Thank you, Andres, for this interesting short manuscript. Our contribution to this phenomenon (Ref 5) is mentioned but I wonder whether you agree with the message in that paper, i.e. that the amplitude of the U-wave depends on the amplitude of the IK1 current. That, in our opinion, is an argument for the idea that a small deviation of the ultimate resting membrane potential due to not fully activated IK1 may lead to a small deviation on the ECG. When this deviation becomes bigger, i.e. in the presence of reduced IK1, the U-wave becomes bigger and when the deviation becomes smaller the U-wave becomes smaller in amplitude. With the mapping of the 2 gain of function IK1 mutations we actually predicted that these 2 pts were the only 2 pts without a U-wave but that appeared not completely true.

I'm interested in your comment(s)

Very best

Arthur AA Wilde

Van: Andrés Pérez-Riera <arperezriera@gmail.com>

Verzonden: woensdag 22 januari 2020 1:03

Aan: Bernard Belhassen <bblhass@gmail.com>; Pedro Brugada <pedro@brugada.org>

Onderwerp: The forgotten wave of the ECG : The U wave

Dear friends I am sending a forgotten topic about the U wave

Enjoy It

Andrés.

Dear Arthur thank for your prompt comments. First excuse me for the extensive explanation but I think that is necessary.

U wave and the cardiac inwardly rectifying K^+ current relationship and the U-wave in genetic entities

The cardiac inwardly rectifying potassium current (I(K1)) stabilizes the resting membrane potential and is responsible for shaping the initial depolarization and final repolarization, and resting phases of the ventricular action potential (AP). (**Ibarra J, Morley GE, Delmar M. Dynamics of the inward rectifier K current during the action potential of guinea pig ventricular myocytes. Biophys J 1991; 60:1534 –1539**). The inwardly rectifying K^+ channel (Kir2.x) subfamily members primarily mediate cardiac I(K1), but other inward rectifiers, including the acetylcholine-sensitive (Kir3.x) and ATP-sensitive (Kir6.x) inward rectifiers, also may modulate cardiac excitability.

I(K1) plays a role in ventricular arrhythmias, highlighted by the described Andersen's Tawil syndrome (ATS) and studies in the guinea pig heart model of VF. (**Plaster NM, Tawil R, Tristani-Firouzi M, Canun S, Bendahhou S, Tsunoda A, Donaldson MR, Iannaccone ST, Brunt E, Barohn R, Clark J, Deymeer F, George AL, Fish FA, Hahn A, Nitu A, Ozdemir C, Serdaroglu P, Subramony SH, Wolfe G, Fu Y, Ptacek LJ. Mutations in kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. Cell 2001;105:511–519**) The classification of ATS as part of the congenital LQTS is polemic. Tristani Firouzi et al. classify ATS as LQT7 variant (**Tristani-Firouzi M, Jensen JL, Donaldson MR , et al. Functional and clinical characterization of KCNJ2 mutations associated with LQTS 7 (Andersen syndrome). J Clin Invest. 2002;110:381–8**.). The first descriptions of ATS and its ECG manifestations included the U–wave as part of the QT interval thus overestimating the true QT interval. In this way, all ATS patients presented with prolonged QT intervals. Zhang *et al*. were the first to offer a solution for this dilemma: the true QT interval is normal in almost all ATS1 patients if the U-wave is excluded from the measurement. The corrected QT interval in ATS1 patients was 440 ms vs 420 ms in matched normal subjects and the distribution of the QTc interval in ATS1 patients overlapped with the normal subjects in 87 %, of cases. The corrected Q-U interval was significantly longer in ATS1 patients than matched normal subjects at 655 ms vs 600 ms respectively. (**Zhang L, Benson DW, Tristani-Firouzi Metal. Electrocardiographic features in Andersen-Tawil syndrome patients with KCNJ2 mutations characteristics T-U-wave patterns**

predict the KCNJ 2 genotype. Circulation. 2005;111:2720–6.) A manifest U-wave is present in about 30 % of patients with CPVT and in about 90 % of ATS1 patients (**Aizawa Y, Komura S, Okada S , et al. Distinct U wave changes in patients with catechoalminergic polymorphic ventricular tachycardia. Int Heart J. 2006;47:381–9**.). A prominent U-wave in ATS1 patients is best seen in leads V2-V3-V4 and in the limb leads. Although U-waves can be observed in normal individuals at low heart rates(HRs), during parasympathetic stimulation or in hypokalemic states (**Surawicz B. U wave: facto. hypothses. misconceptions., and misnomers. J. Cardiovasc. Electrophysiol. 1998; 9:1117–28**.), on the other hands in ATS1 patients U-waves occur at faster HRs.

In LQT4, 4q25–27 (ankyrin B mutation), Ankyrin-B (ANK2) adapter protein the surface ECG can display a prominent U-wave, usually associated with bradycardia or AV dissociation, and borderline QTc prolongation (**Mohler PJ, Schott JJ, Gramolini AO , et al. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. Nature. 2003;421(6923):634–9**.).

In ATS patients, Zhang *et al*. described abnormal prominent U-wave and increased QT-U interval but not QT interval prolongation. They showed that abnormal T- U wave was present in 91 % of the patients with ATS-KCNJ2 mutations. These abnormalities included: Prolonged terminal portion of the T-wave descending in ≈ 70 % of the cases, wide T- U wave junction(≈ 43 % of the cases), biphasic U-wave (≈ 16 % of the cases) and large U-wave in 73 % of the cases. These ECG abnormalities had a high predictive accuracy for KCNJ-2 mutation (ATS1) with sensitivity, specificity, positive and negative predictive value at 84%, 97%, 94% and 91 % respectively. In ATS1, T-wave duration was found to be longer than normal matched subjects or non-KCNJ2-mutation patients; 220 ms vs 190 ms vs 200 ms, respectively. There was no difference in T-wave amplitude between the groups Similarly, the U-wave duration was longer in ATS1 pts compared to ATS-non-KCNJ 2 mutation or normal subjects; 210 ms vs 165 ms vs 170 ms, respectively. The U-wave amplitude was higher in ATS1 – 0. 15 mV than normal subjects - 0.08 mV. Finally, the T peak – U peak interval was increased in ATS1 patients compared to ATS-non-KCNJ 2 mutation and normal subjects; 240 ms vs 175 ms vs 180 ms, respectively. A channel that is "inwardly-rectifying" is one that passes current (positive charge) more easily in the inward direction than out of the cell. It is thought that this current may play an important role in regulating neuronal activity, by helping to stabilize the resting membrane potential. By convention, inward current is displayed in voltage

clamp as a downward deflection, while an outward current is shown as an upward deflection. At membrane potentials negative to potassium's reversal potential, inwardly rectifying K^+ channels support the flow of positively charged K^+ into the cell, pushing the membrane potential back to the resting potential. This can be seen in figure 1 below:

