Evaluation of Genes Encoding for the Transient Outward Current (Ito) Identifies the KCND2 Gene as a Cause of J-Wave Syndrome Associated With Sudden Cardiac Death

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Background—J-wave ECG patterns are associated with an increased risk of sudden arrhythmic death, and experimental evidence supports a transient outward current (Ito)-mediated mechanism of J-wave formation. This study aimed to determine the frequency of genetic mutations in genes encoding the Ito in patients with J waves on ECG.

Methods and Results—Comprehensive mutational analysis was performed on Ito-encoding KCNA4, KCND2, and KCND3 genes, as well as the previously described J-wave–associated KCNJ8 gene, in 51 unrelated patients with ECG evidence defining a J-wave syndrome. Only patients with a resuscitated cardiac arrest or type 1 Brugada ECG pattern were included for analysis. A rare genetic mutation of the KCND2 gene, p.D612N, was identified in a single patient. Co-expression of mutant and wild-type KCND2 with KChIP2 in HEK293 cells demonstrated a gain-of-function phenotype, including an increase in peak Ito density of 48% (P<0.05) in the heterozygous state. Using computer modeling, this increase in Ito resulted in loss of the epicardial action potential dome, predicting an increased ventricular transmural Ito gradient. The previously described KCNJ8-S422L mutation was not identified in this cohort of patients with ECG evidence of J-wave syndrome.

Conclusions—These findings are the first to implicate the KCND2 gene as a novel cause of J-wave syndrome associated with sudden cardiac arrest. However, genetic defects in Ito-encoding genes seem to be an uncommon cause of sudden cardiac arrest in patients with apparent J-wave syndromes. (Circ Cardiovasc Genet. 2014;7:782-789.)

Key Words: arrhythmias, cardiac ♦ death, sudden, cardiac

Clinical Perspective on p 789

J-wave syndromes refer to a spectrum of ECG observations characterized by early ST-segment takeoff from the terminal QRS or J-point. The associated QRS segment may demonstrate terminal slurring, representing a J wave concealed within the QRS complex, or present a more distinctly visible notch representing a J wave. Brugada syndrome is the most well-characterized J-wave syndrome, both in terms of clinical and genetic features. Alternative patterns of J-wave syndromes have long been recognized, commonly involving the inferolateral ECG leads and until recent years were considered a benign ECG pattern. In 2008, Haïssaguerre and colleagues challenged the concept that inferolateral patterns of J-wave syndromes are a benign entity, reporting a higher prevalence of inferolateral J waves in previously well individuals experiencing a sudden cardiac arrest. Further data corroborated the observation that inferolateral J-wave ECG patterns are prevalent in 20% to 30% of survivors of unexplained cardiac arrest, which is considerably higher than that found in healthy controls.

The electrophysiological mechanism underlying the manifestation of J waves on the ECG has been elegantly demonstrated using ventricular wedge preparations and has been shown to be the result of transmural dispersion of the early repolarizing current, the transient outward current (Ito), which...
mediates phase 1 of the cardiac action potential.\textsuperscript{12–14} Despite insight into this pathophysiology, knowledge of the genetic determinants of J-wave syndromes, aside from Brugada syndrome, remains scarce.

In this study, in view of the known role of I\textsubscript{to} in J-wave formation, we sought to determine the frequency of genetic defects in the predominant I\textsubscript{to}-encoding genes in a population of unexplained cardiac arrest survivors with inferolateral J-wave ECG patterns and additionally in a cohort of type 1 Brugada syndrome patients with previously negative genetic testing results.

Methods

Study Population

The study cohort consisted of 51 unrelated J-wave syndrome patients. J-wave ECG pattern was defined as QRS slurring and notching associated with QRS-ST junction (J-point) elevation of \( \geq 0.1 \text{ mV} \) in a minimum of 2 contiguous leads (Figure I in the online-only Data Supplement). Cases with inferolateral J waves (n=31) were only included for analysis if a history of sudden cardiac arrest requiring defibrillation was documented. These cases represent a subgroup of patients enrolled in the Cardiac Arrest Survivors with Preserved Ejection Fraction Registry (CASPER).\textsuperscript{15} The remaining J-wave syndrome patients consisted of patients demonstrating a spontaneous or provoked type 1 Brugada ECG pattern who had previous negative genetic testing results for the most common gene causative for Brugada syndrome, \( \text{SCN5A} \). Patients were excluded if any coronary artery had stenosis >50% or had anomalous coronary arteries, if imaging demonstrated evidence of hypertrophic cardiomyopathy, if they experienced commotio cordis, or if intravenous adrenaline or treadmill testing suggested a diagnosis of catecholaminergic polymorphic ventricular tachycardia or long QT syndrome.

