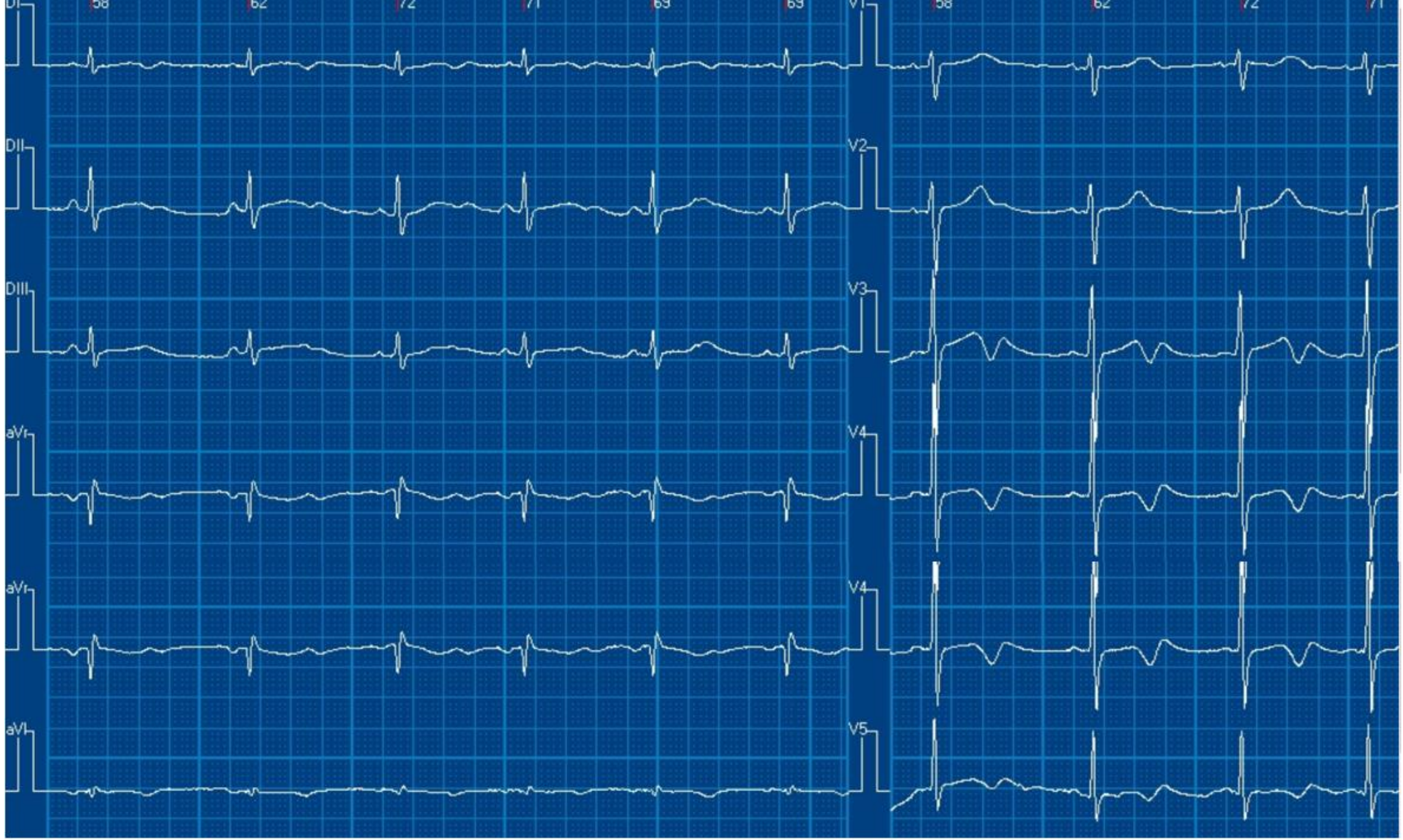