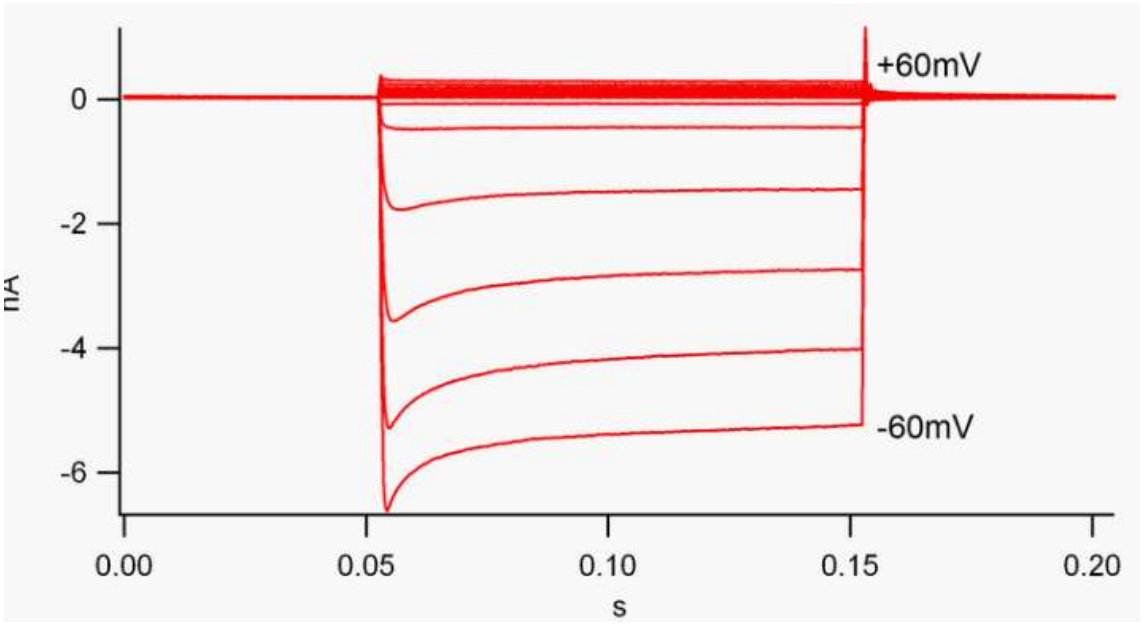


Figure 1. Whole-cell current recordings of Kir2 inwardly-rectifying K^+ channels expressed in an HEK293 cell. (This is a strongly inwardly rectifying current. Downward deflections are inward currents, upward deflections outward currents, and the x-axis is time in seconds.) There are 13 responses superimposed in this image. The bottom-most trace is current elicited by a voltage step to -60mV, and the top-most to +60mV, relative to the resting potential, which is close to the K^+ reversal potential in this experimental system. Other traces are in 10mV increments between the two. when the membrane potential is clamped negative to the channel's resting potential (e.g. -60 mV), inward current flows (i.e. positive charge flows into the cell). However, when the membrane potential is set positive to the channel's resting potential (e.g. +60 mV), these channels pass very little current. Simply put, this channel passes much more current in the inward direction than the outward one, at its operating voltage range. These channels are not perfect rectifiers, as they can pass some outward current in the voltage range up to about 30 mV above resting potential. These channels differ from the K^+ channels that are typically responsible for repolarizing a cell following an AP, such as the delayed rectifier and A-type K^+ channels. Those more "typical" K^+ channels preferentially carry outward (rather than inward) K^+ currents at depolarized membrane potentials, and may be thought

of as "outwardly rectifying." When first discovered, inward rectification was named "anomalous rectification" to distinguish it from outward K^+ currents. (**Bertil Hille (2001). Ion Channels of Excitable Membranes 3rd ed. (Sinauer: Sunderland, MA), p. 151. ISBN 0-87893-321-2**.). Inward rectifiers also differ from tandem pore domain K^+ channels, which are largely responsible for "leak" K^+ currents. Some inward rectifiers, termed "weak inward rectifiers", carry measurable outward K^+ currents at voltages positive to the K^+ reversal potential (corresponding to, but larger than, the small currents above the 0 nA line in figure 1). They, along with the "leak" channels, establish the resting membrane potential of the cell. Other inwardly rectifying channels, termed "strong inward rectifiers," carry very little outward current at all, and are mainly active at voltages negative to the K^+ reversal potential, where they carry inward current (the much larger currents below the 0 nA line in figure 1). The phenomenon of inward rectification of Kir channels is the result of high-affinity block by endogenous polyamines, namely spermine, as well as magnesium ions, that plug the channel pore at positive potentials, resulting in a decrease in outward currents. This voltage-dependent block by polyamines results in efficient conduction of current only in the inward direction. While the principal idea of polyamine block is understood, the specific mechanisms are still controversial. (**Lopatin AN, Makhina EN, Nichols CG (November 1995). "The mechanism of inward rectification of potassium channels: "long-pore plugging" by cytoplasmic polyamines". The Journal of General Physiology. 106 (5): 923–55. doi:10.1085/jgp.106.5.923. PMC 2229292. PMID 8648298**.).

Activation by PIP2

All Kir channels require phosphatidylinositol 4,5-bisphosphate (PIP2) for activation. (**Tucker SJ, Baukrowitz T (May 2008). "How highly charged anionic lipids bind and regulate ion channels". The Journal of General Physiology. 131 (5): 431–8. doi:10.1085/jgp.200709936. PMC 2346576. PMID 18411329**.) PIP2 binds to and directly activates Kir 2.2 with agonist-like properties. (**Hansen SB, Tao X, MacKinnon R (September 2011). "Structural basis of PIP2 activation of the classical inward rectifier K+ channel Kir2.2". Nature. 477 (7365): 495–8. Bibcode:2011Natur.477..495H. doi:10.1038/nature10370. PMC 3324908. PMID 21874019**.) In this regard Kir channels are PIP2 ligand-gated ion channels.

Role of Kir channels

Kir channels are found in multiple cell types, including macrophages, cardiac and kidney cells, leukocytes, neurons, and endothelial cells. By mediating a small depolarizing K+ current at negative membrane potentials, they help establish resting membrane potential, and in the case of the Kir3 group, they help mediate inhibitory neurotransmitter responses, but their roles in cellular physiology vary across cell types:

Location	**Function**
Cardiac Myocyte	Kir channels close upon depolarization, slowing membrane repolarization and helping maintain a more prolonged cardiac AP. This type of inward-rectifier channel is distinct from delayed rectifier K+ channels, which help repolarize nerve and muscle cells after APs; and K+ leak channels, which provide much of the basis for the resting membrane potential.
Endothelial cells	Kir channels are involved in regulation of nitric oxide synthase.
Kidneys	Kir export surplus potassium into collecting tubules for removal in the urine, or alternatively may be involved in the reuptake of potassium back into the body.
Neurons and in heart cells	G-protein activated IRKs (Kir3) are important regulators, modulated by neurotransmitters. A mutation in the GIRK2 channel leads to the weaver mouse mutation. "Weaver" mutant mice are ataxic and display a neuroinflammation-mediated degeneration of their dopaminergic neurons**. (Peng J, Xie L, Stevenson FF, Melov S, Di Monte DA, Andersen JK (November 2006). "Nigrostriatal dopaminergic neurodegeneration in the weaver mouse is mediated via neuroinflammation and alleviated by minocycline administration". The Journal of Neuroscience. 26 (45): 11644–51. doi:10.1523/JNEUROSCI.3447-06.2006. PMC 6674792. PMID 17093086**.) Relative to non-ataxic controls, Weaver mutants have deficits in motor coordination and changes in regional brain metabolism. (**Strazielle C, Deiss V, Naudon L, Raisman-Vozari R, Lalonde R (October 2006). "Regional**

	brain variations of cytochrome oxidase activity and motor coordination in Girk2(Wv) (Weaver) mutant mice". Neuroscience. 142 (2): 437–49. doi:10.1016/j.neuroscience.2006.06.011. PMID 1684430) Weaver mice have been examined in labs interested in neural development and disease for over 30 years.
Pancreatic β cells	KATP channels (composed of Kir6.2 and SUR1 subunits) control insulin release.

