

Fast Sustained Wide Regular Complex Tachycardia



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Portuguese

Paciente feminina, 58 anos, admitida na sala de emergência com taquiarritmia sustentada regular muito rápida, causando instabilidade hemodinâmica: suor frio e profuso, palidez, má perfusão periférica, hipotensão (PA 80/40 mmHg), taquipneia, e baixo nível de consciência. Volume aumentado na região anterior do pescoço e a palpação de consistência dura e multinodular. Ausência de exoftalmia. A filha refere que está em o uso regular de propilracil 600mg/dia há 6 meses.

ECG realizado na admissão (ECG-1), revertido com cardioversão eléctrica (100 Joules). ECG-2 realizado após a cardioversão.

Perguntas:

1. Qual o diagnóstico do ECG-1?
2. Qual o diagnóstico do ECG-2?
3. Qual o valor de contar com ambos os traçados?

English

A 58-year-old female patient was admitted to the emergency room with a very fast regular tachyarrhythmia, causing hemodynamic instability: profuse cold sweat, pallor, poor peripheral perfusion, hypotension (BP 80/40 mmHg), tachypneic, low consciousness level. A multinodular of hard consistency goiter is visualized and palpated in the anterior face of the neck. Absence of exophthalmos.

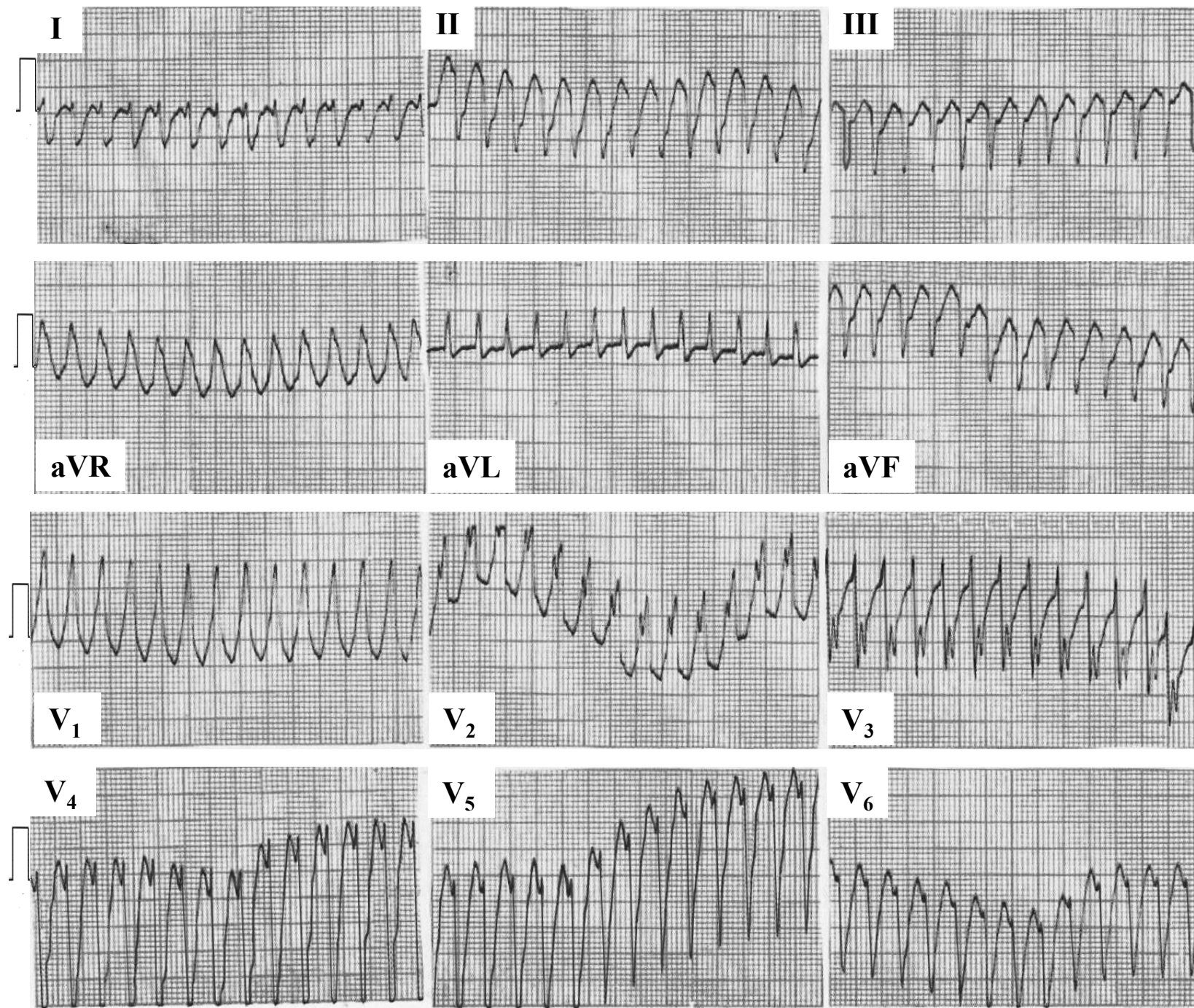
Her daughter refers that she was in regular use of propylthyracil 600mg daily since approximately six months ago.

