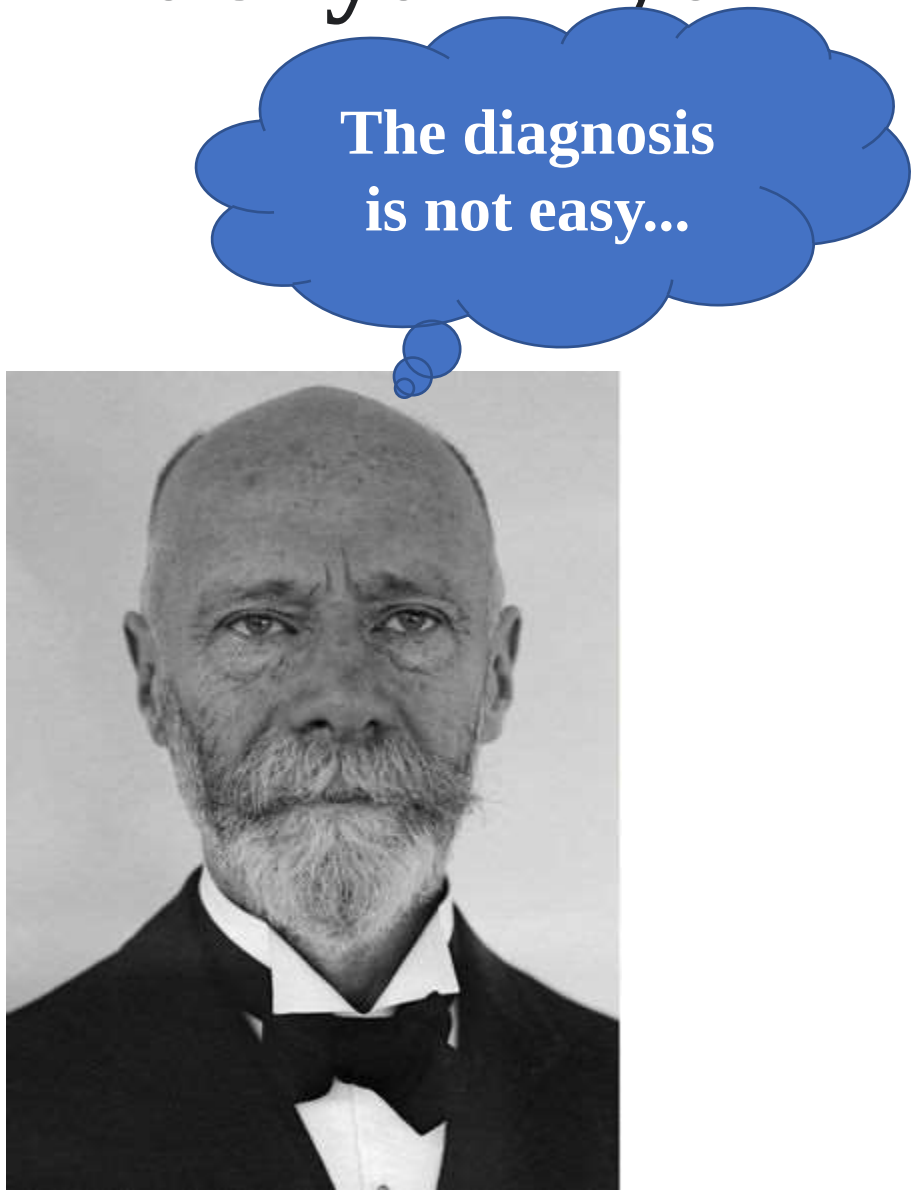
Unusual Tachyarrhythmia



Willem Einthoven

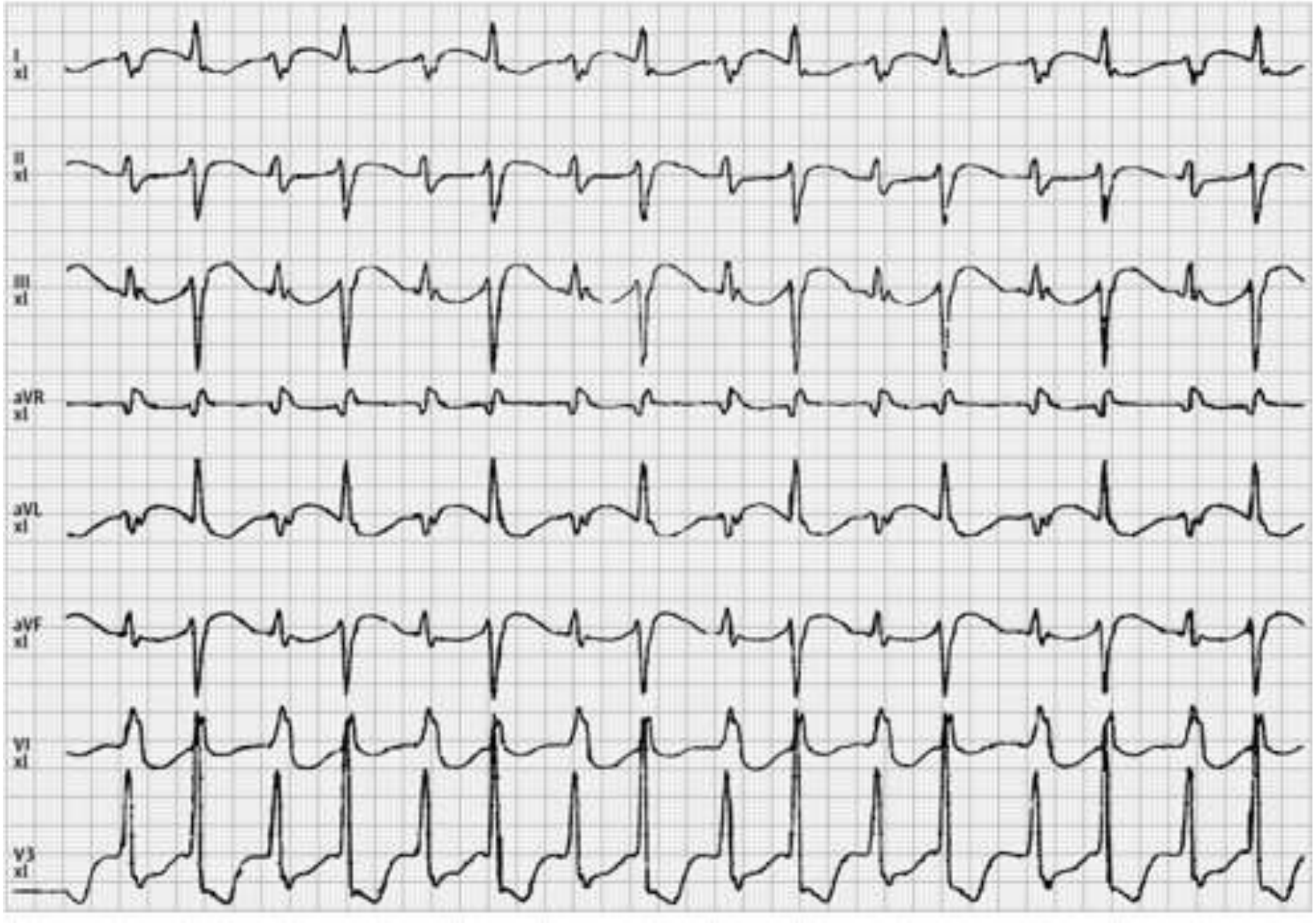
Relato de caso **Case Report.**

Un paciente de 70 años con antecedentes de cáncer de colon metastásico, enfermedad de las arterias coronarias, fibrilación auricular paroxística, hipertensión y en tratamiento a largo plazo con digoxina se presentó al servicio de urgencias con shock séptico y complicaciones de insuficiencia respiratoria aguda que requirieron intubación endotraqueal y ventilación mecánica. Durante el ingreso a la unidad de cuidados intensivos, el paciente desarrolló una taquiarritmia que se registró en la telemetría de divulgación completa (ECG1 de 8 derivaciones por telemetría). Se presenta un electrocardiograma basal de 12 derivaciones registrado previamente en el servicio de urgencias para su comparación (ECG de 12 derivaciones, 2).

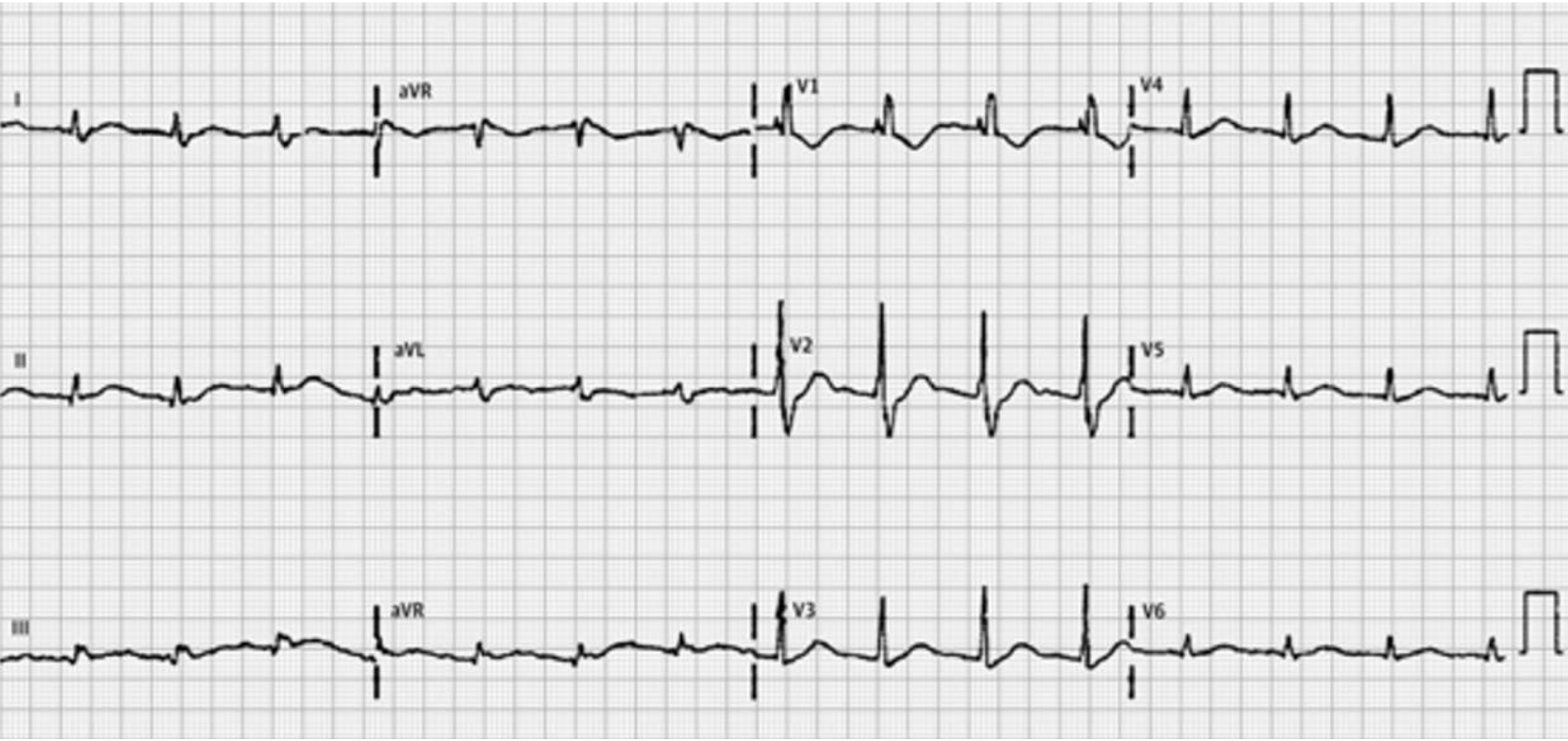
Um paciente de 70 anos com história de câncer de cólon metastático, doença arterial coronariana, fibrilação atrial paroxística, hipertensão e em tratamento de longo prazo com digoxina apresentou-se ao pronto-socorro com choque séptico e complicações de insuficiência respiratória aguda que exigiu intubação. ventilação endotraqueal e mecânica. Durante a admissão na unidade de terapia intensiva, o paciente desenvolveu uma taquiarritmia que foi registrada na telemetria de divulgação completa (8-Lead ECG por telemetria 1). Um eletrocardiograma de linha de base de 12 derivações previamente registrado no departamento de emergência é apresentado para comparação (ECG2 de 12-derivações).