Regulation

Voltage-dependence may be regulated by external K+, by internal Mg2+, by internal ATP and/or by G-proteins. The P domains of IRK channels exhibit limited sequence similarity to those of the VIC family. Inward rectifiers play a role in setting cellular membrane potentials, and closing of these channels upon depolarization permits the occurrence of long duration APs with a plateau phase. Inward rectifiers lack the intrinsic voltage sensing helices found in many VIC family channels. In a few cases, those of Kir1.1a, Kir6.1 and Kir6.2, for example, direct interaction with a member of the ABC superfamily has been proposed to confer unique functional and regulatory properties to the heteromeric complex, including sensitivity to ATP. These ATP-sensitive channels are found in many body tissues. They render channel activity responsive to the cytoplasmic ATP/ADP ratio (increased ATP/ADP closes the channel). The human SUR1 and SUR2 sulfonylurea receptors (spQ09428 and Q15527, respectively) are the ABC proteins that regulate both the Kir6.1 and Kir6.2 channels in response to ATP, and CFTR (TC #3.A.1.208.4) may regulate Kir1.1a.(**WO application 0190360, Wei MH, Chaturvedi K, Guegler K, Webster M, Ketchum KA, Di Francesco V, Beasley E, "Isolated human transporter proteins, nucleic acid molecules encoding human transporter proteins, and uses thereof", published 29 November 2001, assigned to Apperla Corporation**).

Classification of Kir channels

There are seven subfamilies of Kir channels, denoted as Kir1 - Kir7.(**Kubo Y, Adelman JP, Clapham DE, Jan LY, Karschin A, Kurachi Y, Lazdunski M, Nichols CG, Seino S, Vandenberg CA (December 2005). "International Union of Pharmacology. LIV. Nomenclature and Molecular Relationships of Inwardly Rectifying Potassium Channels". Pharmacological Reviews. 57 (4): 509–26. doi:10.1124/pr.57.4.11. PMID**

16382105.) Each subfamily has multiple members (i.e. Kir2.1, Kir2.2, Kir2.3, etc.) that have nearly identical amino acid sequences across known mammalian species. Kir channels are formed from as homotetrameric membrane proteins. Each of the four identical protein subunits is composed of two membrane-spanning alpha helices (M1 and M2). Heterotetramers can form between members of the same subfamily (i.e. Kir2.1 and Kir2.3) when the channels are overexpressed.

Gene	**Protein**	**Aliases**	**Associated subunits**
KCNJ1	$K_{ir}1.1$	ROMK1	NHERF2
KCNJ2	$K_{ir}2.1$	IRK1	$K_{ir}2.2$, $K_{ir}4.1$, PSD-95, SAP97, AKAP79
KCNJ3	$K_{ir}3.1$	GIRK1, KGA	$K_{ir}3.2$, $K_{ir}3.4$, $K_{ir}3.5$, $K_{ir}3.1$ is not functional by itself
KCNJ4	$K_{ir}2.3$	IRK3	$K_{ir}2.1$ and $K_{ir}2.3$ to form heteromeric channel, PSD-95, Chapsyn-110/PSD-93
KCNJ5	$K_{ir}3.4$	GIRK4	$K_{ir}3.1$, $K_{ir}3.2$, $K_{ir}3.3$
KCNJ6	$K_{ir}3.2$	GIRK2	$K_{ir}3.1$, $K_{ir}3.3$, $K_{ir}3.4$ to form heteromeric channel
KCNJ8	$K_{ir}6.1$	K_{ATP}	SUR2B
KCNJ9	$K_{ir}3.3$	GIRK3	$K_{ir}3.1$, $K_{ir}3.2$ to form heteromeric channel
KCNJ10	$K_{ir}4.1$	$K_{ir}1.2$	$K_{ir}4.2$, $K_{ir}5.1$, and $K_{ir}2.1$ to form heteromeric channels
KCNJ11	$K_{ir}6.2$	K_{ATP}	SUR1, SUR2A, and SUR2B

KCNJ12	$K_{ir}2.2$	IRK2	$K_{ir}2.1$ and $K_{ir}2.3$ to form heteromeric channel, auxiliary subunit: SAP97, Veli-1, Veli-3, PSD-95
KCNJ13	$K_{ir}7.1$	$K_{ir}1.4$	
KCNJ14	$K_{ir}2.4$	IRK4	$K_{ir}2.1$ to form heteromeric channel
KCNJ15	$K_{ir}4.2$	$K_{ir}1.3$	
KCNJ16	$K_{ir}5.1$	BIR 9	

Diseases related to Kir channels

Persistent hyperinsulinemic hypoglycemia of infancy is related to autosomal recessive mutations in Kir6.2. Certain mutations of this gene diminish the channel's ability to regulate insulin secretion, leading to hypoglycemia.

Bartter's syndrome can be caused by mutations in Kir channels. This condition is characterized by the inability of kidneys to recycle K+, causing low levels of potassium in the body. Bartter syndrome is a group of very similar kidney disorders that cause an imbalance of potassium, sodium, chloride, and related molecules in the body. In some cases, Bartter syndrome becomes apparent before birth. The disorder can cause polyhydramnios, which is an increased volume of fluid surrounding the fetus (amniotic fluid). Polyhydramnios increases the risk of premature birth. Beginning in infancy, affected individuals often fail to grow and gain weight at the expected rate (failure to thrive). They lose excess amounts of salt (sodium chloride) in their urine, which leads to dehydration, constipation, and increased urine production (polyuria). In addition, large amounts of calcium are lost through the urine (hypercalciuria), which can cause weakening of the bones (osteopenia). Some of the calcium is deposited in the kidneys as they are concentrating urine, leading to hardening of the kidney tissue (nephrocalcinosis). Bartter syndrome is also characterized by low levels of potassium in the blood (hypokalemia), which can result in muscle weakness, cramping, and fatigue. Rarely, affected children develop hearing loss caused by abnormalities in the inner