ECG performed at admission (ECG-1), reverted with electrical cardioversion (100 Joules). ECG-2 performed immediately after cardioversion.

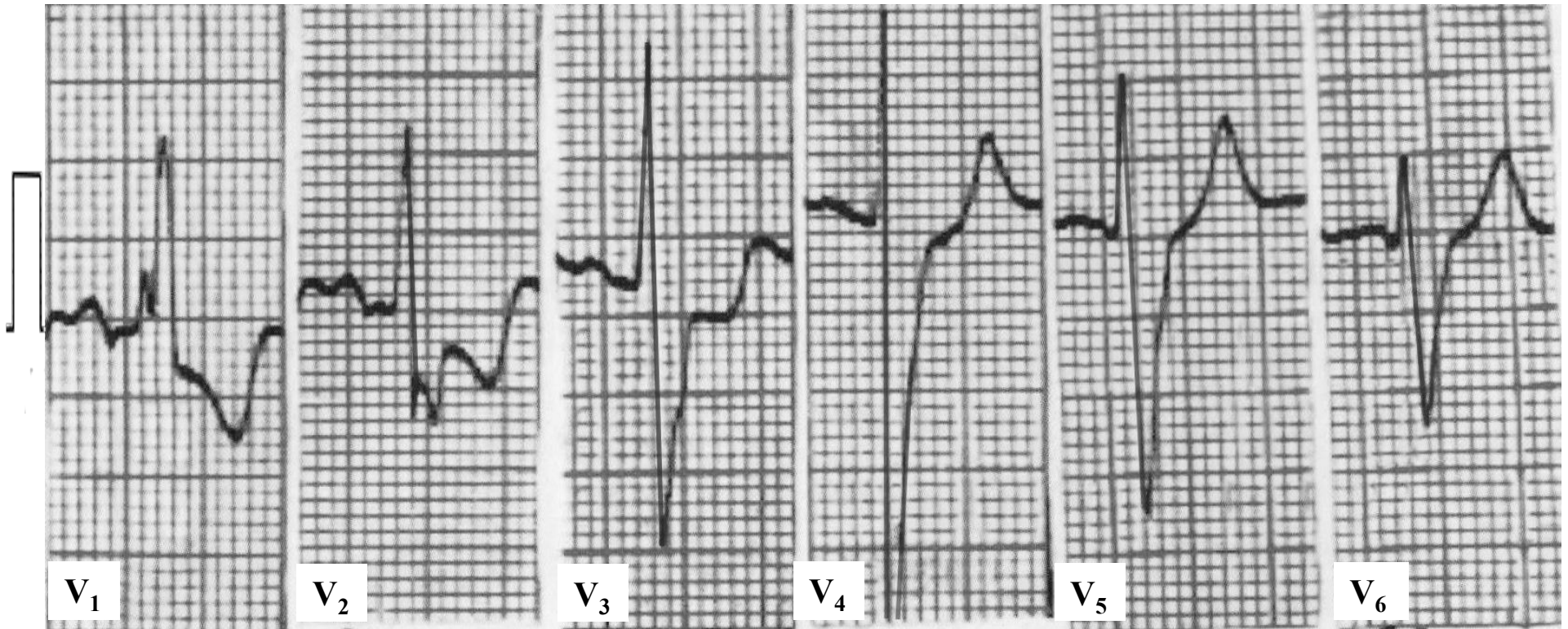
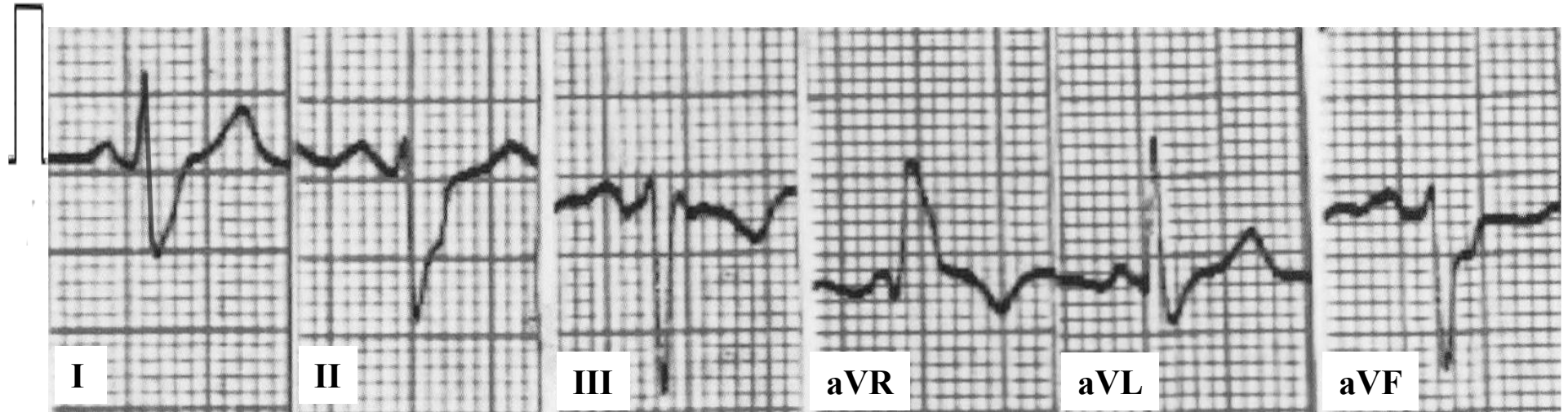
Questions:

1. Which is the ECG-1 diagnosis?
2. Which is the ECG-2 diagnosis?
3. What is the value of having both tracings?

ECG-1



ECG-2



Colleagues opinions

Spanish

Buenas noches estimados Andrés y Raimundo! !! Por la edad de la paciente, y los trastornos de conducción en el ECG-2 post-CVE tiene cardiopatía estructural (Enfermedad de Chagas?) y probablemente portadora de hipertiroidismo por bocio multinodular en tratamiento con propiltiouracilo a dosis relativamente altas (no hay descriptos efectos adversos). Ingresa con taquicardia QRS ancho con descompensación hemodinámica. En base a esto opino:

ECG #1: taquicardia de QRS ancho (130 mseg) y 250 l/x' con imagen de BRD like con eje desviado a extrema izquierda (tierra de nadie). Ausencia de complejos RS en precordiales, R monofásica en V1, rS en V6, R en aVR, complejos predominantemente negativos de V4 a V6 y disociación VA 1:1

Diagnostico: TVMS por reentrada rama-rama.

ECG #2: ritmo sinusal, intervalo PR 170 mseg, duración de la onda P 120 mseg. : probable BIA parcial, onda P plus minus en III y V1, BCRD + HASI (muy frecuente en Chagas+epidemiología). QRS 160 mseg. (más ancho que en taquicardia).

Al tener ambos ECGs se pueden hacer mediciones del QRS que sirven para justificar mi diagnóstico.

Espero el diagnóstico de los maestros del Foro, y así seguir aprendiendo de ellos.

Me despido muy afectuosamente.

Dr Juan Carlos Manzardo

Mendoza - Argentina

English

Good evening dear Andrés and Raimundo: By the age of the patient, and the conduction disturbance in the post- electrical cardioversion, I think that this patient has structural heart disease (Chagas disease?). Additionally, she is probably carrier of multinodular goiter hyperthyroidism on treatment with propylthiouracil at relatively high doses.