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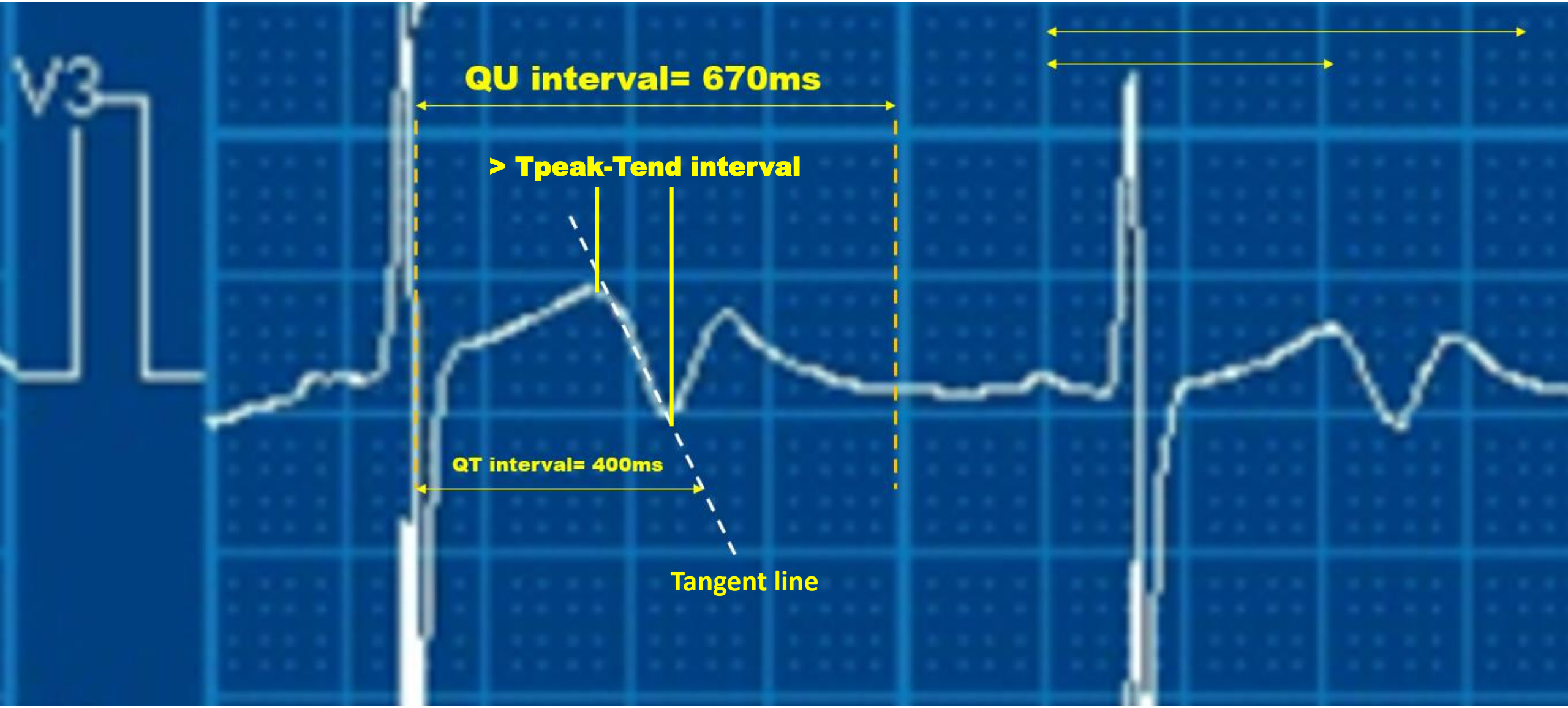