ear (sensorineural deafness). Two major forms of Bartter syndrome are distinguished by their age of onset and severity. One form begins before birth (antenatal) and is often life-threatening. The other form, often called the classical form, begins in early childhood and tends to be less severe. Once the genetic causes of Bartter syndrome were identified, researchers also split the disorder into different types based on the genes involved. Types I, II, and IV have the features of antenatal Bartter syndrome. Because type IV is also associated with hearing loss, it is sometimes called antenatal Bartter syndrome with sensorineural deafness. Type III usually has the features of classical Bartter syndrome. The exact prevalence of this disorder is unknown, although it likely affects about 1 per million people worldwide. The condition appears to be more common in Costa Rica and Kuwait than in other populations. Bartter syndrome can be caused by mutations in at least five genes. Mutations in the SLC12A1 gene cause type I. Type II results from mutations in the KCNJ1 gene. Mutations in the CLCNKB gene are responsible for type III. Type IV can result from mutations in the BSND gene or from a combination of mutations in the CLCNKA and CLCNKB genes. The genes associated with Bartter syndrome play important roles in normal kidney function. The proteins produced from these genes are involved in the kidneys' reabsorption of salt. Mutations in any of the five genes impair the kidneys' ability to reabsorb salt, leading to the loss of excess salt in the urine (salt wasting). Abnormalities of salt transport also affect the reabsorption of other charged atoms (ions), including potassium and calcium. The resulting imbalance of ions in the body leads to the major features of Bartter syndrome. In some people with Bartter syndrome, the genetic cause of the disorder is unknown. Researchers are searching for additional genes that may be associated with this condition.

Andersen's Tawil syndrome (ATS) It is inherited in an autosomal dominant manner. At least 50% of individuals diagnosed with ATS have an affected parent. Up to 50% of affected individuals have ATS as the result of a *de novo* pathogenic variant. Each child of an individual with ATS has a 50% chance of inheriting the disorder. Prenatal diagnosis for pregnancies at increased risk is possible if the *KCNJ2* pathogenic variant has been identified in an affected family member. The entity is a rare condition caused by multiple mutations of Kir2.1. Depending on the mutation, it can be dominant or recessive.

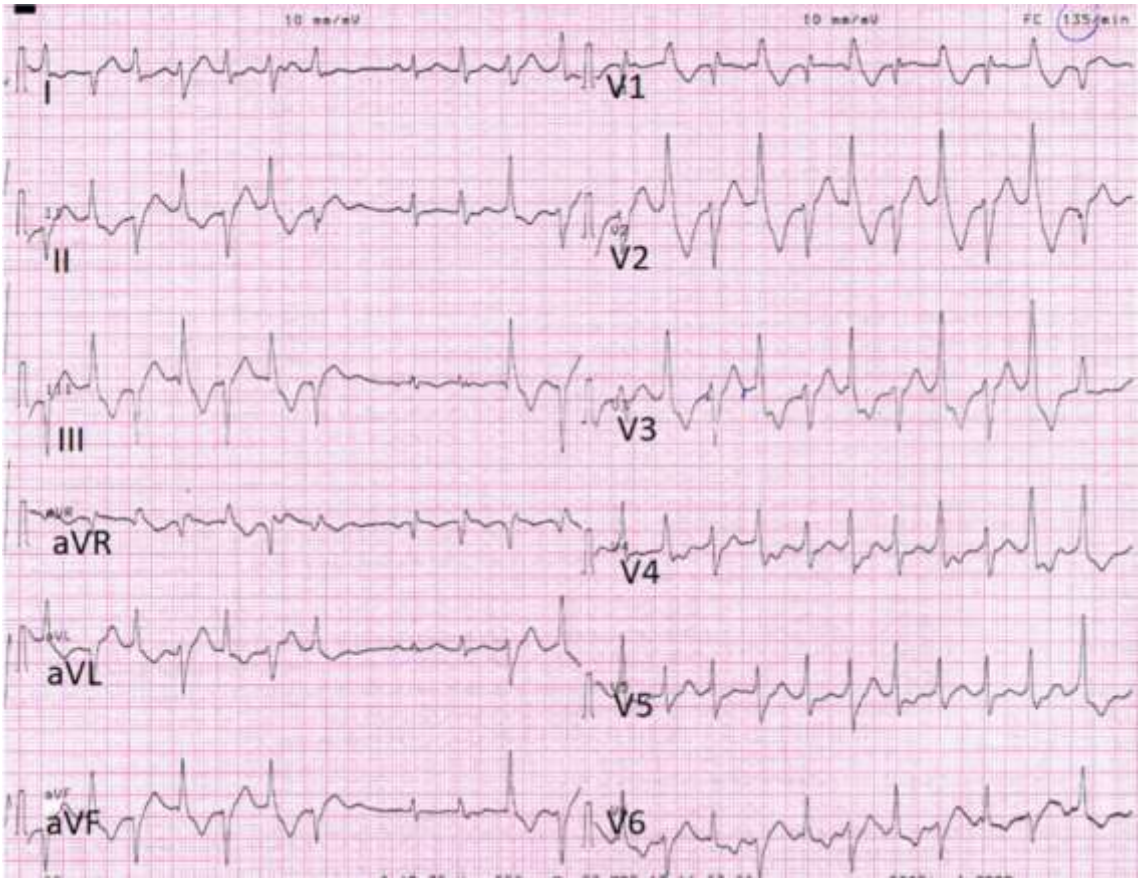
It is characterized by periodic paralysis, cardiac arrhythmias and dysmorphic features. ATS causes rare periodic paralysis with distinct features, and accounts for < 10% of all periodic paralyses (~1/500,000 people)

ATS is a disorder that causes episodes of periodic paralysis, arrhythmias, and developmental abnormalities. Periodic paralysis begins early in life, and episodes last from hours to days. These episodes may occur after exercise or long periods of rest, but they often have no obvious trigger. Muscle strength usually returns to normal between episodes. However, mild muscle weakness may eventually become permanent. In people with ATS, the most common changes affecting the heart are ventricular arrhythmia, and LQTS. The irregular heartbeats can lead to discomfort, such as the feeling that the heart is palpitations. Uncommonly, the irregular heartbeats can cause syncope, and even more rarely, SCD. Physical abnormalities associated with ATS typically affect the face, other parts of the head, and the limbs. These features often include a micrognathia, dental abnormalities such as crowded teeth, low-set ears, widely spaced eyes, syndactyly of the second and third toes, and clinodactyly. Some affected people also have short stature and scoliosis. The signs and symptoms of ATS vary widely, and they can be different even among affected members of the same family. About 60% of affected individuals have all three major features (periodic paralysis, cardiac arrhythmia, and physical abnormalities).