She had a wide QRS tachycardia with hemodynamic instability. Based on this I think:

ECG # 1: Sustained wide complex QRS tachycardia (QRS duration 130 ms), heart rate 250 bpm, RBBB-like pattern with extreme left axis deviation of the QRS axis (“no-man's land”), absence of RS complexes across the precordial leads, monophasic R wave in V1, rS in V6, R in aVR, predominantly negative QRSs from V4 to V6 and 1:1 AV dissociation.

Diagnosis: Sustained Monomorphic Bundle Branch Reentrant Ventricular Tachycardia (BBRVT)

ECG # 2: sinus rhythm, PR interval 170 ms, P wave duration 120 ms: Probable partial biatrial enlargement, P minus plus in III and V1, RBBB + LAFB (very common in Chagas + epidemiology). QRS duration 160 ms. (Wider than in tachycardia).

Having both ECGs to make QRS measurements that help to justify my diagnosis.

I hope hear the diagnosis from the teachers of the Forum, and thus continue to learn from them.

Sincerely,

Juan Carlos **Manzardo MD** Mendoza Argentina



Spanish

Querido amigo Juan Carlos Manzardo: me parece que posiblemente cometiste un error de digitación: escribiste: "con el eje mostrando extremo desvío a la izquierda (“tierra de nadie”). La tierra de nadie que en inglés se conoce como “**No man's land**” en electrocardiografía es aquella área del plano frontal cuando el eje eléctrico del QRS se encuentra localizado en el cuadrante superior derecho “**right upper quadrant**” y no en el superior izquierdo, es decir entre -90° y $\pm 180^\circ$ (el extremo desvío del eje del QRS a la izquierda ocurre cuando el mismo se encuentra entre -30° y -90°). La “tierra de nadie” es aquella donde se localiza la derivación unipolar de los miembros aVR conocida como la derivación “olvidada” o en inglés “**the forgotten lead**” o negligenciada es decir aVR (1) Cuando una taquicardia de QRS ancho tiene el eje en la tierra de nadie debemos pensar en TV. “¿Por qué la denominación de derivación olvidada es dada para aVR? Porque es la única derivación que no enfrenta ninguna pared del ventrículo izquierdo Esta es la derivación que enfrenta el tracto de salida del VD (RVOT)