A patient in their late 70s with a history of metastatic colon cancer, coronary artery disease, paroxysmal atrial fibrillation, hypertension, and long-term treatment with digoxin presented to the emergency department with septic shock and complications of acute respiratory failure that required endotracheal intubation and mechanical ventilation. During admission to the intensive care unit, the patient developed a tachyarrhythmia that was recorded on full disclosure telemetry (8-lead Telemetry Tracing ECG-1). A baseline 12-lead electrocardiogram recorded previously in the emergency department is presented for comparison (12-lead ECG-2).

8-lead Telemetry Tracing ECG-1



Baseline 12-lead electrocardiogram ECG-2



Questions: What rhythm is present in the telemetry tracing, and what is the differential diagnosis for the cause of this rhythm?

Perguntas: Qual ritmo está presente no traçado de telemetria e qual o diagnóstico diferencial para a causa desse ritmo?

Preguntas: ¿Qué ritmo está presente en el trazado de la telemetría y cuál es el diagnóstico diferencial de la causa de este ritmo?

Colleagues opinions

Dear Andrés: The tachycardia is bidirectional with pattern of RBBB in V1. Note that in V1 the RBBB pattern during tachycardia is atypical in contrast to RBB pattern in sinus. One must be very suspicious of the possibility of Digitalis toxicity either due to drug excess and /or decreased K^+ levels.

Await the opinion of the group

Professor Melvin Scheinman. University of California, San Francisco

Dr. Melvin Scheinman is Professor of Medicine, Walter H. Shorenstein Endowed Chair in Cardiology, and one of the founding fathers of the field of cardiac electrophysiology. Dr. Melvin Scheinman is one of the founding pioneers of clinical cardiac electrophysiology. He grew up in Brooklyn, New York and took his undergraduate degree at Johns Hopkins University where he graduated first in his class. Postgraduate medical education included Albert Einstein College of Medicine, residency training at the University of North Carolina (Chapel Hill) and cardiology training at the University of California, San Francisco Medical Center. Dr. Scheinman is best known as the first person to have performed catheter ablation in humans. This was done after extensive animal studies.

Queridos amigos Andrés y Raimundo El primer electro parece ser una biventricular tachycardia y el segundo e 12 derivaciones un bloqueo de rama derecha y ritmo sinusal

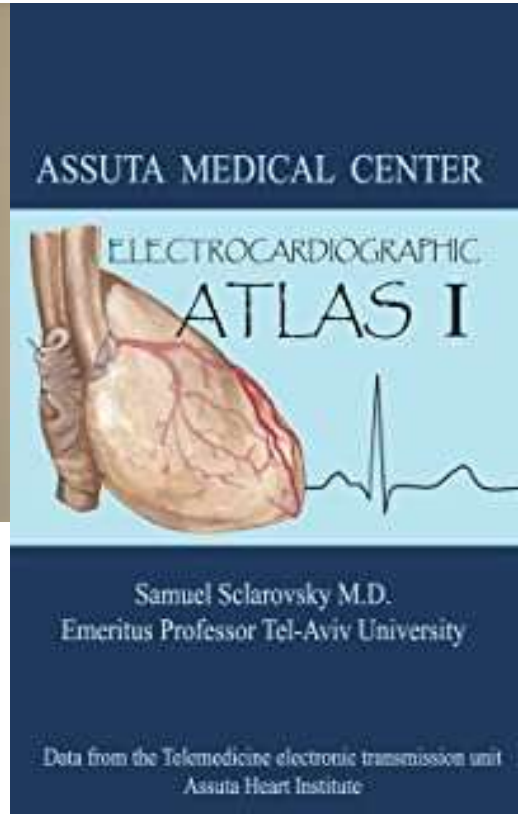
Un abrazo fraternal

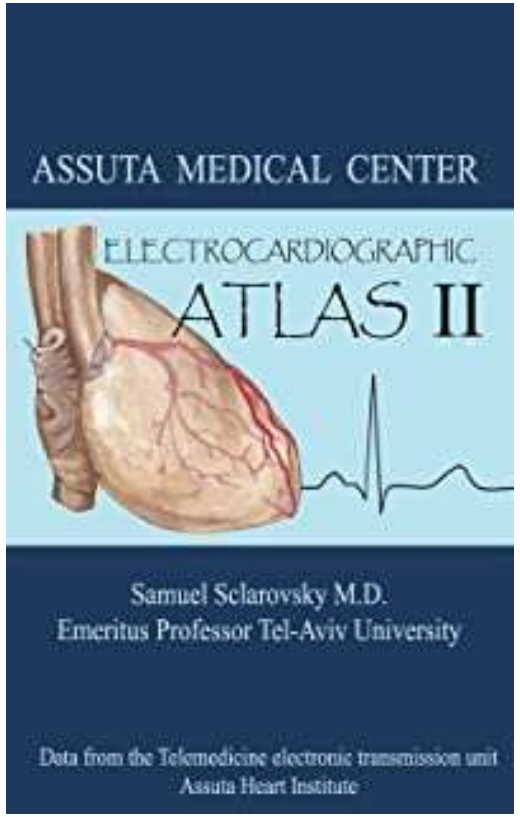
Samuel Sclarovsky MD Profesor Emérito de la Universidad de Tel-Aviv, Israel.

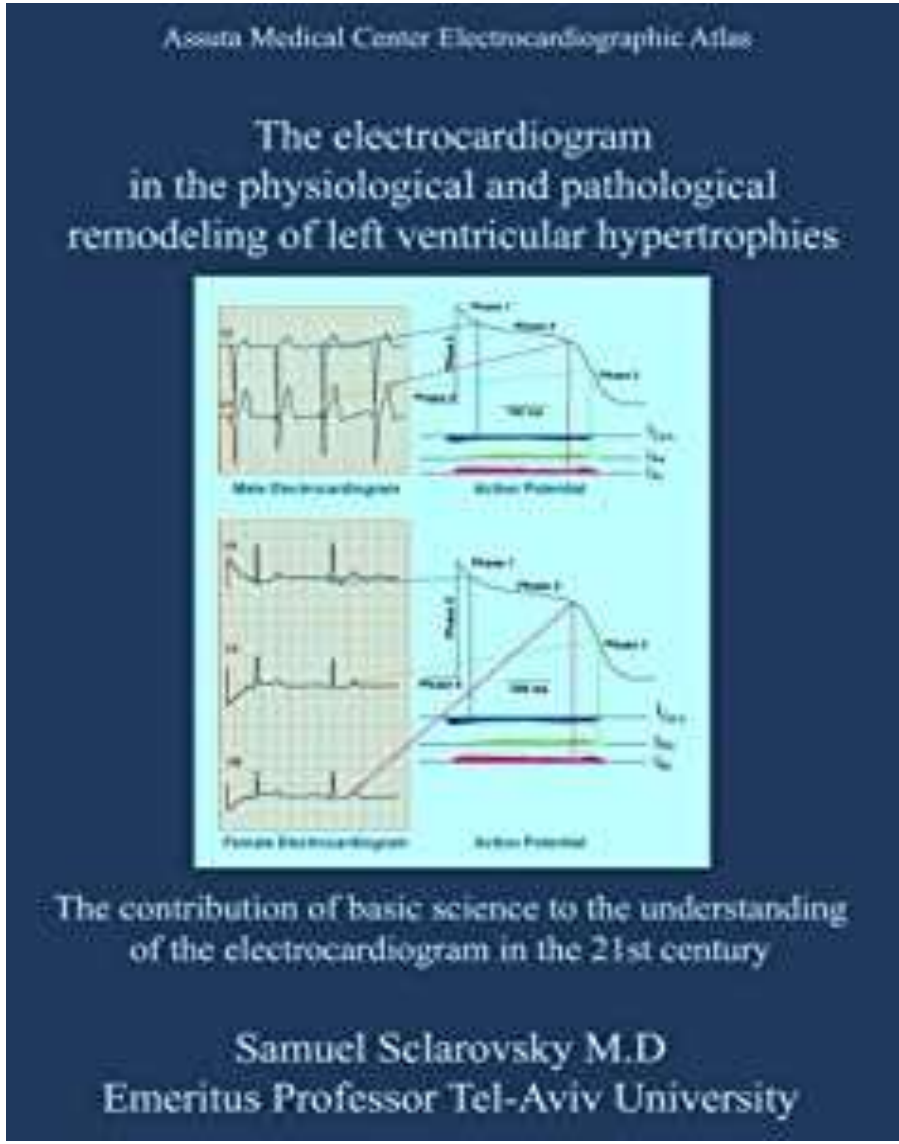
Dear friends Andrés and Raimundo The first eight leads ECG seems to be a biventricular tachycardia and the second one (With 12 leads) a right bundle branch block and sinus rhythm

A brotherly hug

Samuel Sclarovsky MD Emeritus Professor Tel-Aviv University, Israel.