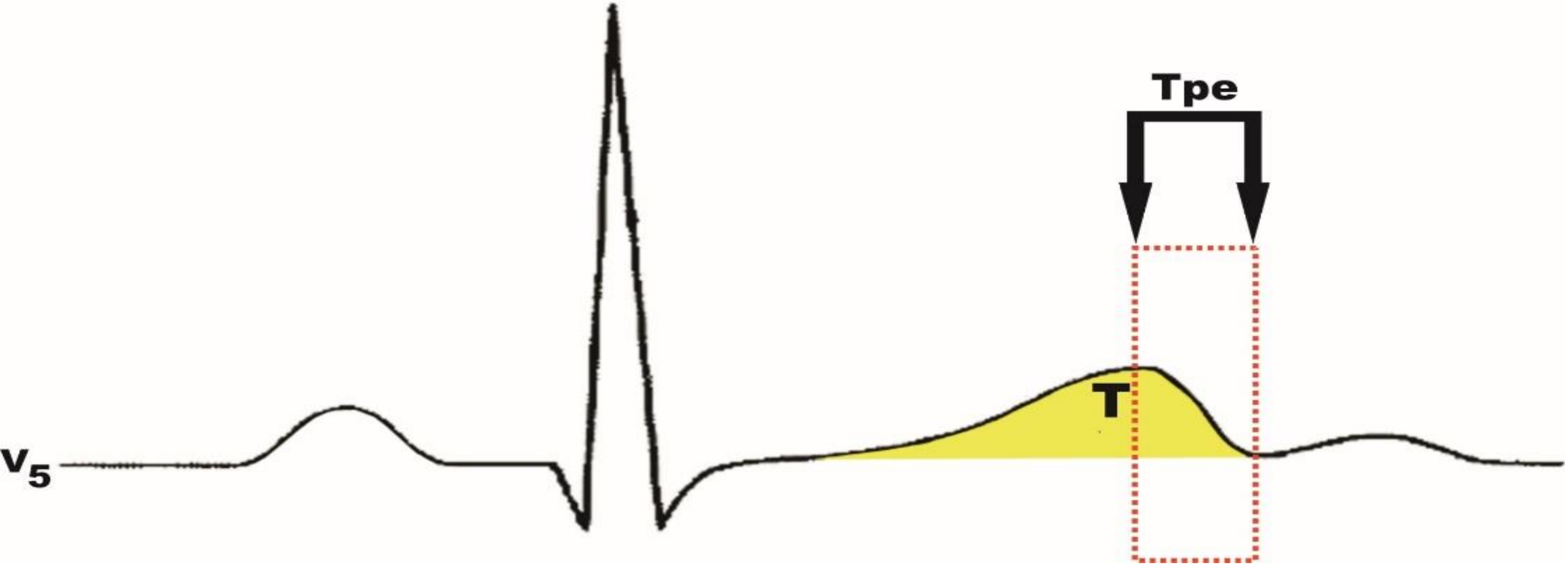