ECG features in ATS

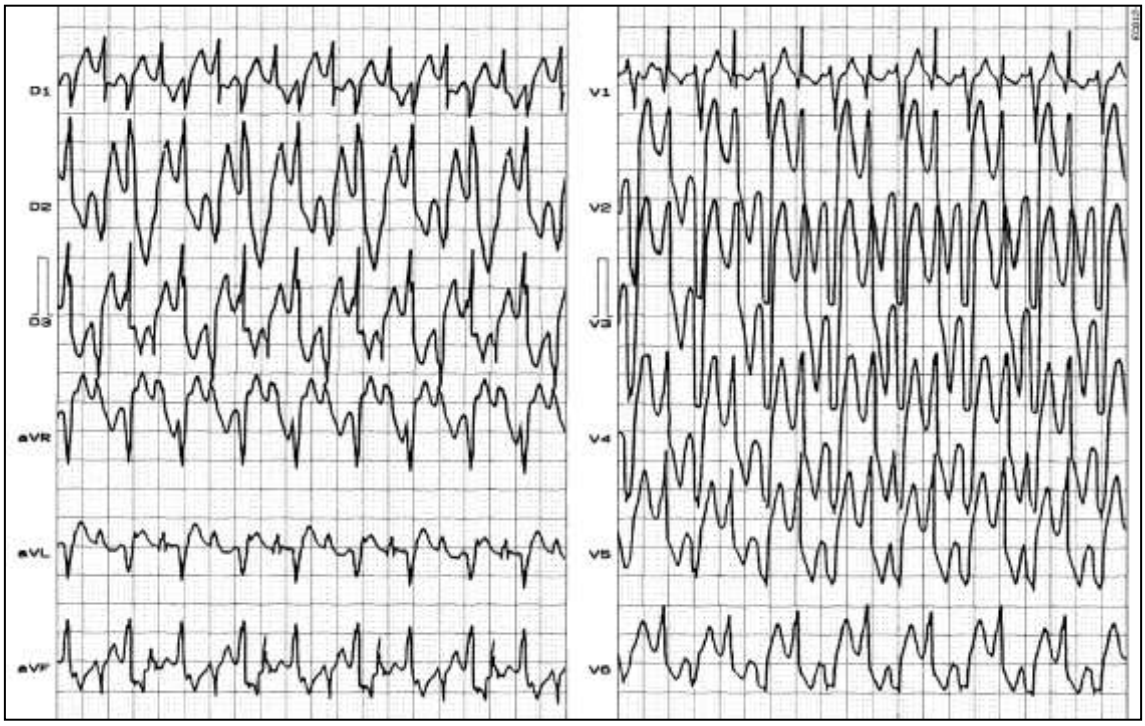
- Prominent U-waves that occur at faster HRs, suggesting that this may represent a manifestation of channelopathy rather than a normal variant.
- U-wave amplitude augmentation after adrenaline infusion.
- Frequent PVCs at rest (differential diagnosis with CPVT),
- Normal true QT interval. The QTc interval is 440 ms
- Post-PVC “pseudo-LQTS-pattern”.
- Q-U interval prolongation with abnormal prominent U-wave and increased QT-U interval but not QT interval prolongation. Abnormal T- U wave is present in > 90 % of ATS1 cases.
- Wide T- U wave junction in 43 % of the cases
- Prominent U-wave from V2 to V4 in >85% of cases
- Biphasic U-wave 16 % of the cases
- Large U-wave in 73 % of the cases
- “U on P” sign: U-wave masquerading P-wave

- Pseudo “Tee-pee sign”. During a PVC, there is a prolongation of the descending limb of the T+U-wave. Hyperkalemia, with concurrent hypocalcemia and hypomagnesemia resulting in (1) peaking of the T wave, (2) a prominent U wave, and (3) prolongation of the descending limb of the T wave such that it overlapped with the next P wave. In this particular ECG from a patient with combined electrolyte imbalance, we have dubbed the unusual appearance of the segment between the peak of the T wave to the next P wave as the "tee-pee" sign.(**Johri AM1, Baranchuk A, Simpson CS, Abdollah H, Redfearn DP.ECG manifestations of multiple electrolyte imbalance: peaked T wave to P wave ("tee-pee sign").Ann Noninvasive Electrocardiol. 2009 Apr;14(2):211-4. doi: 10.1111/j.1542-474X.2009.00283.x**.)
- Bidirectional ventricular tachycardia (BiVT). It is the hallmark for ATS1 and CPVT. In ATS1, PMVT and/or BiVT are relatively slow, well-tolerated, usually asymptomatic with a HR of about 130-140 bpm. Figure



12-lead Electrocardiogram with bidirectional ventricular tachycardia (BiVT). **(ECG From Stefano Maffè, et al. J Electrocardiol, 2020.)**

Note the differences with CPVT caused by bidirectional ventricular tachycardia. In ATS BiVT are relatively slow, well-tolerated, usually asymptomatic with a HR of about 130-140 bpm. On the other hand, in CPVT BiVT is faster See next ECG



Caucasian Female, 20-year-old patient; recurrent syncope of uncertain etiology after physical and emotional stress; carrier of familial catecholaminergic cardiomyopathy. QRS complexes alternans are observed with alternating right and left bundle branch block morphology. The QRS axis shifts from –60º to +120º.

- Torsade de pointes were recorded only in 3 % of ATS1

Management

Drugs: β-blockers are the most frequently used prophylactic drugs, alone or in combination with amiodarone or flecainide (**Stefano Maffè 1, Paola Paffoni 2, Luca Bergamasco 2, Pierfranco Dellavesa 2, Franco Zenone 2, Lara Baduena 2, Nicolò Franchetti Pardo 2, Giulia Careri 2, Emanuela Facchini 2, Valeria Sansone 3, Umberto Parravicini 2. Therapeutic Management of Ventricular Arrhythmias in Andersen-Tawil Syndrome. J Electrocardiol, 58, 37-42 Jan-Feb 2020. PMID: 31710873 DOI: 10.1016/j.jelectrocard.2019.10.009**)

Flecainide alone: Only a few cases involving the use of flecainide alone have been reported in case of intolerance to β-blockers (**Stefano Maffè 1, Paola Paffoni 2, Luca**

Bergamasco 2, Pierfranco Dellavesa 2, Franco Zenone 2, Lara Baduena 2, Nicolò Franchetti Pardo 2, Giulia Careri 2, Emanuela Facchini 2, Valeria Sansone 3, Umberto Parravicini 2. Therapeutic Management of Ventricular Arrhythmias in Andersen-Tawil Syndrome. J Electrocardiol, 58, 37-42 Jan-Feb 2020. PMID: 31710873 DOI: 10.1016/j.jelectrocard.2019.10.009). Intravenous flecainide challenge test may be useful in predicting the efficacy of oral flecainide [11]. The mechanism by which flecainide suppresses ventricular arrhythmias is decreased delayed after depolarization (DAD). Inhibition of the Na^+ channel may directly suppress triggers activity and/or indirectly inhibit Na^+-Ca^{2+} exchange, resulting in a reduced of intracellular Ca^{2+} overload and decreased DAD. Hypokalemia due to diarrhea, prolonged QTc interval prolonged terminal portion of the T-wave descending and large U-wave accentuated by flecainide may cause cardiac arrest

In cases with significant resistance to anti-arrhythmic medication, refractory arrhythmia or drugs intolerance and survivors of a cardiac arrest, with recurrent syncope or sustained, symptomatic ventricular tachyarrhythmias should be considered for ICD implantation (**Smith A.H., Fish F.A., Kannankeril P.J. Andersen-tawil syndrome. Indian Pacing Electrophysiol J. 2006;6:32–43**.)