*The electrocardiogram in the physiological and pathological remodeling of left ventricular hypertrophies: The contribution of basic science to the understanding of ECG's in the 21st cen*tury

Final comments, conclusion and theoretical considerations

Interpretation

The telemetry tracing reveals a wide complex tachycardia with a rate of 125 beats per minute and 2 distinct QRS complexes, 1 with the characteristics of a right bundle-branch block. Additionally, there is evidence of an alternating QRS axis occurring in a beat-to-beat pattern (**8-lead telemetry tracing ECG-1**). The patient's baseline QRS complex (**Baseline 12-lead electrocardiogram ECG-2**) has a typical right bundle-branch pattern, making it difficult to determine whether the new-onset arrhythmia was ventricular or supraventricular in origin. However, on closer examination it became apparent that the QRS complex had changed from the baseline beat, with the initial R-wave deflection in lead V_1 exceeding the R′ wave in amplitude, which suggests ventricular origin. Also, the QRS axis alternates between +150° and −60° on a beat-to-beat pattern, suggesting 2 distinct foci for discharges, both of which are suspected to be ventricular in origin because QRS duration ≥120 milliseconds. These findings for a patient being treated with digoxin support a presumed diagnosis of bidirectional ventricular tachycardia (BVT).

The patient was being treated with long-term therapy of digoxin, 250 µg, for rate control of paroxysmal atrial fibrillation; this therapy was continued after hospital admission. The patient's serum digoxin concentration level at onset of tachyarrhythmia was therapeutic at 1.6 ng/mL (reference range, 0.8-2.0 ng/mL; to convert to nmol/L, multiply by 1.281), serum potassium concentration of 3.1 mEq/L (reference range, 3.5-5.1 mEq/L; to convert to mmol/L, multiply by 1.0), renal function was normal, cardiac biomarkers were unremarkable, and a transthoracic echocardiogram was notable for a left ventricular ejection fraction of 45%.

The BVT was transient and converted to a normal sinus rhythm with discontinuation of the digoxin and repletion of the patient's serum potassium level. He recovered from septic shock and started treatment with a β-blocker for heart rate control. There was no evidence of recurrent BVT after discontinuation of digoxin and maintenance of normokalemia.

Bidirectional wide complex ventricular tachycardia (BVT) with alternating beat-to-beat QRS axis in the FP and 1 QRS complex commonly having a right bundle-branch block pattern, but it can also present with alternating left and right bundle-branch blocking.[1] BVT manifests in limited clinical situations, such as with toxic effects of digoxin, herbal aconite poisoning[21], myocardial ischemia, ischemic cardiomyopathy and conduction system disease, in ACTH-producing pheochromocytoma[22, 23], left ventricular non-compaction,[18] and hypokalemic periodic paralysis, subacute myocarditis,[24] myocardial infarction/ischemia,[25] apical left ventricular aneurysm [26]. and ischemic cardiomyopathy during ablation in the absence of acute coronary syndrome, catecholaminergic polymorphic ventricular tachycardia and Andersen-Tawil syndrome.[1-4] BVT is observed more frequently in elderly patients. The mechanism by which digoxin induces BVT is suspected to be from a digoxin-mediated increase in intracellular calcium associated with DAD, which can trigger activity low in the His-Purkinje system.[5] In an animal model, it was demonstrated that DAD–triggered activity in 2 separate foci in the fascicular branches produced a reciprocating ventricular bigeminy with an alternating QRS axis in a beat-to-beat fashion.[5] Interestingly, digoxin-related BVT has been reported to occur at both supratherapeutic and normal serum digoxin concentration levels, requiring increased clinical suspicion of its toxic effects regardless of serum digoxin levels.[6] Further complicating the assessment and management of patients with normal serum digoxin concentration levels is whether the clinically apparent toxic effects are mediated by digoxin alone or if digoxin's pharmacologic activity is exacerbated by other precipitating factors, such as hypokalemia. A study by Steiness and Olesen[8] focused on cardiac arrhythmias induced by hypokalemia in patients being treated with long-term digoxin therapy. Patients with normal serum digoxin concentrations were intentionally depleted of potassium and monitored for the development of arrhythmias consistent with the toxic effects of digoxin. In just 1 week, 6 of the 12 patients being evaluated developed atrial or ventricular arrhythmias after developing hypokalemia, despite therapeutic serum digoxin concentration levels. That study, although small in size and of short duration, supports the hypothesis that hypokalemia sensitizes the myocardium to the effects of digoxin, thereby creating toxic effects on the myocardium despite

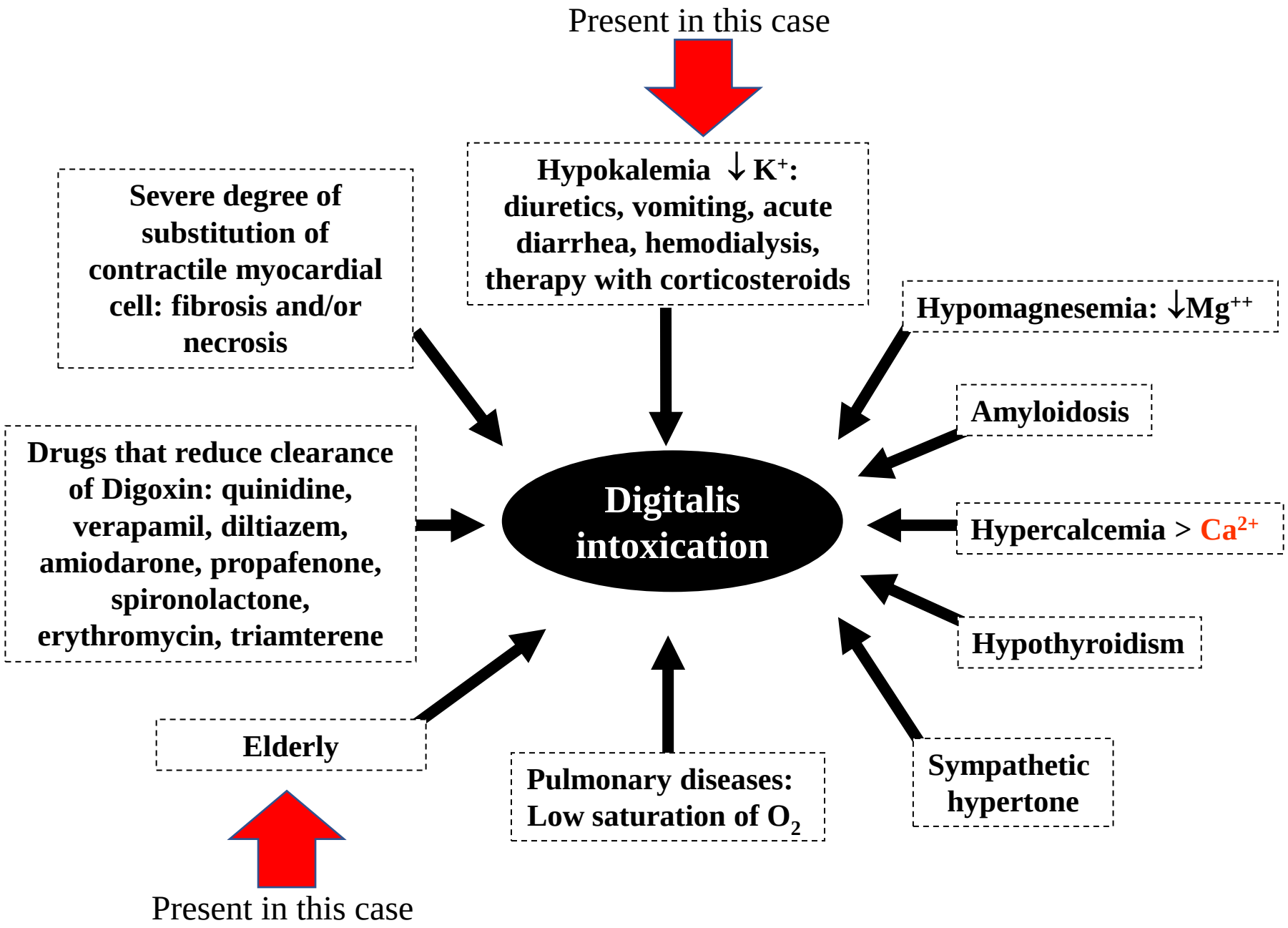
therapeutic serum concentrations.[8] Pertinent to the present case is the fact that this patient's serum potassium was 5.1 mEq/L on admission, but had significantly dropped to 3.1 mEq/L at the onset of the BVT, suggesting that hypokalemia may have been the inciting factor for the development of the appreciated arrhythmia. Furthermore, repletion of the patient's serum potassium without administration of digoxin fragment antibodies coincided with termination of the arrhythmia.mThis case provides an interesting presentation of BVT in a patient with normal serum digoxin concentration levels and hypokalemia. With repletion of serum potassium and without administration of digoxin fragmented antibodies, the patient's arrhythmia resolved and failed to recur.