All patients had documented preserved left ventricular function (ejection fraction >50%) and structure determined by echocardiography and cardiac MRI and normal coronary arteries based on coronary angiography. All patients provided written informed consent, and the study was approved by the institutional review boards of the participating Institutions.

Mutation Analysis

Genomic DNA was extracted from peripheral lymphocytes, and comprehensive open reading frame/splice site mutational analysis of the \( \text{KCNJ8}, \text{KCNA4}, \text{KCND2}, \) and \( \text{KCND3} \) genes was performed using polymerase chain reaction and direct DNA sequencing. DNA from 100 healthy controls was screened for any identified nonsynonymous variant, and cross-reference to the Exome Server Database (http://evs.gs.washington.edu/EVS/) involving >6000 genotyped individuals was used to further assess for the frequency of any identified genetic variant.

Cloning and Mutagenesis

Wild-type \( \text{KCND2} \) (Kv4.2) and \( \text{KCNP2} \) (KChIP2) human cDNA clones were provided by Dr. Peter Backx (University of Toronto). \( \text{KCND2} \) cDNA was subcloned into pRES-DsRed (Clontech, Mountain View, CA) expression vector, and \( \text{KCNP2} \) cDNA was subcloned into pRES-ZsGreen1 (Clontech, Mountain View, CA). The \( \text{KCND2-D612N} \) mutation was engineered from the wild-type \( \text{KCND2} \) clone using the QuikShange XL Site-Directed Mutagenesis Kit (Stratagene, La Jolla, CA). Complete DNA sequencing was undertaken to ensure fidelity of mutant and wild-type clones.

Expression of Kv4.2 and KChIP2 in HEK293 Cells

Heterologous expression of Kv4.2 in HEK293 cells was achieved by cotransfecting 0.5 \( \mu \text{g} \) mutant or wild-type clone with 1.5 \( \mu \text{g} \) of wild-type \( \text{KCNP2} \) clone using 2 \( \mu \text{L} \) of lipofectamine 2000 transfection reagent (Invitrogen, Carlsbad, CA) in 50 \( \mu \text{L} \) OPTI-MEM media (Invitrogen, Carlsbad, CA). For analysis in the heterozygous state, equal quantity of mutant and wild-type clone were mixed (total 0.5 \( \mu \text{g} \)) and cotransfected with \( \text{KCNP2} \).

Electrophysiological Studies and Analysis

After 24 to 48 hours post-transfection, cells emitting both red and green fluorescence were selected for whole cell patch clamp recordings. Patch clamp experiments and analysis were performed blinded to \( \text{KCND2} \)-transfected clones. Patch clamp recordings were made using low-resistance electrodes (<3 \( \text{mL} \)), and a routine series resistance compensation by an Axopatch 200B amplifier (Axon Instruments Inc, Foster City, CA) was performed to minimize voltage-clamp errors. The patch pipette solution contained (mmol/L): 110 KCl, 10 EDTA, 1.42 MgCl\(_2\), 4 MgATP, 5.17 CaCl\(_2\), and 10 HEPES, pH adjusted to 7.2 with Tris-\( \text{OH} \). The extracellular bath solution contained (mmol/L): 148 NaCl, 5 KCl, 2 CaCl\(_2\), 1 MgCl\(_2\), and 10 HEPES, pH adjusted to 7.4 using NaOH. Whole cell current was generated by 500-ms long voltage-clamp command pulses from a holding potential of −80 mV to a voltage of 40 mV in 10 mV increments using pClamp 10.3 software (Axon Instruments Inc). Currents were filtered at 5 kHz and sampled at 10 kHz. Specific voltage-clamp protocols used to determine voltage dependence of activation, inactivation, and recovery from inactivation are illustrated in the figure legend. All experiments were performed at room temperature. Data were digitally stored and analyzed using pClamp 10.3 and Prism 3.03 (GraphPad Software Inc, San Diego, CA) software. The voltage-dependent inactivation curve was fitted with the Boltzmann equation: \( I = I_\text{max} \left( 1 + \frac{V}{V_{50}} \right)^{-k} \), where \( V_{50} \) is the membrane potential of half-maximal inactivation and \( k \) is the slope of the inactivation curve.