Barium poisoning is likely due to its ability to block Kir channels.

Atherosclerosis (heart disease) may be related to Kir channels. The loss of Kir currents in endothelial cells is one of the first known indicators of atherogenesis (the beginning of heart disease).

Thyrotoxic hypokalaemic periodic paralysis has been linked to altered Kir2.6 function. (**Ryan DP, da Silva MR, Soong TW, Fontaine B, Donaldson MR, Kung AW, Jongjaroenprasert W, Liang MC, Khoo DH, Cheah JS, Ho SC, Bernstein HS, Maciel RM, Brown RH, Ptácek LJ (January 2010). "Mutations in potassium channel Kir2.6 cause susceptibility to thyrotoxic hypokalemic periodic paralysis". Cell. 140 (1): 88–98. doi:10.1016/j.cell.2009.12.024. PMC 2885139. PMID 20074522**.).

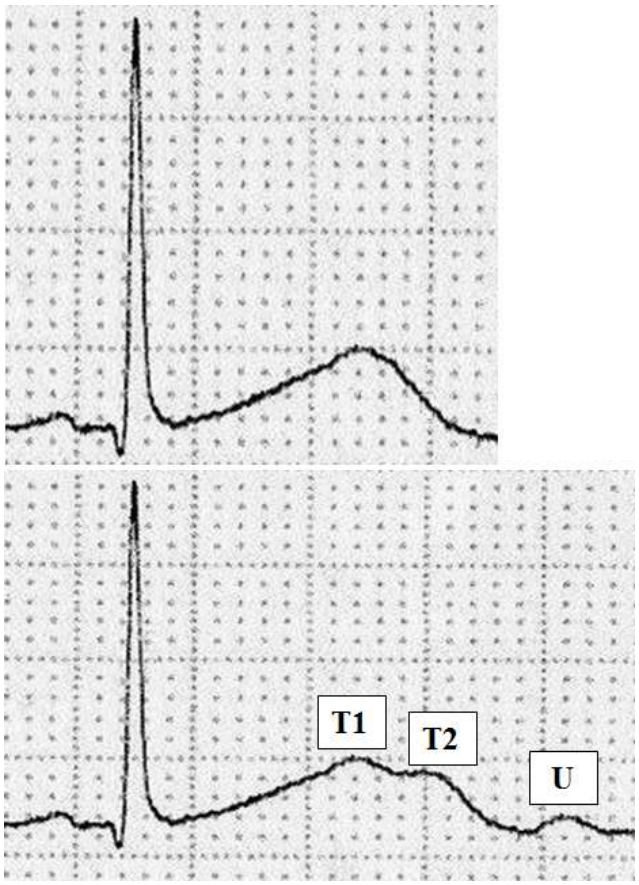
EAST/SeSAME syndrome may be caused by mutations of KCNJ10 characterized by as a syndrome of seizures, sensorineural deafness, ataxia, intellectual disability (mental

retardation), and electrolyte imbalances. It is an autosomal recessive genetic disorder caused by mutations in the KCNJ10 gene, as discovered by Bockenhauer and co-workers.(**Celmina M1,2, Micule I3, Inashkina I4, Audere M5, Kuske S6, Pereca J7, Stavusis J4, Pelnena D4, Strautmanis J8.EAST/SeSAME syndrome: Review of the literature and introduction of four new Latvian patients. Clin Genet. 2019 Jan;95(1):63-78. doi: 10.1111/cge.13374.**)

Long QT2 variant and U wave relationship

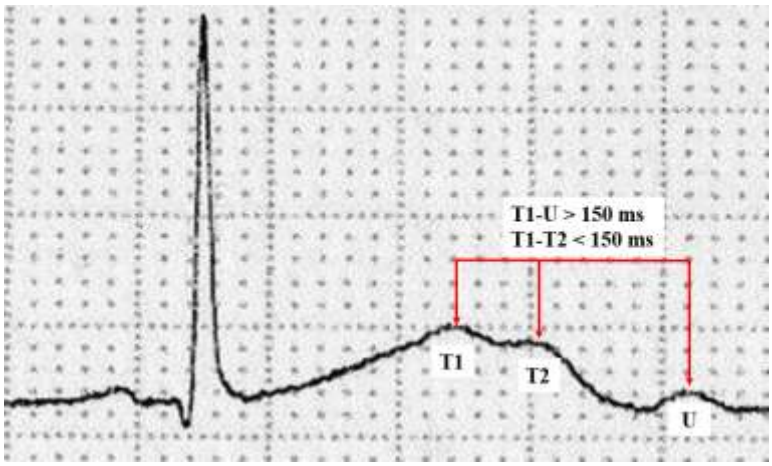
LQTS type 2 (LQTS2) is caused by mutations in the KCNH2 gene, leading to a reduction of the rapidly activating delayed rectifier K+ current and loss of human ether-à-go-go-related gene (hERG) channel function by different mechanisms. Triggers for life-threatening arrhythmias in LQTS2 are often auditory stimuli Jiang et al. (1994) found linkage to D7S483 at chromosome 7q35-q36 in 9 families with the long QT syndrome; the combined lod score was 19.41 at theta = 0.001. Curran et al. (1995) showed that the KCNH2 gene mapped to the same YAC as D7S505, a polymorphic marker tightly linked to LQT2. They found no recombination events using linkage analysis with polymorphisms within KCNH2 for linkage studies of chromosome 7-linked LQT.

ECG in LQT2 variant



LQT2: OMIM 152437. Mutation: alpha subunit of the rapid delayed rectifier potassium channel (hERG = MiRP1). The current through this channel is known as I_{Kr}. This phenotype is also probably caused by a reduction in the repolarizing current. **Event triggers:** *Emotion or stress and noises*: LQT2. Auditory arousal.

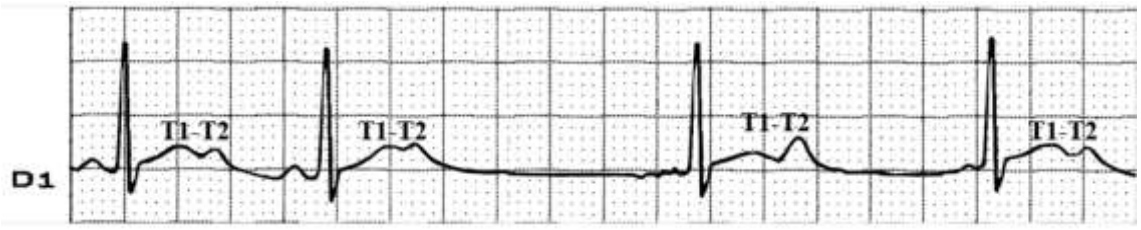
Differentiation between bimodal T waves of LQT2 from the T-U interval



(**Lepeschkin E: The U wave of the electrocardiogram. Arch Intern Med iy55:%:6{K)-617**.)(**Lepeschkin E: Physiologic basis of the U wave. In Schlant RC, Hurst JW, eds: Advances in Electrocardiography. Grune and Stratton, New York**