Figure 1

Shows normal QT interval and very broad QU with prominent U wave. In normal conditions U-wave voltage is always ≤25% that precedent T wave.



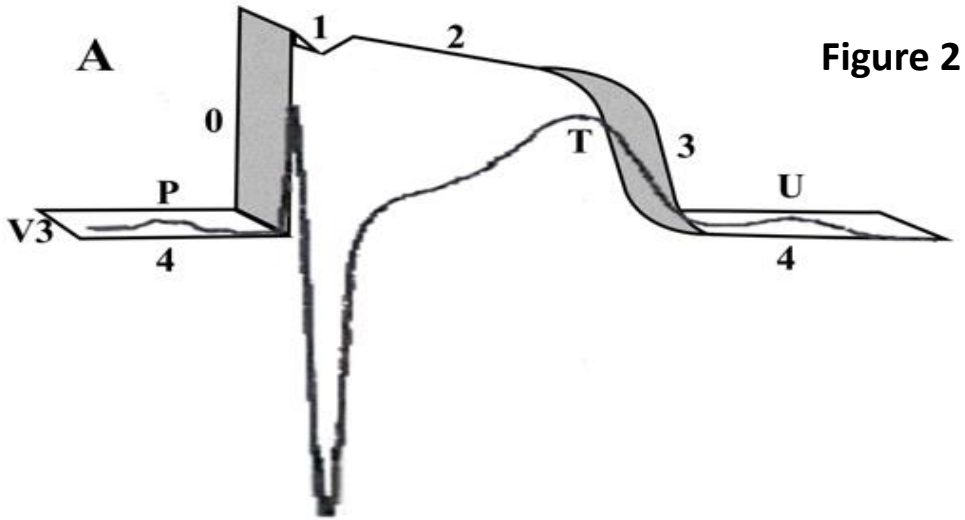
Tpeak-Tend interval or Tpe interval: The interval elapsed from the apex to the end of T wave. Normal Tpe interval is <94ms. In ATS this interval is prolonged as consequence of delayed terminal descending ramp of the T-wave.