Andrés

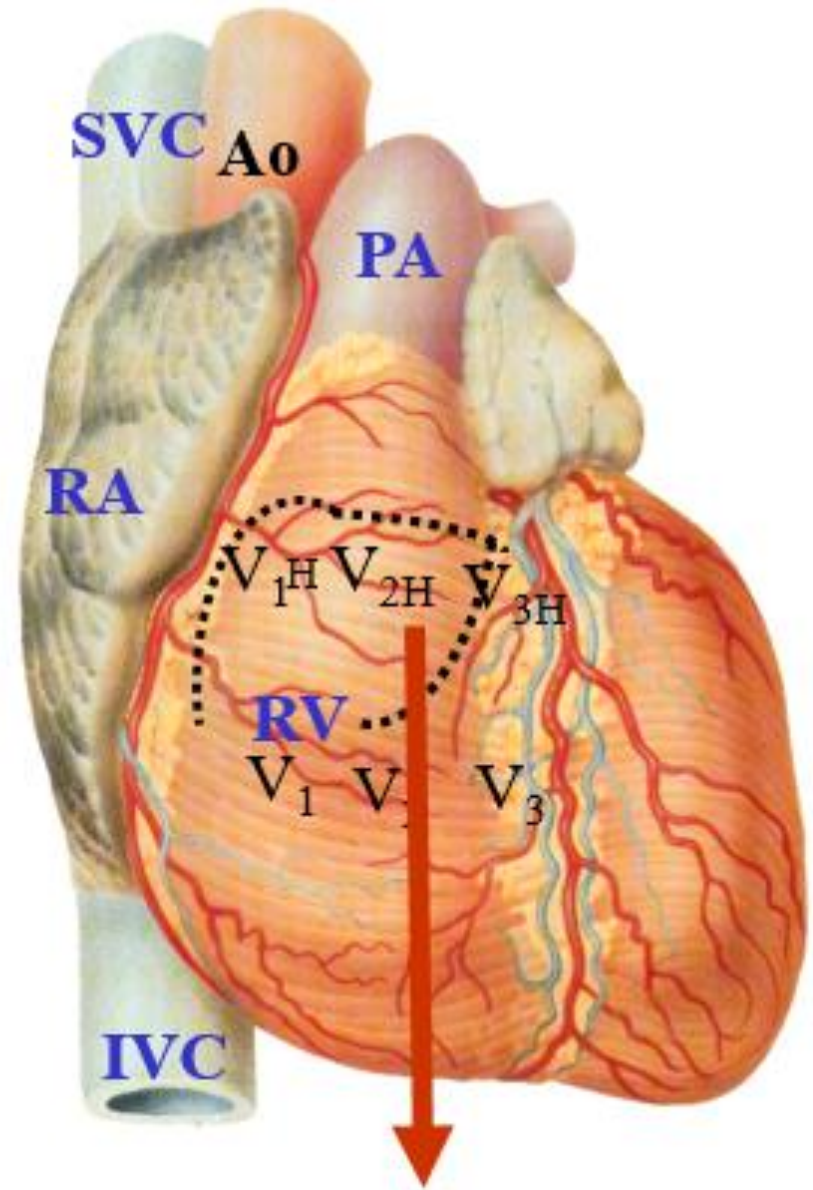
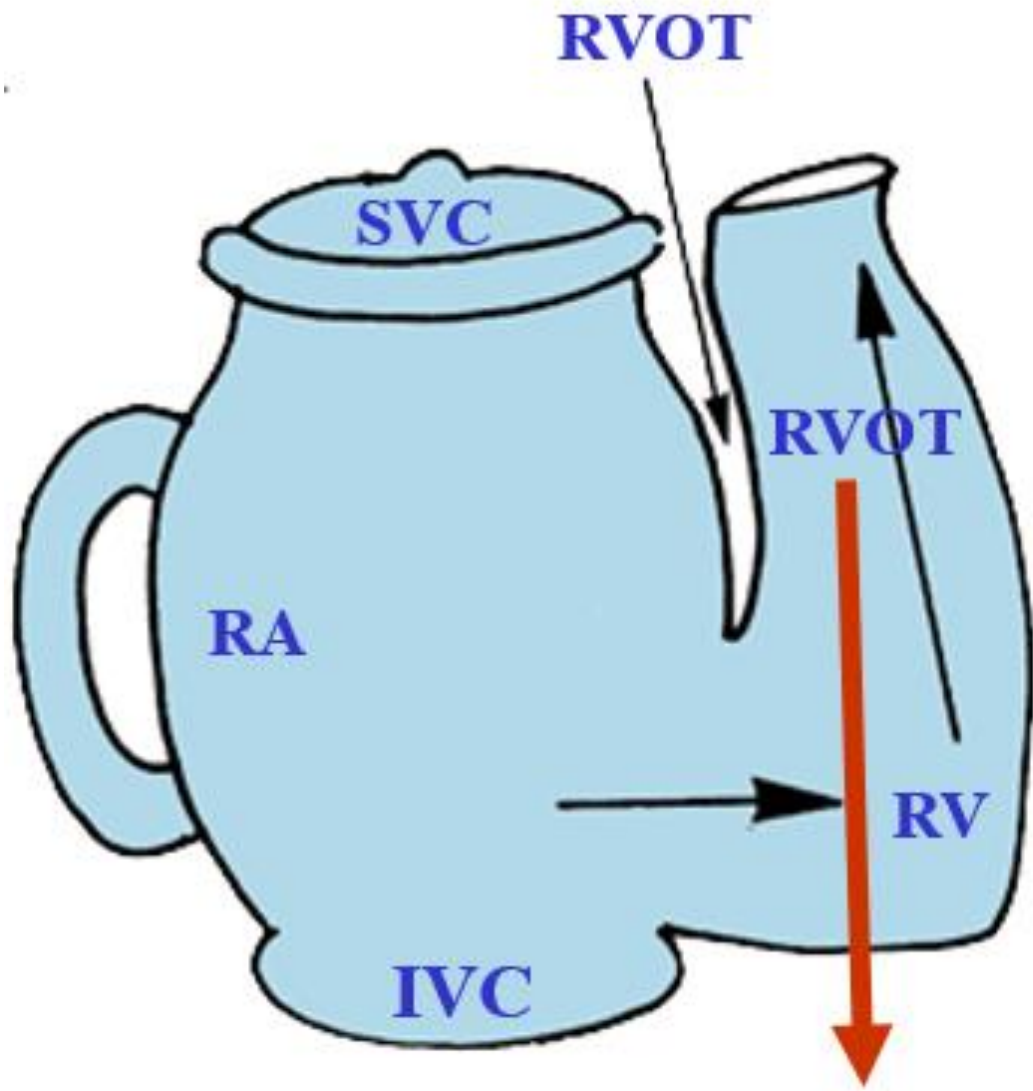
English