Recovery from inactivation curves were fitted with the 1-phase exponential association equation: \( I = I_0 (1 - e^{-\frac{V}{\tau}}) \), where \( \tau \) is the time constant of the exponent.

Simulated Transmural Right Ventricular Action Potential Propagation

We simulated action potential propagation across the right ventricular (RV) wall in a theoretical 1.45 cm fiber using a modified Luo-Rudy II myocyte model adjusted to incorporate \( I_\text{to} \).\textsuperscript{16} For control simulations, the conductance of RV \( I_\text{to} \) was set to 1.1 mS/\( \mu \text{F} \) in the epicardium and 0.93 mS/\( \mu \text{F} \) in the midmyocardial layer; \( I_\text{to} \) was not expressed in the endocardium.\textsuperscript{17} For Kv4.2-wild-type (WT)/D612N, \( I_\text{to} \) was increased by 48% in agreement with our experimental results with heterozygous expression. For mutant and control simulations, the conductance of \( I_\text{to} \) was reduced in the midmyocardium and epicardium by 25% to compensate for a decrease in action potential duration associated with high \( I_\text{to} \) expression.\textsuperscript{16} The density of \( I_\text{to} \) (rapid delayed rectifier potassium current) to \( I_\text{to} \) (slow delayed rectifier potassium current) varied across the fiber: 11:1 (endocardium), 4:1 (midmyocardium), and 35:1 (epicardium).\textsuperscript{17} Extracellular ion concentrations were as follows: [\( \text{Na}_0 \]=150 mmol/L/L, [\( \text{K}_0 \]=4.0 mmol/L/L, and [\( \text{Ca}_0 \]=1.8 mmol/L/L. The fiber was paced with a 1-ms suprathreshold stimulus at a cycle length of 1000 ms and at 37°C for 20 beats before analysis to allow equilibration of intracellular calcium. Simulations were performed in Mathematica 9.01 (Wolfram Technologies, Champaign, IL).

Statistical Methods

All electrophysiological data are expressed as mean±standard error of the mean (SEM). Determinations of statistical significance of differences between means in control (WT) and mutant channel constructs (D612N and WT/D612N mutants) under the various experimental conditions were performed using an unpaired, 2-tailed Student \( t \) test (GraphPad Prism). Differences were deemed significant at a \( P \) value <0.05.

Results

Clinical and Genetic Data

A total of 51 patients with a J-wave syndrome were screened for genetic mutations in genes encoding the potassium
subunits responsible for Ito in the heart (KCND2, KCND3, and KCNA4). These patients were also screened for genetic defects in the cardiac I_{K-ATP} channel (KCNJ8), a channel previously attributed to being a cause of J-wave syndrome.\textsuperscript{18–21}

To avoid screening presumably benign forms of J-wave syndrome, we restricted our inclusion to patients with inferior, lateral, or inferolateral J-wave patterns who had previously experienced an otherwise unexplained cardiac arrest requiring defibrillation for resuscitation. This group comprises 61% of our cohort, all were white, 81% were male, and the average age at the time of cardiac arrest was 43±12 years. An additional 20 patients with spontaneous or drug-provoked type 1 Brugada ECG pattern and previous negative genetic testing for the SCN5A gene were also screened. The average age of this group was 43±15 years, 90% were male, and 2 patients were non-white (1 African, 1 Asian). Sporadic cases represented 75% of this group. A history of resuscitated sudden cardiac arrest was present in 4 patients (20%), and syncope in 6 patients (30%).

In a single patient, a rare missense mutation was identified in the Ito-encoding KCND2 gene (Figure 1A), a gene not previously described to be a cause of inherited arrhythmia syndromes. The identified mutation, denoted c.1834 G>A, leads to the substitution of a highly conserved aspartate (D) residue for asparagine (N) at position 612 in the protein (p.D612N; Figure 1B). This variant was absent from 200 alleles of local, healthy control samples. Reference to the exome server database indicates that KCND2-D612N is a rare allele in individuals of undefined clinical background, observed in 2 of 13,004 alleles, one third of which are of African decent.