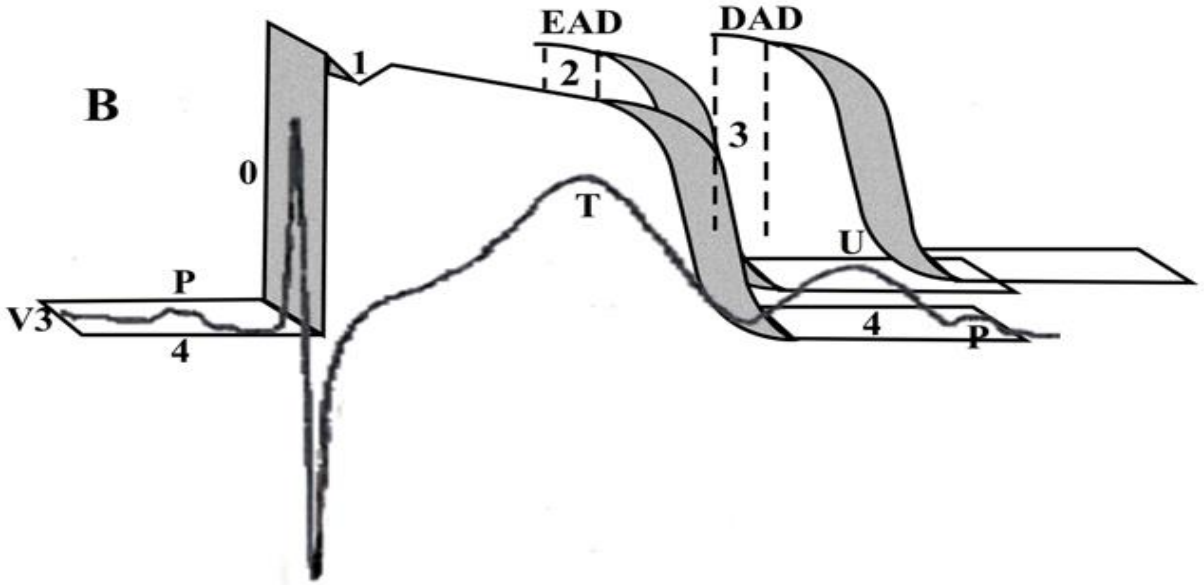
Electrocardiogram and arrhythmic characteristic in Andersen Tawil syndrome (ATS)

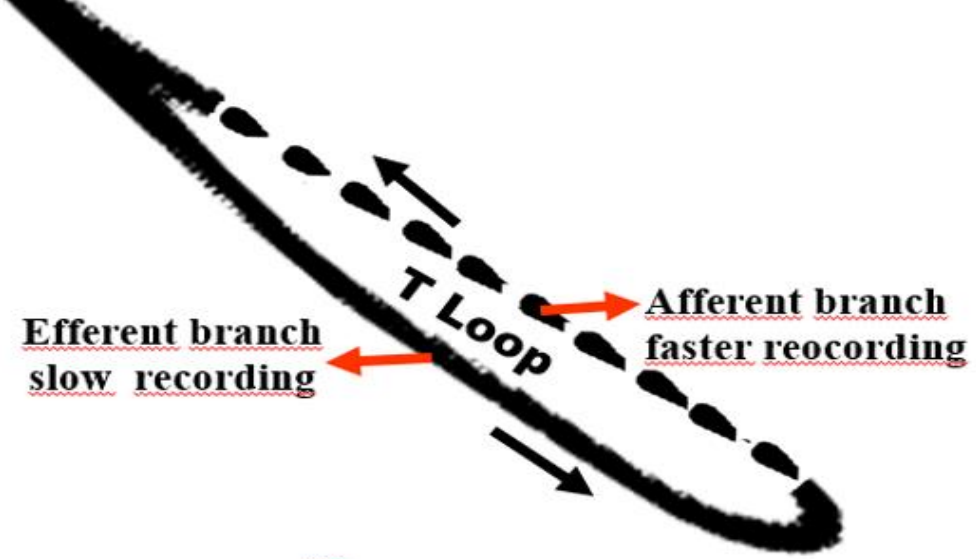
12-lead Electrocardiogram may reveal characteristic abnormalities(**1-5**) Prominent U-waves that occur paradoxically at faster HRs or epinephrine infusion, (figure x) suggesting that this may represent a manifestation of channelopathy rather than a normal variant. In normal conditions, U wave voltage is strongly rate dependent (inversely proportional). U wave is observed better during bradycardia. When heart rate (HR) is ≤ 65 bpm, U waves are visible in 90% of cases. When HR is between 80 bpm and 95 bpm U waves are visible in 65% of cases. When HR is > 95 bpm U waves are visible in 25% of cases (**6**) Prominent and broad U waves in ATS is consequence of slowed terminal phase 3 of AP.(**7**) and terminal phase 4 coincident with U-wave of surface ECG. A prominent U-wave in the inferior leads is another important feature observed in ATS1. In the recent manuscript from Michalina Krych et al. ATS patient with polymorphisms mutation carriers K897T (ATS1) U wave was observed in 52% of cases vs 5% in non-carriers in the inferior leads (**8**) In normal conditions, U-wave is observed in the precordial leads (mainly in V3) (semi direct leads), but not in the frontal plane. In ATS1, the ECG shows frequently clear U-waves in the inferior leads. On the other hand, in normal conditions, the net outward positive current (equal to loss of positive charge from the cell) causes the cell to repolarize. The delayed rectifier K+ channels close when the membrane potential is restored to about -85 to -90 mV, while in IK1, there is conduction throughout phase 4, which helps to set the resting membrane potential (**9**) .