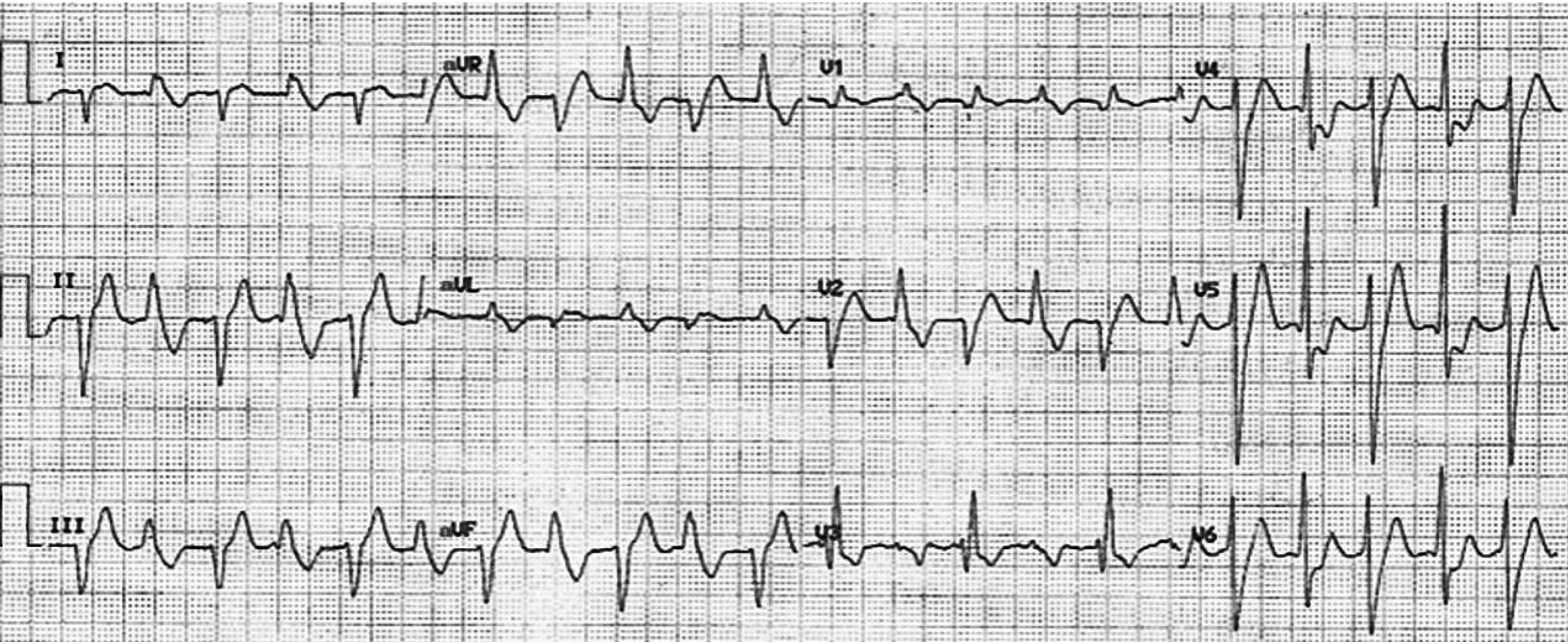
Mechanisms of BVT

1. Triggered activity: in CPVT
2. Enhanced automaticity: Digoxin toxicity
3. Reentrant mechanism (Rare)[8], The fascicular VT mechanism invoked in the presence of organic heart disease and significant conduction system abnormality is typically interfascicular VT, with stable reentry due to slowed conduction which commonly includes bundle branch reentry and sometimes LAF, LPF and LSF[9]
4. **Take-Home Points**

- BVT is characterized by a wide complex tachycardia with an alternating beat-to-beat QRS axis in the frontal plane and is attributed to delayed afterdepolarization–triggered activity in the fascicular branches.
- BVT occurs in few clinical settings, including with toxic effects of digoxin, aconite poisoning, ACTH-producing pheochromocytoma[4], myocardial ischemia, catecholaminergic polymorphic ventricular tachycardia [10], and Andersen-Tawil syndrome [11].
- Hypokalemia[12] may sensitize the myocardium to digoxin, thereby creating toxic effects despite therapeutic serum concentrations of digoxin.

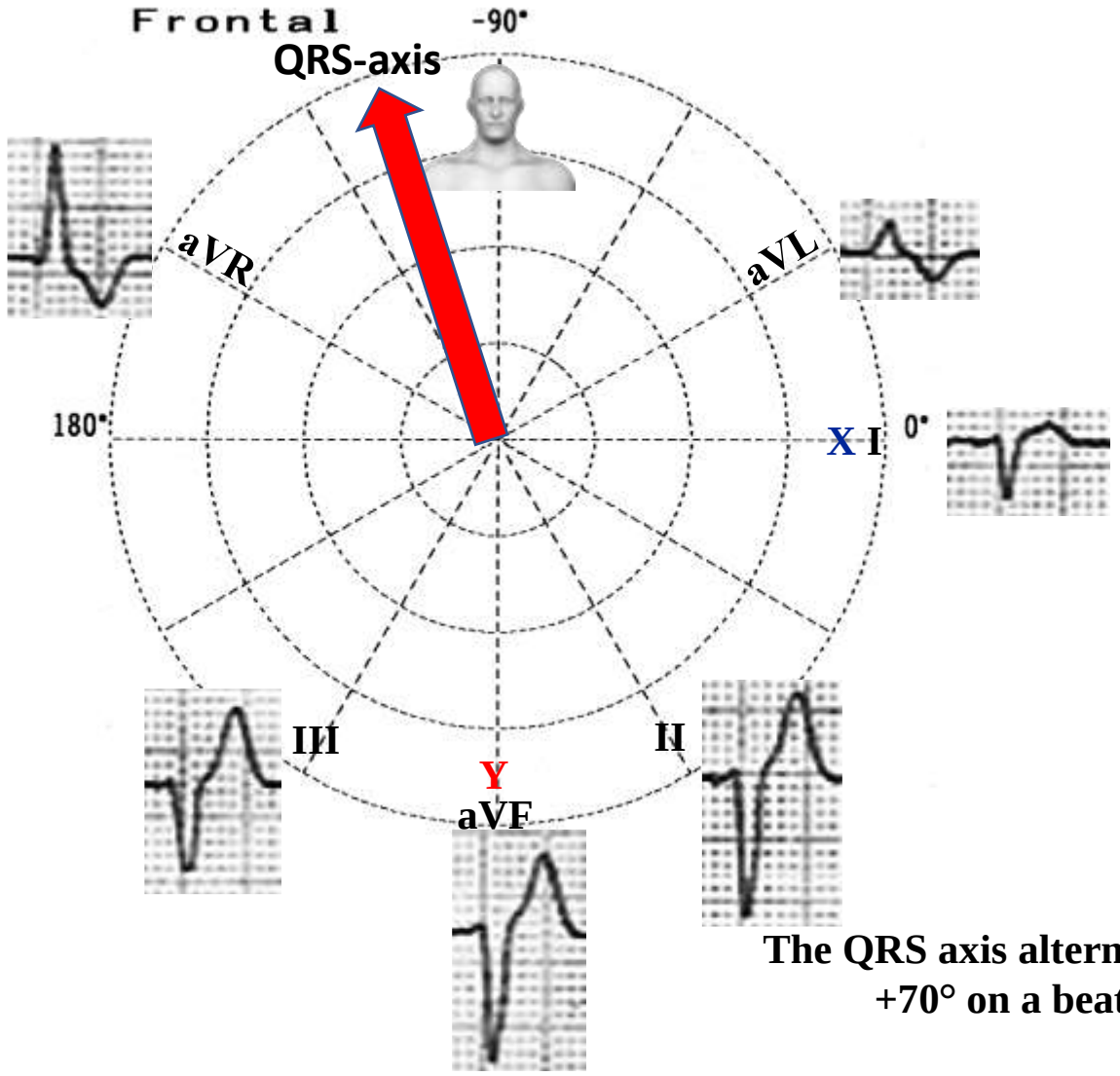
Factors that predispose digitalis intoxication: factors that increase sensitivity to digitalis

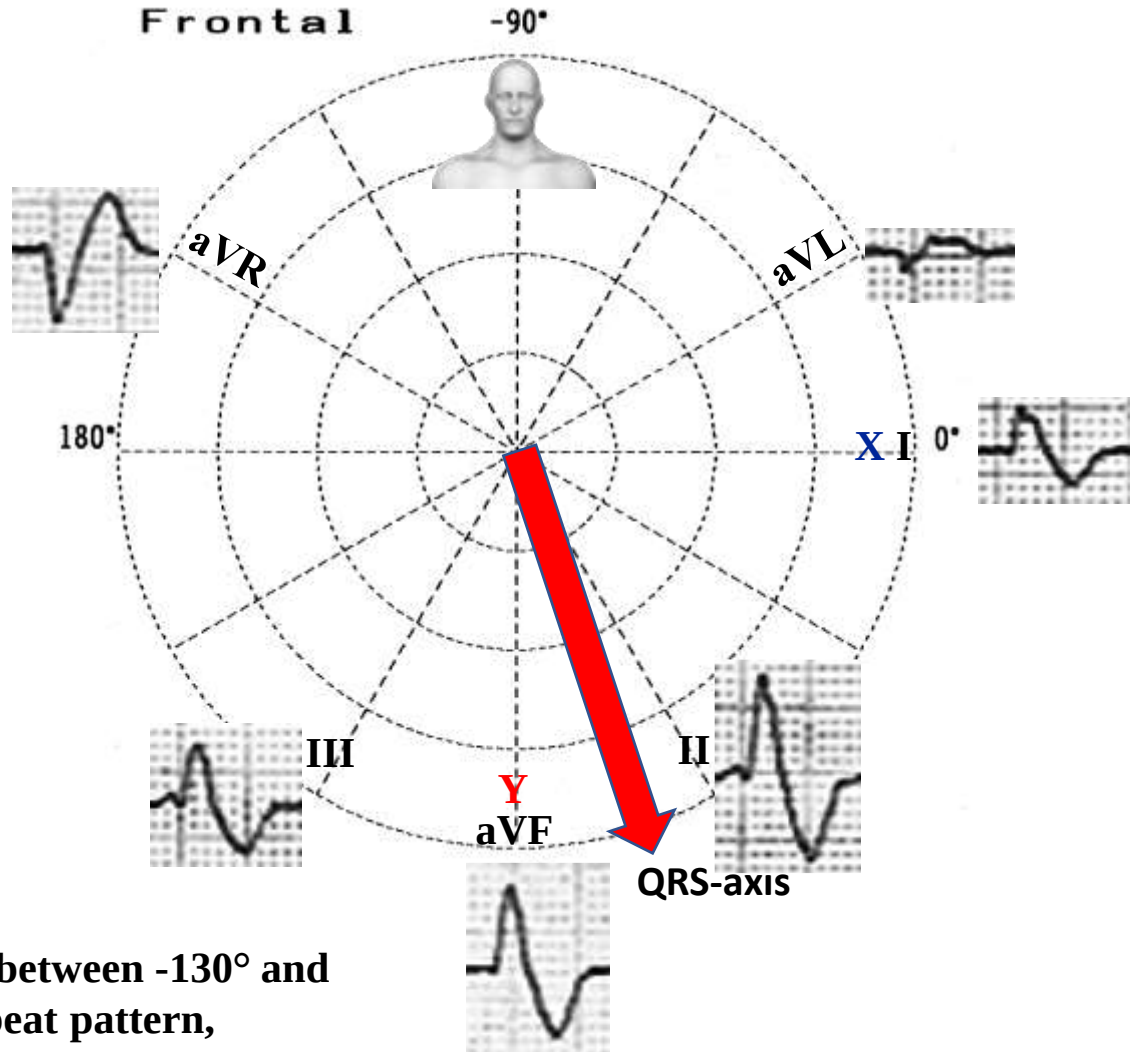




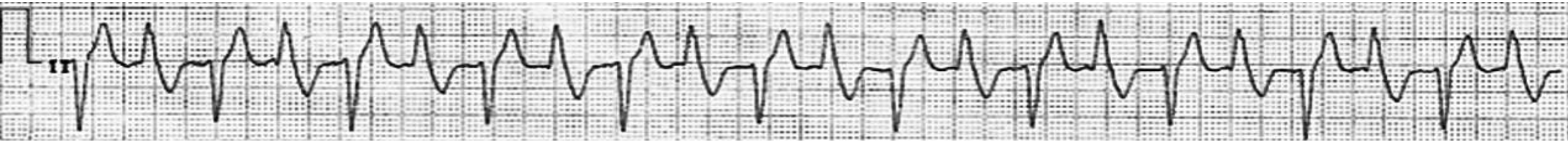
12-lead ECG showing bidirectional ventricular tachycardia in a patient receiving digoxin treatment