The affected patient, previously well and of African decent, experienced a sudden cardiac arrest at age 51 years while eating in a restaurant and received 2 defibrillation shocks by paramedics with ultimate return to normal sinus rhythm. Coronary angiography, echocardiography, and cardiac MRI were all normal. Twelve-lead ECG demonstrated large J waves across the anterior precordial leads, evidence for right bundle conduction delay with shallow S waves in lead I and V6, and notable broad, fractionated QRS complexes in leads V1/V2 (Figure 2). Intravenous procainamide provocation (1 g) did not change the QRS pattern but resulted in a ventricular couplet and triplet at 30 minutes of infusion. Clinically, it was felt that this ECG pattern was not consistent with the Brugada ECG pattern but rather represented an unusual J-wave syndrome. However, because of the similar ECG localization of J waves, the patient was screened for genetic defects in reported Brugada syndrome susceptibility genes, including SCN5A, GPD1L, CACNA1C, CACNB2, SCN1B, KCNE3, and SCN3B. No rare genetic variants were identified. The patient underwent placement of an implantable cardioverter-defibrillator.

Figure 1. KCND2 gene mutation and biological conservation of Kv4.2 amino acid structure. A, DNA sequence chromatogram indicating the mutation within the KCND2 gene. B, D612 is highly conserved across species.
Family history was negative for known premature (age <55 years) sudden cardiac death, and cascade family screening has been declined. Over a clinical follow-up of 7 years, the patient has remained off medical therapy and has not received any device therapy for recurring arrhythmias.

**Cellular Electrophysiological Analysis**

To functionally characterize the biophysical consequences of KCND2-D612N, we coexpressed this mutant clone and KCND2-WT along with KChIP2-WT in HEK293 cells to reconstitute Kv4.2-mediated I\textsubscript{to} in vitro. In the homozygous state, Kv4.2-D612N significantly increased I\textsubscript{to} density over the voltage range from −10 mV to +40 mV compared with Kv4.2-WT (n=13 and 17, respectively; P<0.05; Figure 3A and 3B). To recapitulate the heterozygous state, equal quantities of Kv4.2-WT and Kv4.2-D612N were coexpressed with KChIP2-WT and similarly demonstrated a significant increase in I\textsubscript{to} density, including a 50% increase in peak current density at 0 mV (n=17 and 11, respectively; P<0.05; Figure 3C). Further studies evaluating the kinetics of WT or mutant channels demonstrated that Kv4.2-WT/D612N had a significantly slower decay rate (tau) over the voltage range of 30 to 40 mV compared with Kv4.2-WT channels (Figure 4A; P<0.05). No significant difference was observed in the inactivation of I\textsubscript{to} or recovery from inactivation between WT and heterozygote channels (Figure 4B and 4C). However, Kv4.2-WT/D612N significantly increased I\textsubscript{to} total charge over the range of −30 to 40 mV in comparison with Kv4.2-WT (P<0.05; Figure 4D).

**RV Action Potential Propagation of Kv4.2-WT and Kv4.2-WT/D612N**

We simulated action potential propagation across the RV myocardium with and without the experimentally observed gain in function in KCND2- I\textsubscript{to} using a modified Luo-Rudy II model.\textsuperscript{16} In control simulations at a pacing cycle length of 1000 ms, a deep notch (spike and dome) was observed in the epicardial layer (Figure 5A). In contrast, a 48% increase in I\textsubscript{to} as predicted by heterozygote Kv4.2-WT/D612N channels, resulted in stable loss of the dome of the action potential in the epicardial layer (Figure 5B).