The ultimate resting membrane potential due to not fully activated Kir2.1 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. Figure 2 shows normal-AP (A) in a surface ECG and ATS1-AP (B) in a surface ECG with prominent U-wave. Figure 2

Figure 2







A. Normal monophasic rapid fibers AP/ECG-surface correlation: The shape of the T wave/T loop when positive, is asymmetrical with slow ascending ramp and faster descending ramp and rounded peak and slow efferent limb and fast afferent limb. The T wave/T-loop is coincident with phase 3 e of monophasic AP and its end concomitantly with the maximal diastolic potential(MDP) of AP. MDP is the most negative level attained during the cardiac cycle by the cell membrane of a fiber that does not have a constant resting potential, occurring at the end of phase 3 of the AP. In pacemaker cells this is a point of hyperpolarization.

B. Monophasic rapid fibers AP/ECG-surface correlation in ATS. The shape of the T wave when positive, is symmetrical or near symmetrical as consequence of delayed of the terminal T-wave downslope, Often, the descending ramp of the T wave overlaps with the P wave of the next beat, giving the false impression of being a biphasic U wave.

Proposed mechanism of prolonged QU interval in Andersen-Tawil syndrome and prominent U wave genesis

In normal conditions, during phase 3 of the AP (the "rapid repolarization" phase), concomitant with the T-wave/T-loop of the surface ECG/VCG, the L-type Ca2+ channels close, while the slow delayed rectifier (IKs) K+ channels remain open as more K+ leak channels open. This ensures a net outward positive current, corresponding to a negative change in membrane potential, thus allowing other types of K+ channels to open. These are primarily the rapid delayed rectifier K+ channels (IKr) and the inwardly rectifying K+ current (IK1), which are affected in ATS1. The mutation in the Kir2.1 gene affects the protein of the IK1, causing a decrease in the output of K+, thus preventing the cell from completing its repolarization. As a result of this, repolarization at the end of phase 3 (prolonged terminal T-wave downslope) and phase 4 is prolonged, expressed in the ECG as a broad T-U wave junction (present in 43 % of cases). Additionally, there is a high-voltage, prolonged U-wave in 73 % of the cases, and eventually a biphasic or bimodal U-wave shaped and very prolonged QU interval (600 to 625ms) with normal or near normal QT/QTc intervals. The “U on P” sign may be seen: masquerading of next beat P-wave the by the U-wave - the pseudo “Tee - Pee sign”. During a PVC, there is a prolongation of the descending limb of the T wave + U-wave. In ATS1, the QT interval can appear prolonged and difficult to measure because of a prominent U-wave. In order to properly determine the QT interval, the tangent technique should be carefully applied. While "classic" ECG presentations of common electrolyte disturbances are well described, multiple electrolyte disturbances occurring simultaneously may generate ECG abnormalities that are not as readily recognizable. The tee-pee sign ECG is manifestations of multiple electrolyte imbalance. Amer M Johri et al. reported a case of hyperkalemia, with concurrent hypocalcemia and hypomagnesemia resulting in peaking of the T wave, a prominent U wave, and prolongation of the descending ramp of the T wave such that it overlapped with the next P wave: the "tee-pee" sign.(**10)** similar to ATS1. Increased U-wave amplitude, duration and biphasic U-shape after epinephrine test infusion in an ATS1 patient. Epinephrine administration following Shimizu protocol increases the U-wave amplitude, consequently, the U-wave / T-wave amplitude ratio becomes > 1 after epinephrine