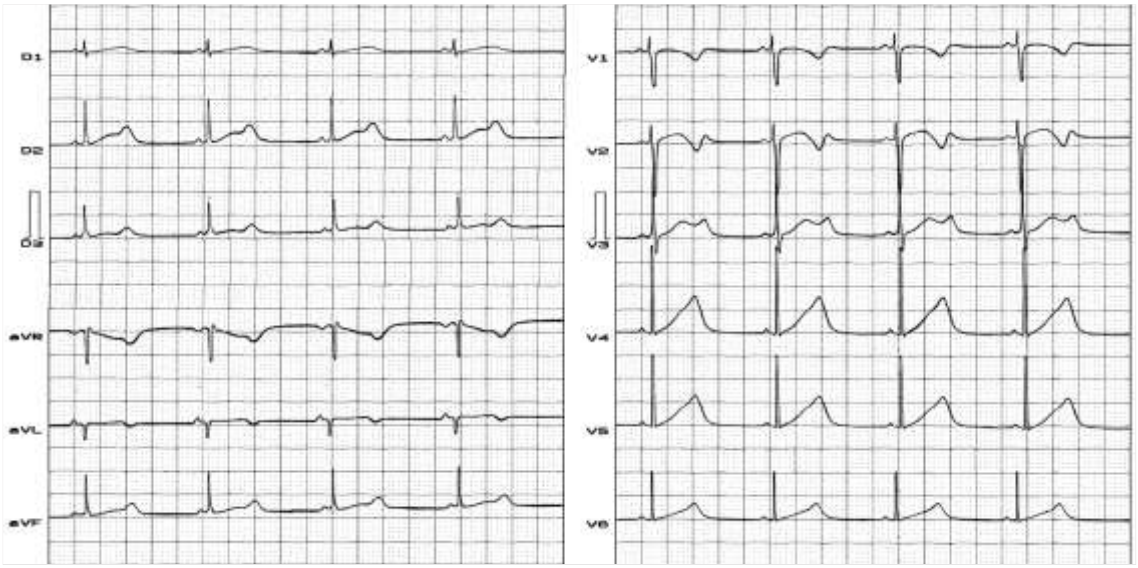
and London. 1972. pp. 431-447.) (**Lepeschkin E, Surawicz B: The duration of the Q-U interval and its components in electrocardiograms of normal persons. Am HeartJ 1953:46:9-29**.)

Bimodal T wave (T1-T2 pseudo U-wave dependent on bradyarrhythmic pause)



Prominent U wave that increases voltage in pauses (Roden DM, Spooner PM. Inherited long QT syndromes: a paradigm for understanding arrhythmogenesis. J Cardiovasc Electrophysiol. 1999 Dec;10(12):1664-83.99).

Name: D.S.F; Age: 11 years old; Sex: Fem. Weight: 38 kg; Height: 1.45 m; Race: white; Date: 09/18/2001 Medication in use: Propanol 240 mg.



Clinical diagnosis: Familial long QT syndrome without deafness. Tracing performed moments after episode of syncope. Marked increase of T-U wave is observed.

ECG diagnosis: sinus rhythm, HR: 63 bpm, long QT interval 500 ms (normal maximal value: 430 ms); very evident prominent U waves in DII and V3.

Hypertrophic cardiomyopathy and U wave

Case report

A 46-year-old Caucasian male without previous medical or surgical history presented for a routine cheek up. He was asymptomatic and was not using any medical treatment. Normal physical examination.

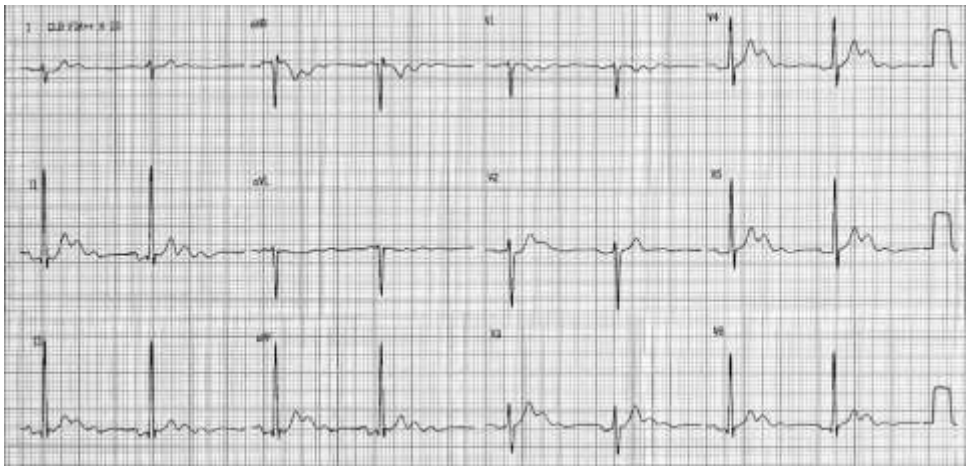
The 12-leads ECG (Fig. 1) demonstrated bizarre middle-end repolarization in the inferior leads and V3–V6.

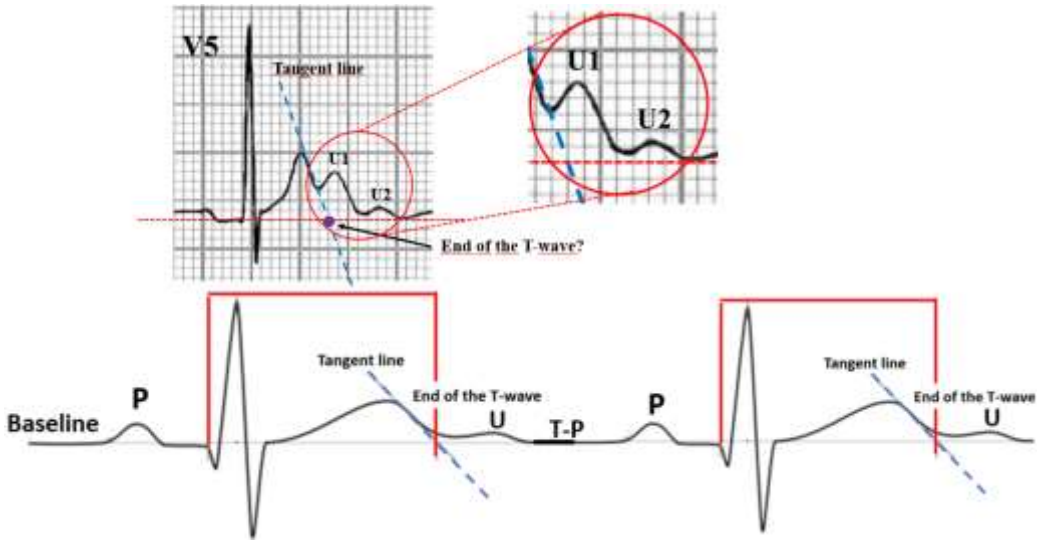
The transthoracic echocardiogram showed a prominent accessory papillary muscle(APM), located between the LV apex and interventricular septum without LVOT obstruction (Figs. 2A, 2B). Normal RV and normal valve structures. The LVEF had 66%, with a mass of 63 grams (37.5 g/m^2), end-systolic volume of 40 ml and end-diastolic volume of 106 ml. IVS with end diastolic ventricular wall thickness was 11. mm, 4-chamber view. Both PMs were also seen to be abnormally hypertrophic, occupying a large part of the LV cavity during systole. The anterolateral papillary muscle (ALPM) had a maximum diameter of 12.5 mm and the posteromedial papillary muscle (PMPM) measured 15 mm on the horizontal axis (end-diastole, short-axis view; (Figure B). Delayed hyperenhancement was not observed. Absence of MV dysfunction. Figure 2 is an echocardiographic image from the short axis and parasternal, long axis view, demonstrating the accessory papillary muscle (APM) (marked with +). Figure 2B is an echocardiographic image, taken from the apical, four-chamber view, also demonstrating the APM, also marked with +.