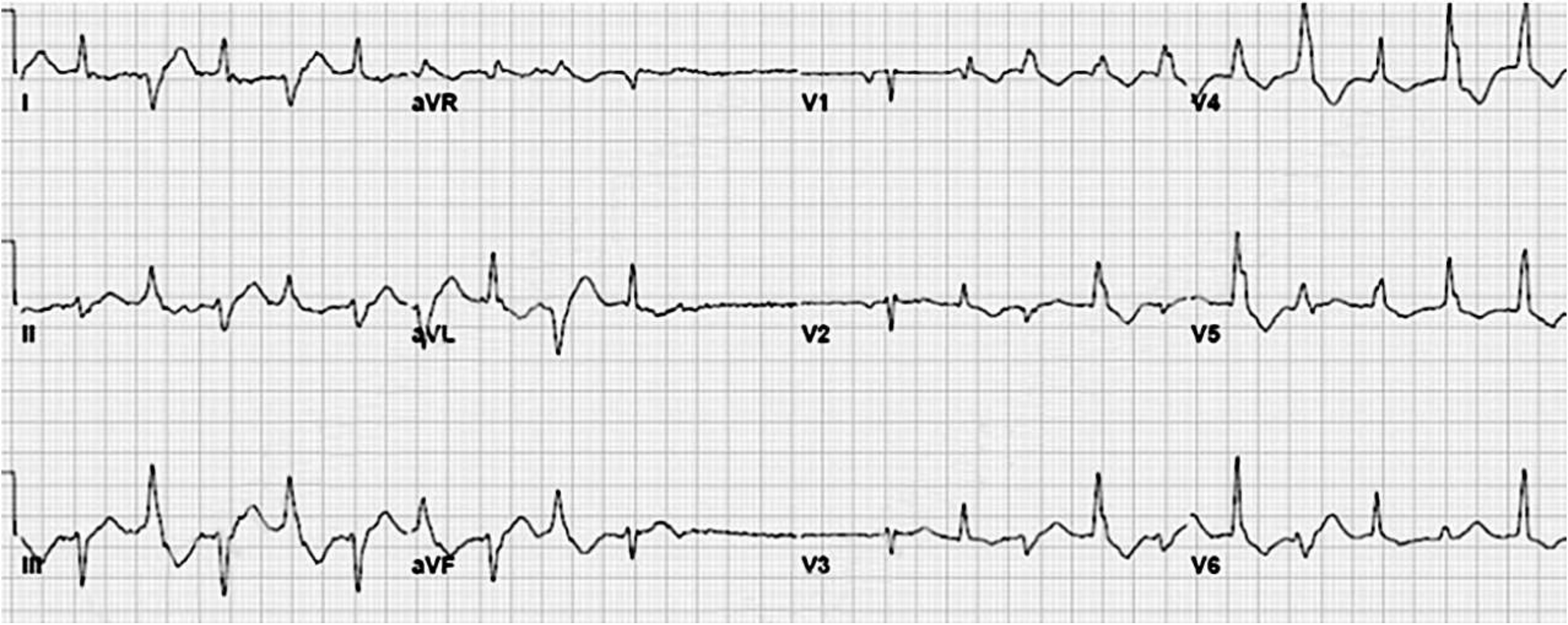
Characteristic alternating beat-to-beat QRS-axis in bidirectional Ventricular Tachycardia in the frontal plane





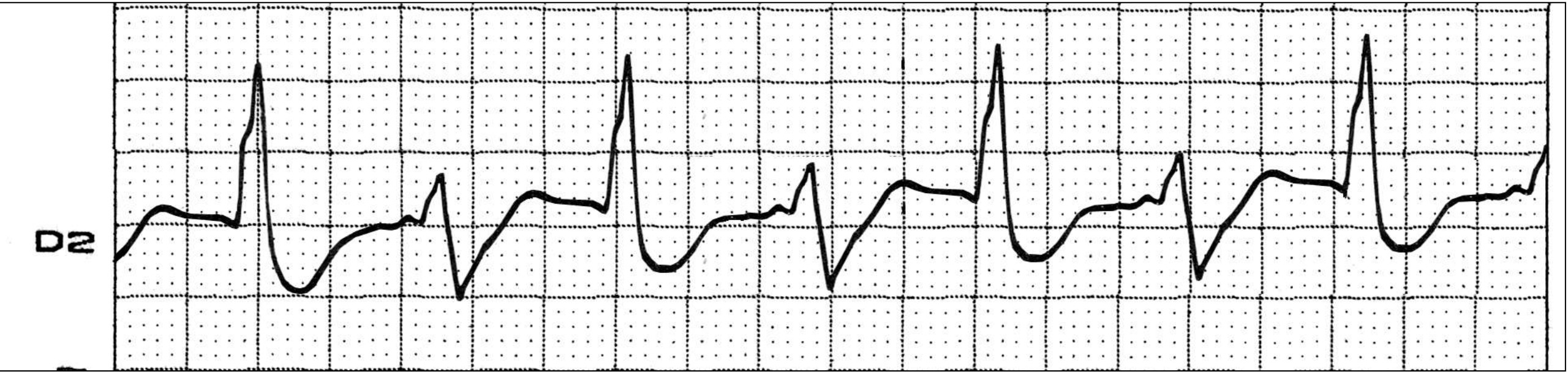
The QRS axis alternates between -130° and +70° on a beat-to-beat pattern,





Bidirectional tachycardia caused by digitalis intoxication Note two distinct QRS morphologies alternating two types of QRS complexes in opposite directions. The QRS complex duration is wide. Both morphologies meet criteria for a ventricular origin. They are both in a right bundle branch block pattern since they are upright in lead V1. One of the QRS complexes is upward concordant in the precordial leads (all upward) indicating a ventricular origin. The other morphology has an R larger than the R' in lead V1 indicating a ventricular origin. Note the pause, one sinus beat, then the resumption of the BVT.

Bidirectional tachycardia caused by digitalis intoxication



The rhythm is regular and fast with HR of 118 bpm. There is no atrial activity observed. QRS complexes are in an alternate fashion, mostly positive or negative, in alternating directions from beat to beat, which indicates that the impulse is alternatively transmitted by the left anterior and posterior fascicles. Frequently, they display RBBB and LBBB pattern in an alternate fashion. These cases may originate in the ventricles (VT) or represent a form of supraventricular tachycardia with aberrance (ventricular aberrance).

The ST segment is depressed, and it displays superior concavity in “spoon”, characteristic of digitalis effect.

Manifestations that suggest digitalis intoxication

➢ **Extracardiac or noncardiac adverse effects**

- **Gastroenteric:** anorexia, nausea, vomiting, diarrhea and abdominal pain. These are the most common symptoms of digoxin intoxication
- **Neuropsychiatric:** headache, confusion, fatigue, weakness, dizziness, restlessness, delirium, mood lability, sleepiness, psychosis, mental confusion, memory lapses, pseudo dementia.
- **Visual:** dyschromatopsia more common for red, green, and yellow, halos, photophobia, red-green or yellow-green vision

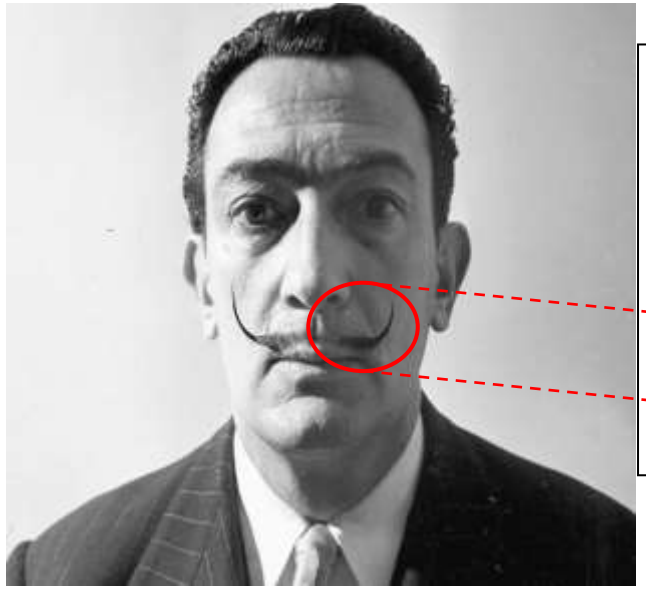
➢ **Cardiac**

- Sinus bradycardia.
- Sinus arrest.
- Blocks: of SA outflow, E.g.: Wenckebach AV block of all degrees with predominance of first degree (conduction slowing and prolongation of refractory period in AV node), of outflow.
- AV dissociation: dominant suppression of pacemaker with passive escape of a low junctional focus or inappropriate acceleration of subsidiary pacemaker or more rarely, dissociation within the AV node proper.
- Atrial tachycardia with variable AV conduction: the most common one and almost pathognomonic.
- Sudden appearance of atrial tachycardia during digitalis therapy in patient with AF.
- Accelerated junctional rhythm or non-paroxysmal junctional tachycardia with frequent isorhythmic dissociation.
- Isolated or bigeminal premature contractions.
- Fascicular VT.
- Accelerated idioventricular rhythm (AIVR).
- **Bidirectional or bifascicular VT.**
- Ventricular flutter.
- Slow VF.

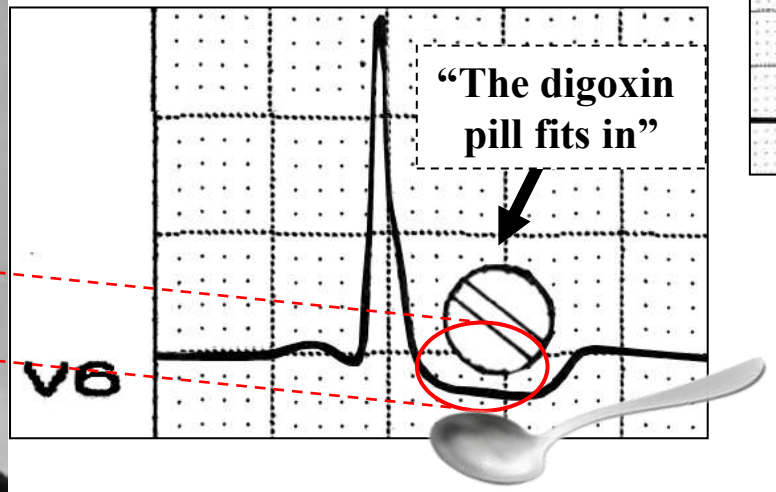
Digitalis effect/intoxicaction on ECG

The earliest modification of digitalis effect on ECG or “digitalis action” are:

- Prolonged PR interval.
- ST segment: shortening and superior convexity (“in spoon”) by shortening of phases 2 and 3 of action potential (AP);
- QT and QTc intervals shortening: main cause of acquired short QT;
- T wave flattening with apiculate form of terminal portion in 10% of cases. Possible symmetrical inversion of T wave (pseudo-ischemic T wave);
- Prominent U wave.