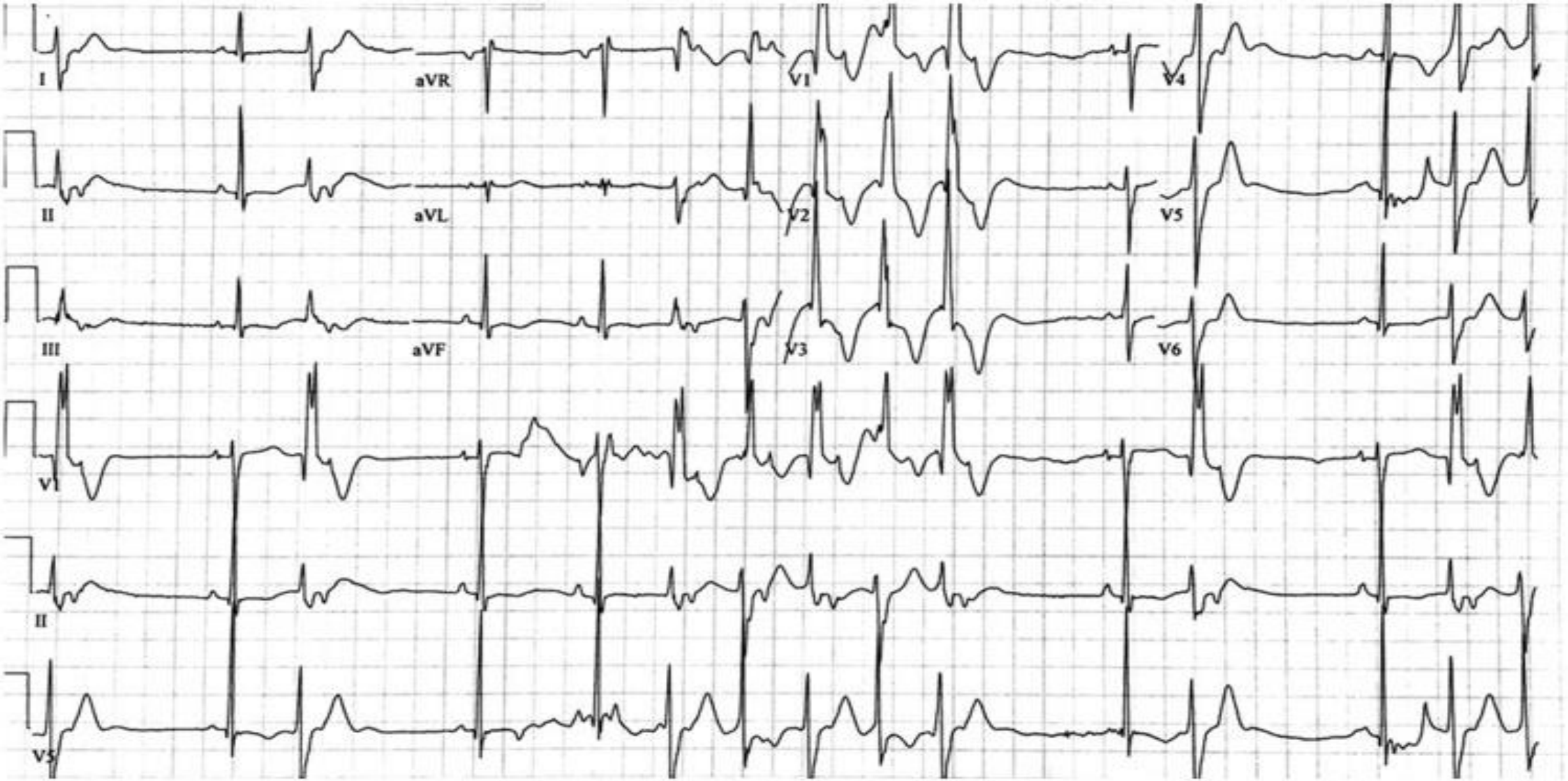
administration. (11) 0.1 ug/kg of epinephrine is given under monitoring. This is immediately followed by a continuous infusion 0.1 µg/kg/min for 5 min. Frequent PVCs at rest. This observation is important for differential diagnosis with CPVT, with RBBB pattern, suppressed at peak exercise, and increased at recovery during exercise treadmill test. Exceptionally, in malignant variant with deletion of the KCNJ2 protein (c.271 282del12 (p.Ala91 Leu94deletion).) exercise test triggered PVCs and BVT was observed similar to CPVT. (**12**) Normal true QT interval. The normal QTc interval is 440 ms. Normal value for QTc are : 350 to 440 ms or 446 + - 15% Definitions of normal QTc varies around being ≤400ms),(**13-14**) ≤420ms) or ≤440ms). For risk of SCD "Borderline QTc" in males is 431-450 ms, and in females 451-470 ms. An "abnormal" QTc in males is a QTc above 450 ms, and in females, above 470 ms. If there is not a very high or low HR, the upper limits of QT can roughly be estimated by taking QT=QTc at a HR of 60 bpm, and subtracting 20ms from QT for every 10bpm increase in HR. For example, taking normal QTc ≤ 420ms, QT would be expected to be ≤420ms at a HR of 60bpm. For a HR of 70 bpm, QT would roughly be expected to be ≤0.420ms. Likewise, for 80 bpm, QT would roughly be expected to be ≤380ms. In ATS1 QTc > 440 for men and 460 for women was of 28% vs5% in carriers versus non-carriers (8).