Dear friend Juan Carlos Manzardo: it seems to me that you have made a typing error: you wrote: "**with the QRS axis showing extreme left axis deviation (“No man's land”)**". "In electrocardiography when the QRS axis is located in the right upper quadrant and not in the upper left quadrant (between -90° and $\pm 180^\circ$). Extreme left axis deviation occurs when the QRS axis is located between -30° and -90° . The “**No man's land**” is the one where the unipolar derivation of the aVR members is located known as the "forgotten" lead” or the neglected lead aVR (1). When a wide QRS tachycardia has its axis in “No-man's land” we must think in TV." Why the forgotten lead denomination is given for aVR? Answer: Because it is the only lead that does not face any left ventricle wall. This lead facing the Right Ventricular Outflow Tract (RVOT)

Andrés

1. **Riera AR, Ferreira C, Ferreira Filho C, Dubner S, Barbosa Barros R, Femenía F, Baranchuk A. Clinical value of lead aVR. Ann Noninvasive Electrocardiol. 2011 Jul;16(3):295-302.**

See ludic explanation on the next slide.....



High right precordial leads V_{1H} , V_{2H} and V_{3H} and unipolar aVR face the right ventricular outflow tract (RVOT) (A) Basal infundibular region, right ventricular outflow tract (RVOT) or crista supraventricularis: aVR, V_{1H} , V_{2H} and V_{3H} **RA** right atrium; **SVC** Superior Vena Cava; **IVC** Inferior Vena Cava; **PA** Pulmonary Artery; **RV** Right Ventricle.

Spanish

Buenas noches Andrés y Raimundo, Si bien es una taquiarritmia con QRS ancho y bizarro, mantiene una aberrancia de BRD con desvío de eje a la izquierda "like", lo que podría deberse a un aleteo auricular con conducción 1:1.

La ventaja de tener el ECG completo inmediato post CVE es que dado el trastorno de conducción de base, se puede sospechar la posibilidad de una taquiarritmia SV con mayor aberrancia debido a la alta frecuencia ventricular.

Un abrazo fraterno para ambos y muchas gracias por los aportes constantes al foro y a la pagina de FIAI!

Alberto **Bezerra MD** cardiólogo de staff de la Clínica Colón de Mar del Plata, Buenos Aires, Argentina y coordinador del Departamento de Hemodinamia y Cardiología Intervencionista

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English

Good evening Andrés and Raimundo, Although it is a tachyarrhythmia with wide and bizarre QRS, it maintains a RBBB- aberrancy with left-axis deviation "like", which could be due to an **atrial flutter with 1: 1 conduction**.

The advantage of having the complete ECG immediately after CVE is that given the underlying conduction disorder, one may suspect the possibility of an SV tachyarrhythmia with greater aberrancy due to the high ventricular rate.

A fraternal hug for both of you and thank you very much for the constant contributions to the forum and to the FIAI website!

Alberto **Bezerra MD**. Cardiologist at Colón Clinic in Mar del Plata, Buenos Aires, Argentina and coordinator of the Department of Hemodynamics and Interventional Cardiology

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Alberto Bezerra was born in the province of Córdoba Argentina in the city of Rio Cuarto, known for its prosperity as “The empire”.

Dear friends:

As usual a superb ECG tracing !!!.

The most likely diagnosis is certainly a rapid SVT (280/min) associated with a preexisting RBBB and left anterior fascicular block.

The other (much more unlikely diagnosis) is "Belhassen VT"

In a forthcoming issue of the Circulation Arrhythmia Electrophysiology you will be able to read a superb paper by Michowitz and Belhassen on the ECG differences between the 2 diagnoses:

In brief, a typical pattern of RBBB (rSR'), a prominent S wave in V6 (as compared to R), and a positive QRS in aVR are respectively present in:

- 92%, 88% and 94% of cases when we are dealing with SVT + RBBB

- 54%, 59% and 51% of cases when dealing with Belhassen VT.