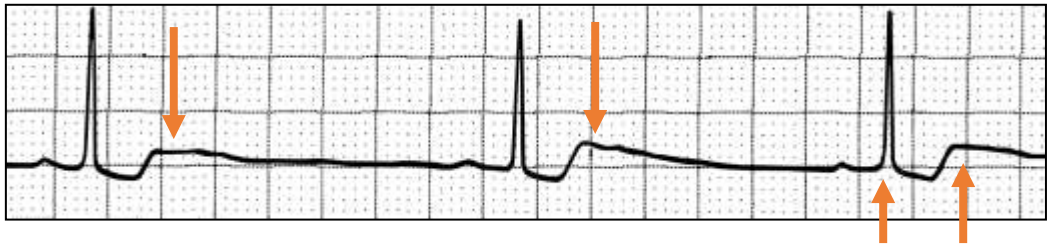


Digitalis effect causes an ST shape segment that resembles Salvador Dalí's mustaches

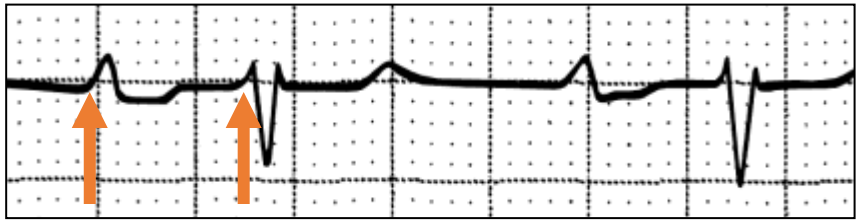


Short ST segment “in spoon”

Apiculate form of terminal portion of wave

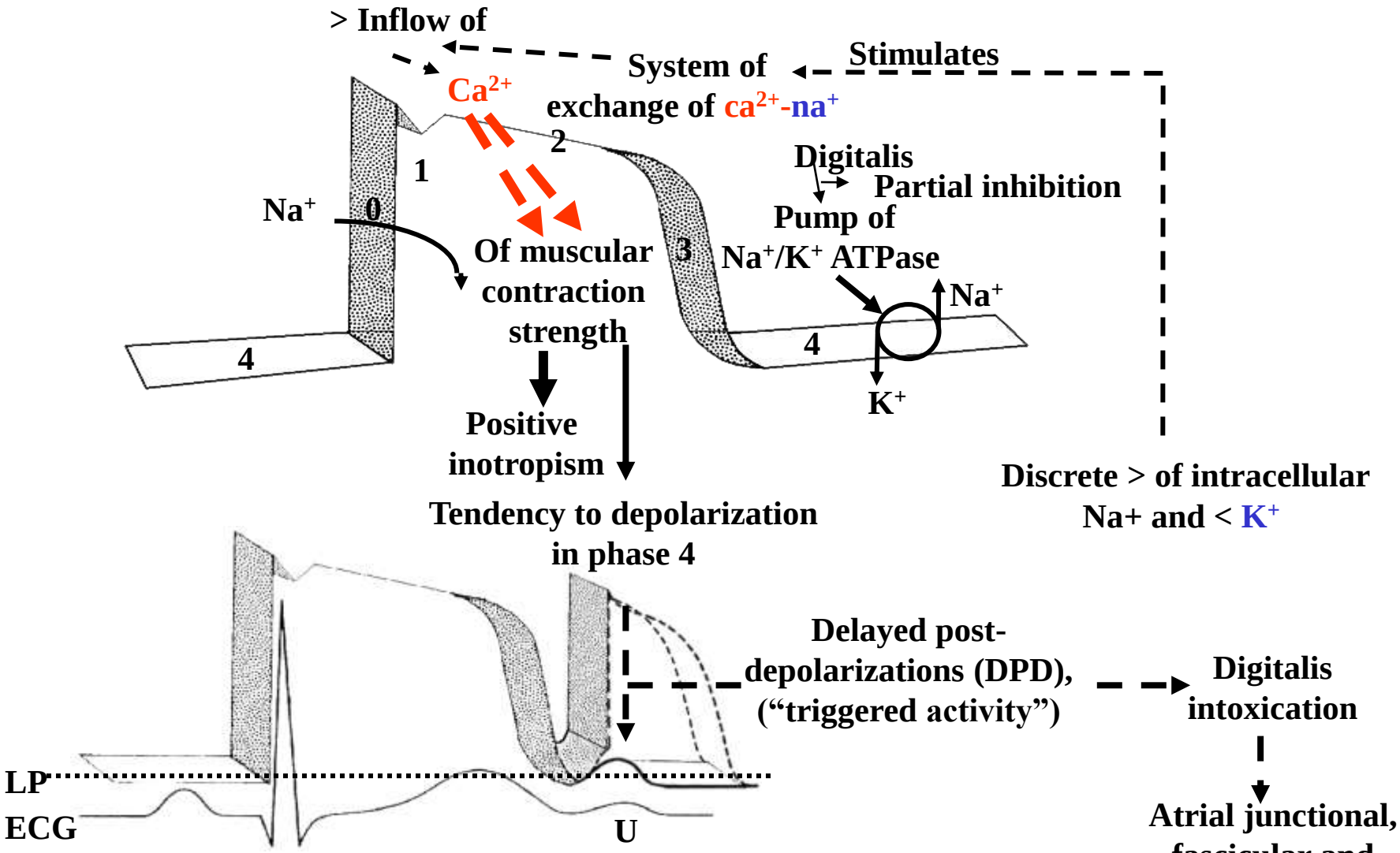


QTc interval shortening

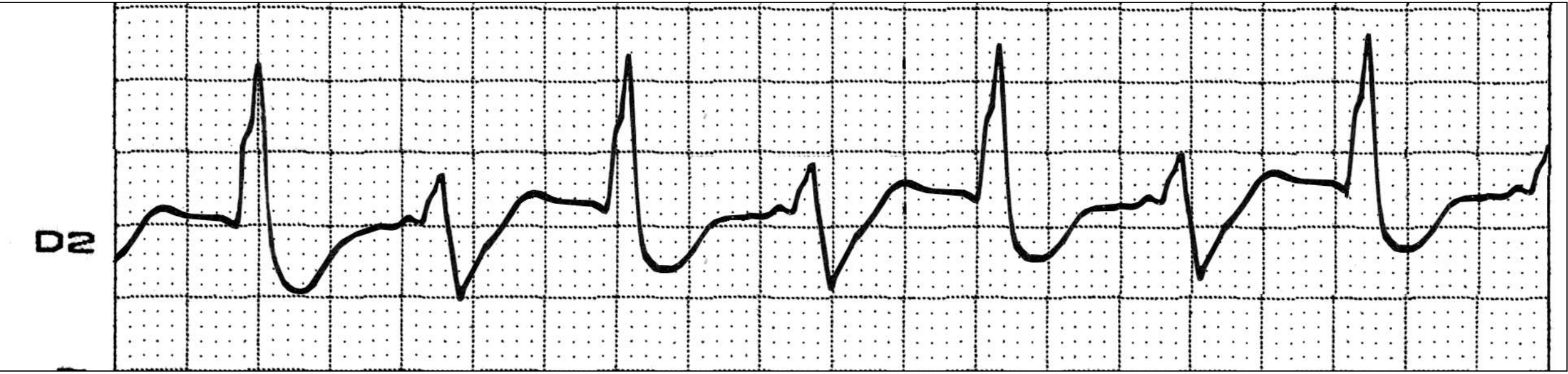


Prolonged PR interval

Electrophysiological mechanism of digitalis effect in arrhythmogenesis



Bidirectional tachycardia caused by digitalis intoxication



The rhythm is regular and fast with HR of 118 bpm. There is no atrial activity observed.

QRS complexes are in an alternate fashion, mostly positive or negative, in alternating directions from beat to beat, which indicates that the impulse is alternatively transmitted by the left anterior and posterior fascicles.

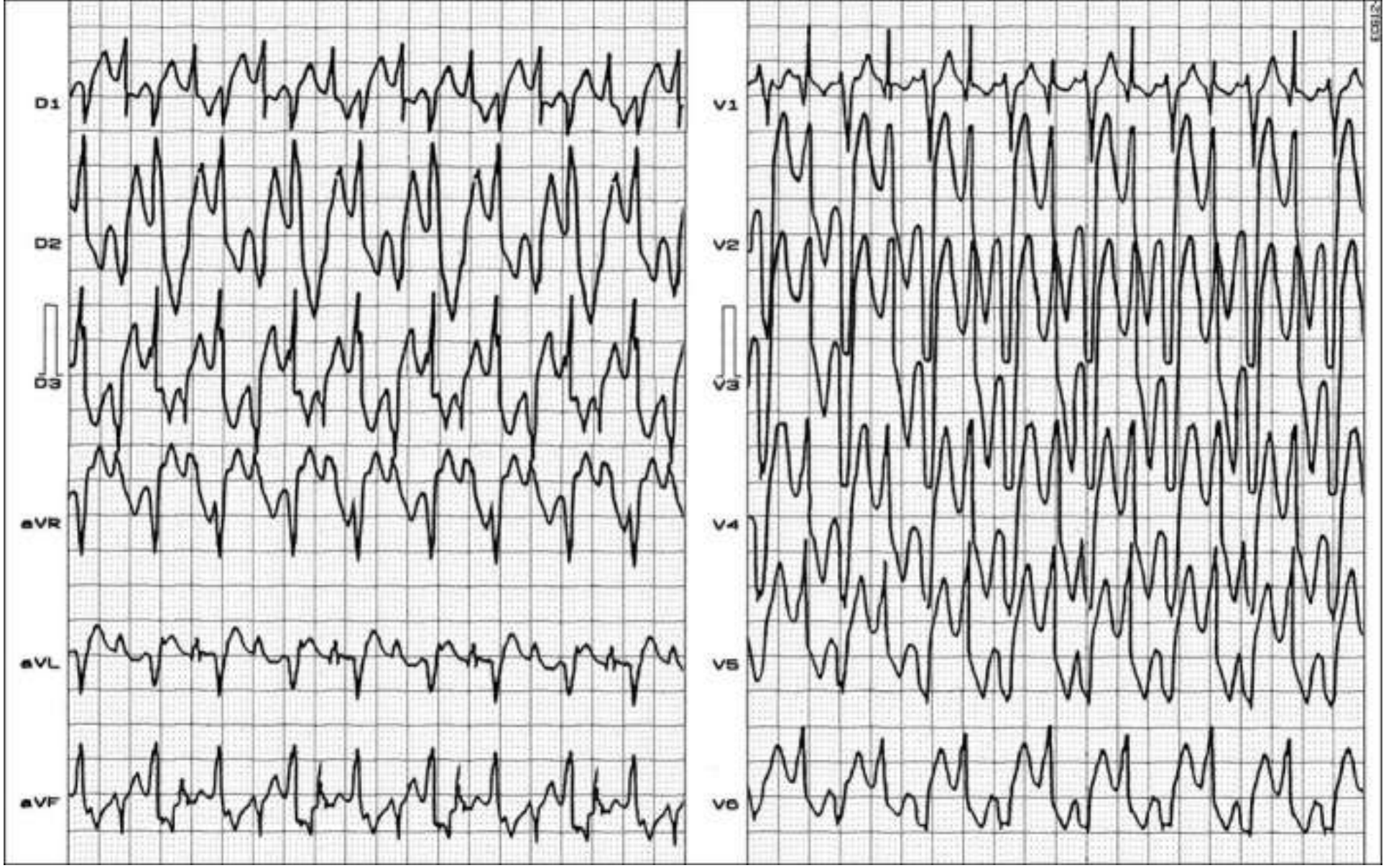
Frequently, they display RBBB and LBBB pattern in an alternate fashion. These cases may originate in the ventricles (VT) or represent a form of supraventricular tachycardia with aberrance (ventricular aberrance).