Post-PVC “pseudo – LQTS pattern” (arrows). This is detected in a sinus beat following a PVC. The fusion of T+U-waves can mimic LQTS. This pattern is not observed in the subsequent sinus beats.

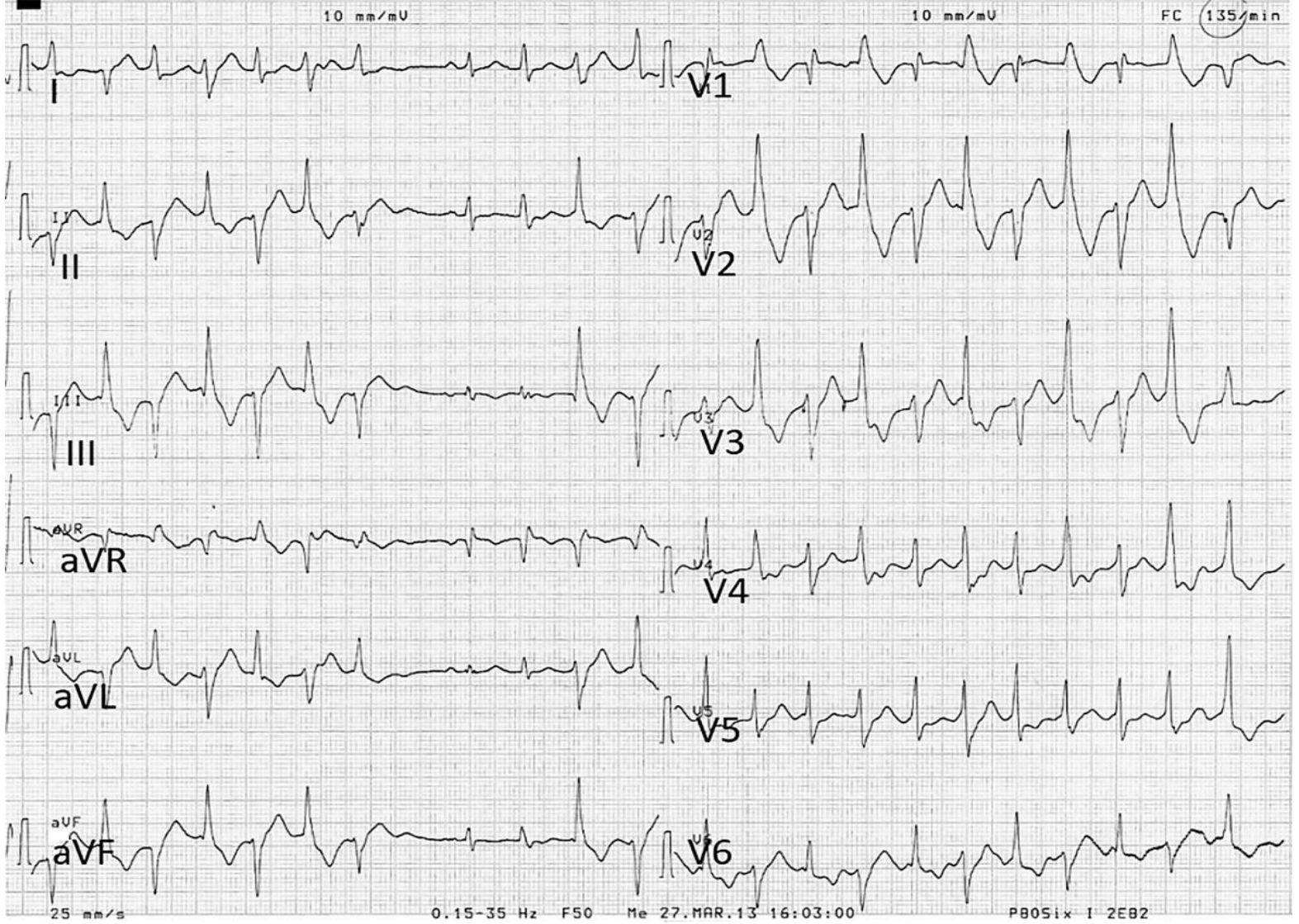
Q-U interval prolongation with abnormal prominent U-wave and increased QT-U interval but not QT interval prolongation. Abnormal T- U wave is present in > 90 % of ATS1 cases.

In ATS the interval elapsed from the apex to the end of T wave (Tpeak-Tend interval or Tpe) is prolonged (>94ms) as consequence delayed descendent limb o the T wave (near symmetric T-wave/T-U wave.) Tpe may correspond to transmural dispersion of repolarization and consequently, the amplification of this interval is associated to malignant ventricular arrhythmias. Figure next slide shows normal Tpe interval.

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 next beat P-wave and Pseudo “Tee-pee sign”. During a PVC, there is a prolongation of the descending limb of the T+U-wave (Figure). 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.(**15)** Pseudo “Tee - Pee sign” (black arrow). Pseudo “Tee-pee sign” during a PVC, there is a prolongation of the descending limb of the T+U-wave. In ATS1, the QT interval can appear prolonged and difficult to quantify because of a prominent U-wave. In order to properly determine the QT interval, the tangent technique should be carefully applied. Prominent U-wave in the inferior leads. In normal conditions U-wave is observed in precordial leads (semi direct leads) when compared to frontal plane In the following ECG we observe clear U-wave in the inferior leads suggesting ATS



12-lead ECG showing frequent PVCs at rest with R-on-T phenomenon (superimposition of an ectopic beat on the T wave of a preceding beat) and QRS axis in the frontal plane with LPFB-like morphology (PVC-QRS axis +120°) alternating with normal baseline QRS axis. In the precordial leads. Non-sustained BVT with RBBB morphology.



12-lead ECG with BiVT.(16) With RBBB pattern at rest. Bidirectional ventricular tachycardia (BVT). It is the hallmark for ATS1 and CPVT. In ATS1, PMVT and/or BVT are relatively slow, well-tolerated, usually asymptomatic with a HR of about 130-140 bpm

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