous missense *KCNJ2* mutation in 1 family each, respectively; (3) the number of probands whose family members were clinically diagnosed as having CPVT was significantly larger in the *RYR2* mutation-positive group, and exercise-induced bVT was significantly more prevalent in the *RYR2* mutation-positive patients; and (4) β-blocker treatment was significantly more prevalent (P=0.027) in *RYR2* mutation-positive probands, and there was a tendency for more of them to receive combination therapy with β-blockers and verapamil or flecainide or ICD.

In the beginning of 2000, genetic testing of the *RYR2* gene was performed only in some of the 105 exons of the *RYR2* gene.[8,19,26] Yano et al summarized more than 30 *RYR2* mutations between 2001 to 2005 and showed that most mutations were clustered in 3 main regions (3 hotspot regions: *N*-terminal domain; FKBP12.6 binding region of central domain; channel region).[27,28] Therefore, we first started the analysis on the 34 *RYR2* exons in the reported hotspots and then changed the protocol to examine all the exons of the *RYR2* gene. We could identify 6 additional *RYR2* mutations outside of the hotspots. The positive rate for *RYR2* mutations was increased from 41.6% to 56.0%. Similar to a previous report,[18] we found most of the *RYR2* mutations in the 3 main regions (70%).

The *RYR2* mutation site appeared not to be associated with phenotype differences, probably because of the relatively small number of genotyped patients. Van der Werf et al, however, extensively examined family members of *RYR2*-positive CPVT probands and found that those carrying mutations in the channel pore-forming domain had a higher prevalence of non-sustained VT than those carrying mutations in the *N*-terminus or central domains.[29]

In the present cohort, we identified a proband with compound heterozygous *CASQ2* mutations. To our knowledge, this is the second report of a compound heterozygous subject in the world.[30] Thus, *CASQ2* mutations can be causative of CPVT even under non-consanguineous conditions. In the first report, family members who carried either of 2 different *CASQ2* mutations also remained asymptomatic (**Figure 3B**).[30] More recently, van der Werf et al reported that the phenotype of homozygous *CASQ2* mutation carriers tends to be more malignant than those of *RYR2* mutation carriers.[29] By analogy to Jervell and Lange-Nielsen syndrome,[31] homozygous or compound heterozygous *CASQ2* mutations may cause very severe functional damage in cellular Ca-handling and thereby fatal phenotypes in probands, but not in their heterozygous relatives.

The percentage of the probands whose family members were clinically diagnosed as having CPVT was significantly larger in the *RYR2* mutation-positive group (**Table 2**; 33.3% vs. 5%). Van der Werf et al reported that 50% of relatives carrying an *RYR2* mutation with no CPVT phenotype at the initial cardiac evaluation developed the phenotype later during follow-up.[29] When *RYR2* mutations are identified in CPVT probands, the presence of *RYR2* mutation in the family members should be investigated, especially if young, even if there is an absence of clinical phenotype.

Because LQTS type 1 patients may also have exercise-related syncope,[32] and some have borderline or normal QT intervals, the clinical presentation resembles that of CPVT.[9] Medeiros-Domingo et al found that the presence of bVT or pVT was of critical importance for differential diagnosis between CPVT and LQTS.[18] In the present study, exercise-induced bVT was significantly more prevalent in the *RYR2* mutation-positive patients compared to the mutation-negative patients, indicating that the exercise tolerance test would be a useful differential diagnostic tool.

Beta-blocker treatment was significantly more prevalent (P=0.027) in *RYR2* mutation-positive probands, and there was a tendency for more of them to receive combination therapy with β-blockers and verapamil or flecainide or ICD. More recently, Watanabe et al found that flecainide, a potent sodium channel blocker, prevented cardiac events in CPVT by directly inhibiting *RYR2* receptor channels.[33,34] Chan et al found that multiple pharmacological approaches targeting the Na^+/Ca^+ exchanger (INaCa) may be potentially useful as adjunctive therapy to β-adrenergic blockers in suppressing CPVT-related arrhythmias.[35] Although preliminary, combination therapy with oral flecainide and β-blocker appeared to be most effective in preventing symptomatic arrhythmia events.