The ST segment is depressed, and it displays superior concavity in “spoon”, characteristic of digitalis effect. The etiology of bidirectional ventricular tachycardia may be acquired or congenital (next slide).

Characteristic of the ventricular tachycardias in the siting of Catecholaminergic Polymorphic Ventricular Tachycardia

Characteristic is the sequence of junctional tachycardia, PVCs with quadrigeminy, trigeminy, and bigeminy; shorter or longer salvoes of BVT; and bursts of rapid, irregular PVT; depending on the intensity of the adrenergic stimulation, the disappearance occurs in the reverse order. VTs elicited exclusively by exercise or adrenergic stress. In addition, VTs are typically induced by isoproterenol infusion. PVCs: Ca^{2+} channel antagonist, verapamil, can suppress PVCs and NSVT salvoes in CPVT caused by RyR2 mutations. Modifying the abnormal Ca^{2+} handling by Ca^{2+} antagonists might have therapeutic value[13]. Ca^{2+} antagonists partially suppressed CPVT in AD cases. PVT: it is defined as the VT with an irregularly variable axis of the QRS. In CPVT it occurs during physical exercise or emotional stress. Mean HR during CPVT is 192 bpm. Most cases are NSVTs (≈70%), but ≈20% are SVTs and 7% are associated with VF. PVT and BVT in association are observed in ≈20% of cases in the pediatric group. There is 100% inducement of CPVT by exercise, 75% by catecholamine infusion, and none by programmed ventricular stimulation. No late potentials on signal-averaged electrocardiography are recorded. The onset is in the right ventricular outflow tract in more than 50% of the cases[14]. The His-Purkinje system is an important source of focal arrhythmias in CPVT[15]. BVT is a more typical feature. It is identified as a VT characterized by a beat-to-beat alternation of the QRS axis in most of the documented runs of VT (>4 consecutive beats)[16]

See typical ECG in the next slide



Female, Caucasian, 20-year-old patient with recurrent syncope of uncertain etiology after physical and emotional stress; carrier of familial CPVT. QRS complexes alternans are observed with alternating RBBB and RBBB patterns. The QRS axis shifts in a beat-to-beat alternation from −60 to +120°

Characteristic of the ventricular tachycardias in Andersen-Tawil syndrome

Andersen-Tawil syndrome (ATS) is a very rare orphan genetic multisystem channelopathy without structural heart disease (with rare exceptions). ATS type 1 (ATS1) is inherited in an autosomal dominant fashion and is caused by mutations in the *KCNJ2* gene, which encodes the α subunit of the K^+ channel protein Kir2.1 (in ≈ 50 to 60% of cases). ATS type 2 (ATS2) is in turn linked to a rare mutation in the *KCNJ5-GIRK4* gene that encodes the G protein-sensitive-activated inwardly rectifying K^+ channel Kir3.4 (15%), which carries the K^+ current IK(ACh). About 30% of cases are de novo/sporadic, suggesting that additional as-yet unidentified genes also cause the disorder. A triad of periodic muscle paralysis, repolarization changes in the electrocardiogram and structural body changes characterize ATS. The typical muscular change is episodic flaccid muscle weakness. Prolongation of the QU/QUc intervals, and normal or minimally prolonged QT/QTc intervals with a tendency to ventricular arrhythmias are typical repolarization changes. Bidirectional ventricular tachycardia is the hallmark ventricular arrhythmia, but also premature ventricular contractions, and rarely, polymorphic ventricular tachycardia of torsade de pointes type may be present. Patients with ATS have characteristic physical developmental dysmorphisms that affect the face, skull, limbs, thorax and stature. Mild learning difficulties and a distinct neurocognitive phenotype (deficits in executive function and abstract reasoning) have been described. About 60% of affected individuals have all features of the major triad. The purpose of this review is to present historical aspects, nomenclature (observations/criticisms), epidemiology, genetics, electrocardiography, arrhythmias, electrophysiological mechanisms, diagnostic criteria/clues of periodic paralysis, prognosis, and management of ATS.

Bidirectional Ventricular Tachycardia

BVT is a unique ventricular arrhythmia characterized by regular (or irregular) VT with complete RBBB or complete left bundle branch block (LBBB) patterns, determining the presence of two morphologies of the QRS. In addition, there is typically alternating beat-to-beat QRS axis (SÂQRS) in the frontal plane, with differences of ≈180°: one beat has SÂQRS between –60° and –90°, and the following ≈+120° to +130°. Triggered activity (TA) and reentry are possible mechanisms. Possible causes of BVT are:

Cardiac channelopathies and genetic entities: familial CPVT, ATS,[17] left ventricular non-compaction,[18] and hypokalemic periodic paralysis.[19] *Acquired:* severe digoxin toxicity,[20] BVT herbal aconite poisoning,[21] pheochromocytoma,[22, 23] subacute myocarditis,[24] myocardial infarction/ischemia,[25] and ischemic cardiomyopathy during ablation in the absence of acute coronary syndrome. BVT is observed more frequently in elderly patients. Both severe digoxin intoxication and ATS have BVT as the ventricular arrhythmia hallmark.

When a patient presents with de novo VT with alternating morphology on the ECG, scar-mediated reentry VT should be considered as a differential diagnosis. Scar-mediated VT may present with VT of various morphologies as a consequence of multiple exit sites,[27] and may be caused by cardiac metastasis,[28] cardiac sarcoidosis,[29] dilated cardiomyopathy,[30] and hypokalemia.[31]

Pseudo BVT was observed by Serra JL et al[32] in a patient with transient complete atrioventricular block after DDD pacemaker implantation, which was secondary to extrasystoles with retrograde ventriculoatrial conduction and alternating anterograde atrioventricular conduction.

ATS increases the risk of arrhythmias by disturbing the electrical signals that normally coordinate individual heart cells. The genetic variant disturbs an ion channel responsible for the flow of K+, reducing the IK1 current. This prolongs the cardiac AP - the characteristic pattern of voltage changes across the cell membrane that occur with each heartbeat, and depolarizes the resting membrane potential of cardiac and skeletal muscle cells. When relaxed, these cells have fewer positively charged ions on the inner side of their cell membrane than on the outer side,

referred to as being polarized.[32]

The main ion current responsible for maintaining this polarity is IK1, and a decrease in this current leads to less polarity at rest, or a depolarized resting membrane potential. When these cells contract, positively charged ions, such as sodium and calcium, enter the cell through ion channels, depolarizing or reversing this polarity. After a contraction has taken place, the cell restores its polarity by allowing positively charged ions, such as potassium to leave the cell, restoring the membrane to its relaxed, polarized state.[34] The genetic variant found in ATS, leads to a decrease in the flow of potassium, slowing of the rate of repolarization, which can be seen in individual cardiac muscle cells as a longer AP, and on the surface ECG as a prolonged QT interval. The underlying mechanisms responsible for the arrhythmias seen in ATS are early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs).

Arrhythmias by Triggered Activity

TA depends on the oscillations of AP that originate potentials that spread during the process of repolarization in phases 2 or 3 (EAD) or when repolarization is completed in phase 4 (DAD). TA is defined by impulse initiation caused by afterdepolarizations (membrane potential oscillations that occur during or immediately following a preceding AP).[35] Afterdepolarizations occur only in the presence of a previous AP (the trigger), and when they reach the threshold potential, a new AP is generated. This may be the source of a new triggered response, leading to self-sustaining TA.

EAD-Induced Triggered Activity

EADs occur when AP duration is prolonged and stop when repolarization is complete, are suppressed by “fast pacing”, and are observed in two AP levels (between 0 and –30 mV and between –60 mV and –70 mV). They have a tendency to occur in runs. Agents and manipulations that may lead to EADs include slow rate (bradycardia, complete heart block), mechanical stretch, hypokalemia, hypoxia, aconitine, hypothermia, low

extracellular K^+, Ca^{2+}, or magnesium (Mg^{2+}) concentration, Class IA antiarrhythmic drugs [quinidine, disopyramide, procainamide], Class IB antiarrhythmic drugs [flecainide, encainide, indecainide], Class III antiarrhythmic drugs [amiodarone, sotalol, bretylium], phenothiazines, tricyclic and tetracyclic antidepressants, erythromycin, antihistamines, cesium, amiloride, barium, hyperadrenergic state [subarachnoid hemorrhage], mitral valve prolapse, and ethylenediaminetetra-acetic acid.

This type of TA is not expected to follow premature stimulation (which is associated with an acceleration of repolarization that decreases the EAD amplitude), with the exception of a long compensatory pause following a premature stimulus, which can be even more important than bradycardia in initiating torsade de pointes.[35] Some antiarrhythmic agents, especially Class IA and III drugs, may become proarrhythmic because of their therapeutic effect of prolonging the AP. Many drugs can predispose to the formation of EADs, particularly when associated with hypokalemia and/or bradycardia, additional factors that result in prolongation of the AP. Catecholamines may enhance EADs by augmenting the Ca^{2+} current, however the resultant increase in HR along with the increase in K+ current effectively reduces the AP duration and thus abolishes EADs.[37]

EADs are divided into:

Phase 2 AP, dome, or “plateau” phase of the AP: in this phase the AP remains almost constant, as the membrane balance between K^+ (moving out of the cell) and Ca^{2+} (moving into the cell) currents. In this phase slow inward Ca^{2+} traffic by the slow ICa-L channel occurs.