As far as the SVT mechanism, all options are opened: I will slightly favor the one of **atrial flutter 1:1 taking into account the rate of 280/min and the context of hyperthyroidism but all other options (AVNRT, AVRT) are possible too.**

Warmest regards to all of you from Jerusalem a few days before our Shavuot Jewish holiday (Feast of Weeks, Jewish Pentecost)

Prof Bernard **Belhassen M.D. PhD.**

Head of the Electrophysiology Laboratory, Department of Cardiology, Tel-Aviv Medical Center, Tel-Aviv Israel

Comments by Andrés Pérez-Riera: The Hebrew is *shah-voo-oat*, but it is also correct to say Shavuot (*shah-voo-ohs*). Shavuot means weeks." The Greek word for this holiday is Pentecost, which means "50th." Shavuot in the Old Testament. Shavuot occurs 50 days or seven weeks after Passover. It is a harvest celebration commemorating God's provision for and sustenance of His people. Shavuot shares two important characteristics with the holidays Pesach (Passover) and Sukkot (The Feast of Tabernacles):

All three holidays involved a pilgrimage to Jerusalem.

All three holidays involved first fruit offerings at the Temple.

Passover, in early spring, included first fruits from the first harvest, barley.

Shavuot, in late spring, included first fruits from the wheat harvest.

Among the many offerings given, was a "wave offering" of two loaves of leavened bread.

This was the first fruits offering.

Sukkot, in the fall, was the final harvest and included first fruits of olives and grapes.

Andrés.



Portuguese

Baseado apenas na avaliação do ECG 1 o diagnóstico seria taquicardia ventricular. Os critérios de Brugada e Vereckei são concordantes com TV. Porém, ao avaliar o ECG após a reversão, observamos que o padrão morfológico em ritmo sinusal é o mesmo da taquicardia. Portanto, apesar de haver uma discordância com os critérios para TV, essa é uma taquicardia supraventricular em uma paciente com hipertireoidismo e ECG basal com morfologia de BRD. Sem o ECG pós reversão, esse diagnóstico não seria possível!

Abs,

Acácio Fernandes Cardoso MD São Paulo Brasil



English

Based only in the evaluation of ECG-1 the diagnosis would be ventricular tachycardia. The criteria of Brugada and Vereckei are concordant with TV. However, when evaluating the ECG after the reversion, we observed that the morphological pattern in sinus rhythm is the same of tachycardic event. Therefore, although there is a disagreement with the criteria for TV, this is a supraventricular tachycardia in a patient with hyperthyroidism and basal ECG with RBBB morphology. Without the post reversal ECG, this diagnosis would not be possible!

Acácio Fernandes Cardoso MD São Paulo Brazil

Specialist in cardiology by the Brazilian Society of Cardiology. Specialization in arrhythmias and invasive electrophysiology at Instituto do Coração / HCFMUSP. Certificate in the area of invasive electrophysiology conferred by the Brazilian Society of Cardiac Arrhythmias - SOBRAC and by the Brazilian Medical Association - AMB.

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Spanish

Estimados maestros buen día.

ECG-1 aleteo auricular conducción 1/1 con morfología semejante a ritmo sinusal fundamentalmente por la frecuencia de la misma.

ECG-2 con trastornos de conducción de rama derecha y HAI que orientan a una aleteo con trastornos de conducción previos.

Muchas gracias por enviar el caso.

Ricardo Ramón Corbalán MD

Tucumán Argentina

English

Dear teachers, good morning

ECG-1 atrial flutter with 1/1 conduction with the morphology similar to sinus rhythm mainly due to the frequency of it.

ECG-2 with right bundle branch block and left anterior fascicular block leading to flutter with previous conduction disturbance.

Thank you very much for sending the case.

Ricardo Ramón Corbalán MD

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Tucuman Argentina

.....
Muy de acuerdo con Ricardo. Aleteo Auricular 1:1 con bloqueo bifascicular. Tratamiento Ablación.

Lindo ECG. Gracias profesores!