**Discussion**

We evaluated the role of I\textsubscript{to}-encoding genes in a cohort of patients with J-wave syndromes, the majority of individuals having experienced a sudden cardiac arrest. Our data suggest a low yield of genetic abnormalities in the major genetic contributors of the I\textsubscript{to} for patients with established cardiac arrest and evident inferolateral or anterior ECG J waves. However, we did observe the novel association of a rare, gain-of-function mutation in the KCND2 gene in a patient with sudden cardiac arrest and an anterior J-wave ECG pattern.\textsuperscript{12} Exacerbation of this natural epicardial to endocardial gradient, either by increased outward current (I\textsubscript{to}, I\textsubscript{KATP}) or
decreased inward current ($I_{Na}$, $I_{Ca}$), results in the manifestation of the ECG J wave and creates an arrhythmia substrate for arrhythmia (phase 2 reentry).\textsuperscript{13,14} Based principally on remote gene expression studies using canine left ventricular tissue, the molecular correlates for $I_{to}$ have been deemed to predominantly involve the \textit{KCND3}-encoded Kv4.3 channel, and \textit{KCHIP2}, which encodes an accessory subunit required for channel function.\textsuperscript{22,23} Traditionally, the role of the pore-forming Kv4.2 subunit encoded by \textit{KCND2} has not been considered significant within human myocardium in light of these previous observations. However, in a unique study evaluating regional gene expression of 79 ion channel genes within nondiseased human hearts, \textit{KCND2} gene expression demonstrated the highest differential expression pattern between RV epicardium and endocardium, the gradient exceeding but mirrored by \textit{KCHIP2} expression.\textsuperscript{24} Conversely, \textit{KCND3} did not exhibit a transmural gradient in expression within the RV or LV.\textsuperscript{24} These data suggest that Kv4.2 channels, along with \textit{KCHIP2}, may represent the molecular correlate for $I_{to}$ gradient across the RV myocardium.

Our data are the first to implicate the \textit{KCND2} gene as a cause of an atypical anterior J-wave pattern associated with sudden cardiac death. Although the ECG features were not typical of the more classically recognized anterior J-wave pattern of Brugada syndrome, the observations of right bundle conduction delay and notable QRS fractionation have been recognized features in some cases of Brugada syndrome.\textsuperscript{25} Giudicessi et al\textsuperscript{17} have reported the identification of mutations within \textit{KCND3} in 2 patients with more classic type 1 Brugada ECG patterns. Similar to our observation, the observed genetic variants in \textit{KCND3}, Kv4.3-L450F and Kv4.3-G600R, occurred within the C-terminus of the channel and were highly conserved across mammals. All these mutants result in a significant increase in $I_{to}$, whereas Kv4.3-G600R and our described Kv4.2-D612N mutant share the observation of a significant decrease in current decay rate. Interestingly, site-directed mutagenesis studies in vitro of the highly homologous Kv4.1 channel indicate that deletion of C-terminal residues 422 to 651 results in a significant delay of current decay, suggesting a major role of C-terminal residues in channel inactivation.\textsuperscript{26}

The possible in vivo effect of the \textit{KCND2} mutant was confirmed in simulated cardiac action potential propagation across the RV wall using a modified Luo-Rudy II human myocyte model.\textsuperscript{16} With an increase in $I_{to}$ (48%) in line with our experimental results from heterozygous expression of Kv4.2-WT/D612N, we observed complete and stable loss of the dome of the action potential in the epicardial layer. This observation predicts the formation of ECG J waves, as demonstrated by Antzelevitch and Yan,\textsuperscript{14} and creates the risk of propagation of the action potential dome from sites where it is maintained to sites where it is lost, producing local reexcitation (phase 2 reentry) and generation of polymorphic ventricular arrhythmia.\textsuperscript{12,13} Furthermore, the facilitation of

![Figure 3. Kv4.2-D612N plus KChIP2 increase $I_{to}$ in heterologously transfected cells.](http://circgenetics.ahajournals.org/)

A, Representative whole-cell Kv4.2-WT plus KChIP2-WT (left), Kv4.2-WT/D612N plus KChIP2-WT (middle), and Kv4.2-D612N traces recorded in HEK293 cells in response to a series of depolarizing step voltage commands of 500-ms duration, shifting the membrane potential from a holding potential of −80 mV to +40 mV in 10 mV increments. B, The current-voltage relationships for Kv4.2-WT (n=17) and Kv4.2-WT/D612N (n=11) channels coexpressed with KChIP2-WT. Each experimental data point represents mean±SEM. C, Bar graph showing peak current density at 0 mV for WT (n=17), WT/D612N (n=11), and D612N (n=13) Kv4.2 channels coexpressed with KChIP2-WT. *P<0.05.
heterogeneous action potential durations within the RVOT induced by Kv4.2-D612N may lead to relative delayed activation of epicardial regions, delaying depolarization in some regions and manifesting as late potentials or a fractionated QRS, as observed in our patient. This phenomenon has been elegantly demonstrated by Morita and colleagues using a canine, RV transmural myocardial preparation. Delayed pacing of the epicardial tissue relative to endocardium reproduced increasing QRS duration and fractionation, dependent on the degree of epicardial activation delay.