Phase 2 AP is a period in which membrane potentials become relatively stable for up to several hundred milliseconds. During this phase, Ca2+ entry, via L-type calcium channels, triggers contraction. Counter-balancing the Ca2+ influx, K+ cations pass through the membrane in the outward direction, resulting in a balance between inward and outward currents.[38] This phase is a period of high membrane resistance[39] and little current flow. Consequently, small changes in either repolarizing or depolarizing currents can have profound effects on the AP duration and profile. As a wide variety of agents and conditions can result in a decreased outward current or increased inward current (thereby shifting the normal outward

current), they can establish the conditions necessary for EAD.

Phase 3 of fast repolarization: these post-depolarizations occur during phase 3 of AP by reduction in the activity of outward K+ channels (I_{kR} or I_{ks}) as it happens in congenital LQT2 and LQT1, respectively. The latter differentiates from the former in that they present Ca2+ release from the Ca^{2+} release channel or ryanodine receptor. Both phases may appear during similar experimental conditions, but they differ morphologically as well as in the underlying ionic mechanism.

Phase 2 EADs appear to be related to $I_{Ca\text{-}L}$ current, while phase 3 EADs may be the result of electronic current across repolarization or the result of low I_{K1}.[40]

DAD-Induced Triggered Activity

A DAD is an oscillation in membrane voltage that occurs after completion of the repolarization of the AP (during phase 4). These oscillations are caused by a variety of conditions that raise the diastolic intracellular Ca^{2+} concentration, which cause Ca^{2+} mediated oscillations that can trigger a new AP if they reach the stimulation threshold.[40] Digitalis intoxication was the first observed cause of DAD.41 This occurs via inhibition of the Na^+/K^+ pump, which promotes the release of Ca^{2+} from the sarcoplasmic reticulum. Clinically, BVT caused by digoxin toxicity is considered an example of TA.[42] Catecholamines can cause DADs by causing intracellular Ca^{2+} overload via an increase in $I_{Ca\text{-}L}$ and the Na^+-Ca^{2+} exchange current, among other mechanisms. Ischemia-induced DADs are thought to be mediated by the accumulation of lysophosphoglycerides in the ischemic tissue,[44] with subsequent elevation in Na+ and Ca^{2+}. Abnormal sarcoplasmic reticulum function (mutations in the ryanodine receptor) can also lead to intracellular Ca^{2+} overload, facilitating clinical arrhythmias such as CPVT.[43] A critical factor for the development of DADs, is the duration of the AP. Longer APs are associated with more Ca^{2+} overload and facilitate DADs. Therefore, drugs that prolong AP (Class IA antiarrhythmic agents) can occasionally increase DAD amplitude. Triggered arrhythmias induced by DADs may be terminated by single stimuli.

Therefore, other electrophysiologic features are needed to distinguish them from the reentrant tachycardias. The rate dependency of the coupling interval may be useful, because in most cases of DAD-induced arrhythmias, the shorter the cycle of stimulation, the shorter the coupling interval to the induced arrhythmia. This is in contrast to the inverse relationship seen in reentrant arrhythmias, where the shorter the coupling intervals of the initiating stimuli, the longer the coupling interval of the first arrhythmic beat. Since this is not always the case, other electrophysiologic properties must be taken into account. Adenosine has been used as a test for the diagnosis of DADs. Adenosine reduces the Ca^{2+} inward current indirectly by inhibiting effects on adenylate cyclase and cyclic adenosine monophosphate. Thus, it may abolish DADs induced by catecholamines, but does not alter DADs induced by Na^{+}/K^{+} pump inhibition. The interruption of VT by adenosine points toward catecholamine-induced DADs as the underlying mechanism.

Clinical examples, where DADs may be involved, are atrial tachycardia, digitalis toxicity-induced tachycardia, accelerated ventricular rhythms in the setting of acute myocardial infarction, some forms of repetitive monomorphic VT, reperfusion-induced arrhythmias, right ventricular outflow tract VT, exercise-induced VT (CPVT), and ATS1.

The main clinical causes and arrhythmias responsible for DAD are ischemia and reperfusion, digitalis intoxication (atrial tachycardia, junctional VT and BVT), catecholamine-dependent VT, hypercalcemia, multifocal or chaotic atrial tachycardia, multiple foci with triggered automaticity by delayed APs in phase 4, originated by increase of circulating catecholamines, hypoxia, increase of CO_2, hypopotassemia, hypomagnesemia, idiopathic VT of the right and left ventricular outflow tract and some idiopathic VTs CPVT, and ATS. Decreased amplitude of the I_{K1} causes a repolarizing current at the end of the AP and less current to keep the resting membrane stable. In the experimental isolated canine tissue model, Morita et al[40] demonstrated that in ATS the extrasystoles/VT result from DADs in ventricular myocytes. Also, adrenergic stress increases the ectopic load,[36] which fits with TA as the mechanism. Additionally, an increased automaticity as a consequence of decreased I_{K1} could be the

arrhythmogenic substrate,[46] and arrhythmias based on this mechanism also increase during epinephrine infusion. An eventual specific role of Purkinje fibers in ATS has not been studied experimentally. A highly vulnerable arrhythmic substrate exists in the specialized conduction system with high local loss of I_{K1} activity. Ventricular extrasystoles, although highly polymorphic, are characterized by narrow QRS complexes, suggesting a Purkinje fibers origin.

Ventricular extrasystoles originating from Purkinje fibers was reported by Smith et al.[46] However, radiofrequency catheter ablation is not indicated due to the polymorphic nature.[48]

The prolonged APs can lead to arrhythmias through several potential mechanisms. The frequent extrasystoles and BVT typical of ATS are initiated by a triggering beat in the form of an afterdepolarization. EADs, occurring before the cell has fully repolarized, arise due to reactivation of calcium and sodium channels that would normally be inactivated until the next heartbeat is due. Under the right conditions, reactivation of these currents can cause further depolarization of the cell, facilitated by the Na^+- Ca^{2+} exchanger. [49,50] EADs may occur as single events, but they may also occur repeatedly leading to multiple rapid activations of the cell.[51]

DADs, occurring after an AP is completed, arise from the spontaneous release of Ca^{2+} from the sarcoplasmic reticulum. This Ca^{2+} release then leaves the cell through the Na^+- Ca^{2+} exchanger in exchange for Na^+, generating a net inward current and depolarizing the cell membrane.[52] If this transient inward current is large enough, a premature AP is triggered. The muscle weakness seen in ATS arises from the depolarization of the resting membrane potential caused by a decrease in I_{K1}. The depolarized resting membrane potential means that sodium channels, which are responsible for initiating APs, are unable to fully recover from inactivation, leading to a less excitable membrane and less forceful muscle contraction. The mechanisms underlying the skeletal abnormalities seen in ATS have not been fully explained. Potential factors include impaired function of osteoclasts, cells which regulate bone growth, or disruption of the bone morphogenetic protein signaling cascade.

THE POSTULATED EXPERIMENTAL “PING PONG” MECHANISM IN THE HIS-PURKINJE SYSTEM TO EXPLAIN BVT

Baher et al[51] evaluated a "ping pong" experimental model of reciprocating bigeminy to explain BVT. In human heart studies, alternating ectopic foci originating from the distal His–Purkinje system in-both ventricles were attributed to the origin of BVT. They constructed a two-dimensional anatomic model of rabbit ventricles with a simplified His–Purkinje system, in which different sites in this location had different heart rate thresholds for DAD-induced bigeminy. They speculated that the full spectrum of BVT can be accounted for based on the known properties of DAD-triggered arrhythmias. In the case of a single arrhythmic focus in the distal His–Purkinje system or ventricular myocardium, a DAD-triggered extrasystole alternated with each sinus beat in bigeminy. On the other hand, when two foci are involved, ventricular bigeminy results from the foci activating each other like a ping pong mechanism. In rare cases, of TdP, three or more foci develop bigeminy. When bigeminy progresses to repetitive DADs, a run of TA is generated, and the site with the most rapid rate of TA overdrives the other slower sites, causing a monomorphic VT. VF is registered when two mechanisms operate concomitantly: reentry and DAD TA.[51] ECG characterization of BVT consists of a regular VT, HR between 140 and 200 bpm, RBBB pattern, sudden change of QRS morphology by changing of the SÂQRS, successively from beat to beat, SÂQRS in the FP with differences close to 180º; one beat presents ÂQRS between -60º and -90º (complete RBBB + LAFB) and the following between +120º to +130º (complete RBBB + LPFB), occasionally there is alternating RBBB and LBBB morphology. The origin of the tachycardia is located near the His bundle bifurcation. This suggests a single focus at the interventricular septum with two exit sites, depolarizing the RV and LV in an alternate fashion. Two sets of fairly constant and alternating ventricular arrhythmia intervals can be recorded. This fact is consistent with two ventricular circuits used alternatively. It is postulated that the tachycardia is due to macro-reentry involving the two fascicles of the LBB. Reentry may be a possible mechanism in some cases of BVT. An association in the ECG of sinus bradycardia + normal QTC interval + stress-related, BVT or polymorphic VT without apparent structural heart disease are clues for the diagnosis of CPVT.[51-53]

Demonstration of left septal fascicle in fascicular tachycardia

Fascicular tachycardia (FT) is an uncommon cause of monomorphic sustained VT Sung & Scheinman[9] described six cases of of 823 consecutive VT cases FT with multiform QRS morphologies. They analyzed retrospectively FT with multiform QRS patterns, with 3 cases exhibiting narrow QRS VT as well. All underwent electrophysiology study including fascicular potential mapping, entrainment pacing, and electroanatomic mapping. The first 3 cases describe similar multiform VT patterns with successful ablation in the upper mid septum. Initially, a RBBB-VT with superior axis was induced. RFCA targeting the left posterior fascicle (LPF) resulted in a second VT with RBBB inferior axis. RFCA in the upper septum just apical to the LBB potential abolished VT in all cases. Cases 4 and 5 showed RBBB VT with alternating fascicular block compatible with upper septal dependent VT, resulting in bundle branch reentrant VT (BBRT) after ablation of LPF and left anterior fascicle (LAF). Finally, Cases 5 and 6 demonstrated spontaneous shift in QRS morphology during VT, implicating participation of a third fascicle. In Case 6, successful ablation was achieved over the proximal LAF, likely representing insertion of the auxiliary fascicle near the proximal LAF. Multiform FTs show a reentrant mechanism using multiple fascicular branches. We hypothesize that retrograde conduction over the septal fascicle produces alternate fascicular patterns as well as narrow VT forms. Ablation of the respective fascicle was successful in abolishing FT but does not preclude development of BBRT unless septal fascicle is targeted and ablated.

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Thank you very much for your attention!

Andrés Ricardo Pérez-Riera & Raimundo Barbosa-Barros