A biochemical evaluation, did not reveal any abnormalities which could explain the bizarre repolarization.

Figure 1

12-leads ECG preformed at the first consult





To determine the end of ventricular repolarization we draw an oblique tangent that follows the descending ramp of the T wave. The end of the QT interval is marked by the finding of this tangent with the baseline.

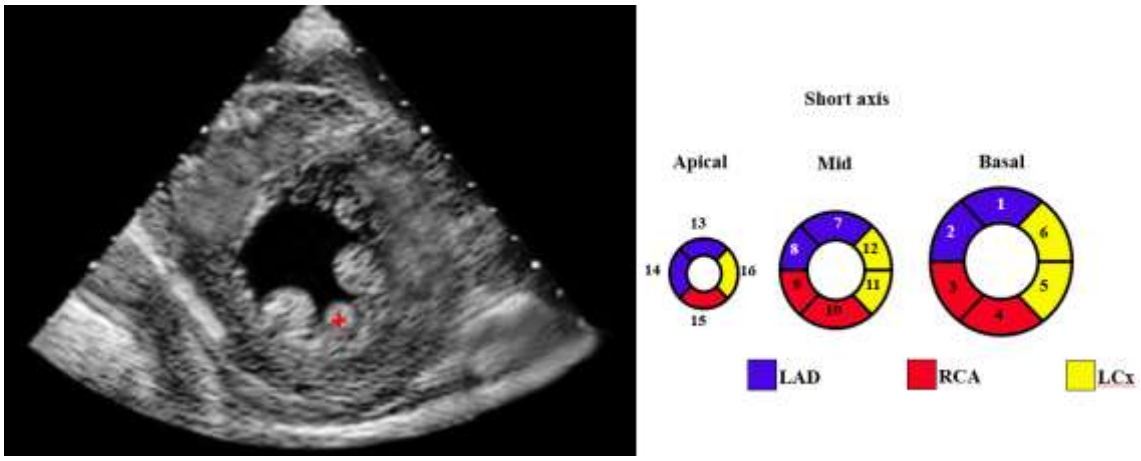


Fig 2A Echocardiogram. Parasternal, short-axis view.

Note the accessory papillary muscle, marked with +.

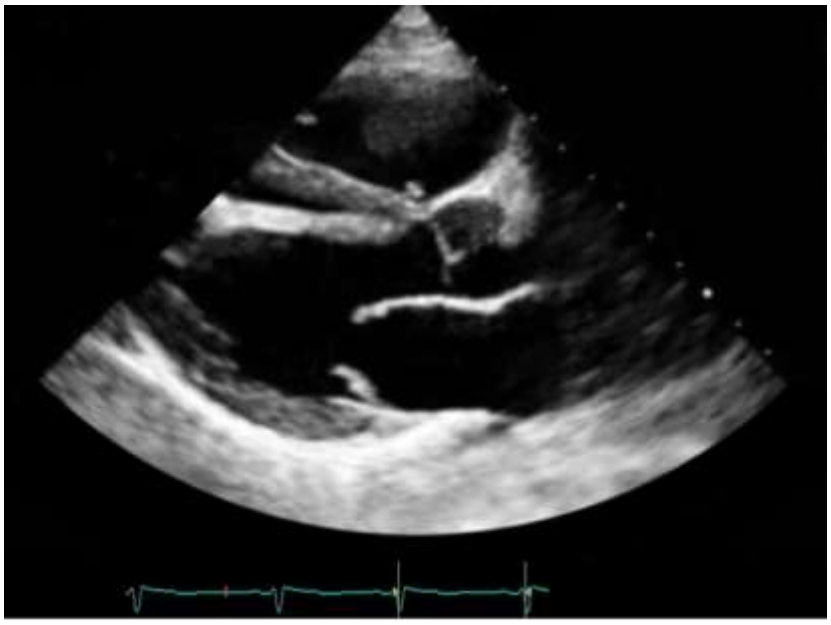


Figure 2B: Echocardiographic image four-chamber view demonstrating the accessory papillary muscle (+) An accessory PM is defined as a PM with origins separated from the ALPM and PMPMs, or a PM that branched into two or three bellies at the base of the ALPM or PMPM. PM hypertrophy is defined as at least one of the two PMs having a diameter of ≥1.1cm. Hypertrophy or accessory papillary muscle could be a form of hypertrophic cardiomyopathy (**A. Kobashi, M. Suwa, T. Ito, *et al.* Solitary papillary muscle hypertrophy as a possible form of hypertrophic cardiomyopathy Jpn Circ J, 62 (1998), pp. 811-816**). An uncommon but important finding of isolated hypertrophy of the PMs, with an abnormal ECG is possible. The structural characteristics of the PMs have received scant attention in this setting and there is little information in the literature on this entity, whose real prevalence and clinical significance remain to be determined. The available information relates solitary PM hypertrophy or accessory PM with an early form or a different pattern of HCM detected frequently by an abnormal ECG, with LVH and giant U waves which prompted further diagnostic tests and a search for possible etiologies. Isolated papillary muscle hypertrophy without features of phenotypic LV hypertrophy is an uncommon variant of HCM.(**Kobashi A, Suwa M, Ito T, Otake Y, Hirota Y, Kawamura K: Solitary papillary muscle hypertrophy as a possible form of hypertrophic cardiomyopathy. Jpn Circ J 1998, 62:811–816.)(Correia AS, Pinho T, Madureira AJ, Araujo V, Maciel MJ: Isolated papillary muscle hypertrophy: a variant of hypertrophic cardiomyopathy? Do not miss a hypertrophic cardiomyopathy. Eur Heart J Cardiovas Imaging 2013, 14:296.) (Ferreira C 1, Delgado C 2, Vázquez M 3,Carmen Trinidad C 2, Vilar M 3. Isolated Papillary**

Muscle Hypertrophy: A Gap in Our Knowledge of Hypertrophic Cardiomyopathy? Isolated Papillary Muscle Hypertrophy: A Gap in Our Knowledge of Hypertrophic Cardiomyopathy?, 33 (6), 379.e1-5 Jun 2014. PMID: 25001167 DOI: 10.1016/j.repc.2014.01.015)