Conclusion

We identified 28 *RYR2* mutation carriers, 1 compound heterozygous *CASQ2* and 1 novel *KCNJ2* mutation carriers in 50 CPVT probands. This is the first report in Japan to analyze 3 different types of CPVT gene and the clinical characteristics of the genotyped CPVT patients. The penetrance of the CPVT phenotype was significantly higher in *RYR2* mutation carriers, thus *RYR2* gene screening in CPVT patients would be indispensable to prevent unexpected cardiac sudden death of young family members.

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Gouty Tophus of the Second Metacarpal Simulating a Malignancy With Pathologic Fracture

To the Editor:

We report on an intraosseous gouty tophus in the second metacarpal causing a pathologic fracture and simulating a malignancy.

A 5-year-old girl with a swollen hand was referred with a diagnosis of a bone tumor. She had been treated for hypoplastic left heart syndrome with protein-loosening enteropathy. She has had 5 surgical interventions, including a fenestrated Fontan procedure. She took many medications, including enalapril maleate. She had generalized edema, hepatosplenomegaly, and ascites. A 2 × 2 cm mass was palpable over the second metacarpal. Slight redness, local heat, and swelling without tenderness were noted. The blood urea nitrogen and uric acid levels were 75.5 mg/dL and 19.1 mg/dL, respectively, much higher than usual, whereas the creatine level was normal, 0.7mg/dL. Total protein was 4.4 g/dL; albumin was 2.8 g/dL; and immunoglobulins were IgG, 128mg/dL; IgA, 30mg/dL and IgM, 56mg/dL, lower than usual. Radiographs showed an ill-marginated lytic and sclerotic legion with a pathologic fracture and periosteal reaction (Fig. 1). Magnetic resonance imaging showed a low–signal-intensity mass on T1-WI and marked high signal intensity on T2-WI surrounding the metacarpus. A needle biopsy was performed. The birefringent crystals suggesting gouty tophus were seen without distinctive inflammatory cellular infiltration histologically. Because of progressively deteriorating renal function, the enalapril maleate was discontinued. Consequently, her renal dysfunction improved, and the uric acid level decreased to 6.4mg/dL. The gouty tophus decreased in size.

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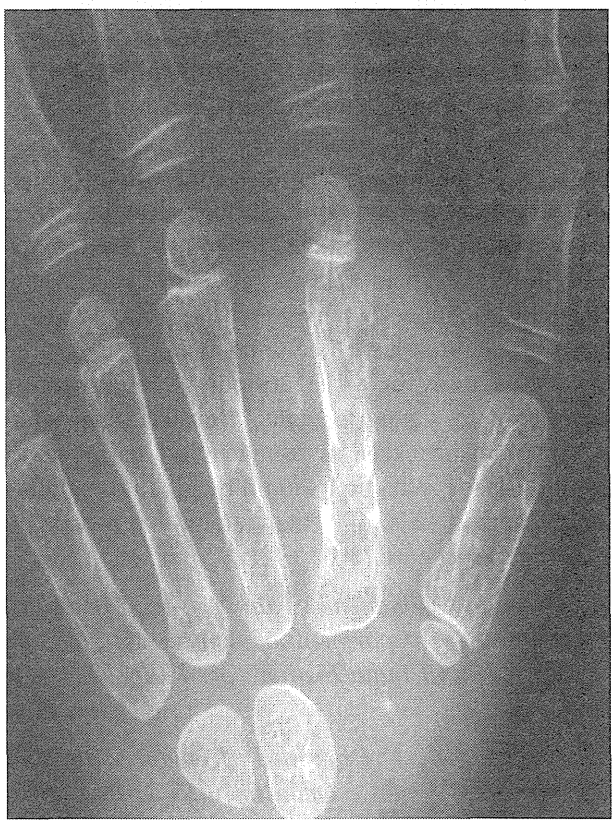

FIGURE 1: Posteroanterior x-ray of the left hand showing a poorly marginated lytic and sclerotic lesion in the second metacarpal associated with periosteal reaction and a pathological fracture.

Enalapril maleate might have caused hyperuricemia and the gouty tophus, which was painless. Hypo-γ-globlinemia might have been responsible for the patient's lack of pain. The immunoglobulin G was strongly absorbed from serum to monosodium urate