In addition to evaluating genes that specifically encode the subunits responsible for $I_{to}$, we screened the KCNJ8 gene that encodes $I_{K-ATP}$. Previous studies, using a candidate gene approach, have implicated the gain-of-function mutation KCNJ8-S422L mutation as a susceptibility mutation for inferolateral and anterior J waves in 1% to 2% of patients. In a manner similar to the direct evidence demonstrated for enhanced $I_{to}$, increased early repolarizing $I_{K-ATP}$ current is speculated to accentuate phase 1 of the cardiac action potential, leading to loss of the epicardial action potential dome and ECG J-wave formation. In our cohort of 51 J-wave patients, the majority of which had experienced cardiac arrest, we did not identify this specific mutation or other rare variants within KCNJ8. Recent data from the exome server database in over 4000 whites suggest a frequency of 0.5% of KCNJ8-S422L. Furthermore, Veeramah et al report a 4% frequency of this variant in Ashkenazi Jews, including a homozygote 12-year male with apparent normal ECG. These observations do not preclude the role of KCNJ8 in J-wave syndromes. However, cautious interpretation and consideration of other modifying genes in the presence of KCNJ8-S422L should be considered.

Overall, genetic interpretation based on candidate gene studies for J-wave syndromes remains a challenge in view of the often sporadic, nonfamilial nature of these cases and
relatively common frequencies of these ECG patterns in otherwise healthy individuals. A recent genome-wide association study in J-wave syndromes did not succeed in identifying a definitive genetic locus, likely reflecting the considerable genetic heterogeneity and possible polygenic nature of the phenotype.28

Study Limitations
Our cohort represents patients with persistent J-wave patterns and therefore because of study design has excluded cases of sudden death that may have occurred as a result of dynamic J-wave changes. Such a population may represent a genetically unique cohort. We did not screen the comprehensive list of reported susceptibility genes for Brugada syndrome in all our cases of Brugada syndrome. However, our goal was not to reassess the already known low frequency of non-SCN5A mutations in this cohort but rather to assess novel genes responsible for I_{to} in the heart in patients with various J-wave patterns. We have not provided the most robust genetic evidence supporting KCND2 as a disease-causing gene, which is best exemplified by segregation of the mutation with multiple affected individuals within a family. However, our data are consistent with previous reports implicating altered I_{to} physiology in the heart as a cause for J-wave formation and arrhythmogenesis. Follow-up data in larger cohorts will better clarify the role of the KCND2 gene in sudden death associated with J-wave ECG patterns.

Conclusions
This study provides clinical, molecular, and functional evidence, implicating the KCND2 gene as a novel susceptibility gene contributing to an anterior J-wave ECG pattern associated with sudden cardiac death.

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Disclosures
None.

References


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**CLINICAL PERSPECTIVE**

J-wave syndrome refers to an ECG pattern characterized by terminal QRS slurring and notching associated with QRS-ST junction (J-point) elevation of ≥0.1 mV in a minimum of 2 contiguous leads, coupled with an established or presumed risk of malignant ventricular arrhythmia. The most common J-wave syndrome, the Brugada syndrome, has been well characterized at the molecular level, and experimental evidence has implicated a transmural gradient of the transient outward potassium current (Ito) as a mechanism for ECG J-wave formation. In this study, we provide clinical and functional data implicating the KCND2 gene, which encodes a major subunit of the Ito channel, as a potential cause of anterior ECG J waves associated with sudden cardiac death. Overall, however, genetic defects in genes encoding components of Ito or directly influencing Ito seem to be an uncommon cause of typical J-wave syndromes.
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Supplemental Material
Most common ECG of cohort demonstrating infero-lateral J wave pattern in a patient who experienced a sudden cardiac arrest while sleeping. The patient was successfully resuscitated.
Supplemental Figure 1B

ECG of case subject showing predominant lateral J wave pattern. The patient experienced a sudden cardiac arrest while eating dinner.