I agree with Ricardo diagnosis: 1:1 atrial flutter with bifascicular block. Treatment: Ablation. Thank you teachers!

Remberto Torres MD Argentina

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Spanish

Hola Potro y Raimundo:

ECG-1 taquicardia con QRS ancho de 120 ms, eje eléctrico con extremo desvío para la izquierda (-150°), se observa disociación AV.

Diagnóstico Taquicardia Ventricular Monomórfica Sostenida en una paciente hipertiroidea en tratamiento. Los criterios de TV son: en V1 en presencia de Bloqueo de Rama derecha serán complejos R, qR o RR' en V1 y $R/S < 1$ en V6.

Por la localización de la transición precordial y el eje eléctrico impresiona originarse en la parte septal inferior del VI en la región del fascículo pósteroinferior. Una sospecha sería si tiene aneurisma o microaneurisma asociado, ya que no se trata de una TV idiopática, sino una TV en una paciente portadora de miocardiopatía chagásica.

ECG-2 ritmo sinusal, crecimiento biauricular, eje eléctrico en -60° por bloqueo del fascículo anterior izquierdo asociado a bloqueo completo de rama derecha (QRS 160 ms).

Un cordial saludo

Martín **Ibarrola MD** Provincia de Buenos Aires Argentina



English

Hello, Andrés and Raimundo:

ECG-1 tachycardia with wide QRS (120 ms), QRS axis with extreme deviation to the left (-150°), AV dissociation is observed.

Diagnosis Sustained Monomorphic Ventricular Tachycardia in a hyperthyroid patient under treatment.

The VT criteria are: in V1 in the presence of Right Branch Block with monophasic R wave and $R/S < 1$ in V6.

The localization of the precordial transition and the QRS axis, it surprises me that originates in the inferior septal part of the LV in the region of the posterior inferior fascicle. A suspicion would be whether she has an aneurysm or associated microaneurysm, since it is not an idiopathic VT, but a VT in a patient with Chagasic cardiomyopathy.

ECG-2 sinus rhythm, biatrial enlargement, QRS axis at -60° by LAFB associated with complete RBBB (QRS duration 160 ms).

Kind regards

Martín **Ibarrola MD** Province of Buenos Aires Argentina

Portuguese

Caros Potro, Barbosa e amigos (as)

Portadora de tireopatia em tratamento. A arritmia mais comum neste caso é a fibrilação atrial que não está presente nos ECGs apresentados. O Bloqueio do Ramo Direito pode estar presente em até 15% dos pacientes tireotóxicos. Não há referência na história clínica a cardiopatia chagásica, doença coronária ou hipertensão. É razoável a hipótese de cardiopatia chagásica pela epidemiologia e pelo ECG.

1. ECG 1 - Taquicardia ventricular

2. ECG 2 - Bloqueio de ramo direito - bloqueio divisional anterossuperior esquerdo - bloqueio interatrial avançado

Comparativamente os dois são ECG úteis para diferenciar a TV da TSV c/ aberrância.: Padrão do BRD em V1 - duração do QRS - eixo elétrico - padrão em aVR e outros critérios

Adail **Paixão Almeida** Vitória da Conquista Bahia Brasil

English

Dear Andrés, Raimundo and friends

This woman is carrier of a thyroid disease under treatment. The most common arrhythmia in this case is atrial fibrillation that is not present in the ECGs presented. Right bundle branch block may be present in up to 15% of thyrotoxic patients. Chagas' heart disease, coronary disease, or hypertension are not mentioned in the clinical history. The hypothesis of Chagas' heart disease by epidemiology and ECG is reasonable.

1. ECG 1 - Ventricular tachycardia

2. ECG 2 - Right bundle branch block - left anterior fascicular block - advanced interatrial block

Comparison of the two ECGs are useful to differentiate VT from SVT with aberrancy: The RBBB pattern in V1, QRS duration, QRS axis, the pattern in aVR and other criteria suggest VT.

Adail **Paixão Almeida** Vitória da Conquista Bahia Brazil



Spanish

Hola, también me parece que es un aleteo auricular 1:1, si bien lo primero a descartar es TV, es sugestivo de flutter atrial porque que la morfología del QRS y el eje de la taquicardia son similares al RS, y la frecuencia cardiaca es cerca de 280 lpm.

Saludos y escuchemos mas opiniones.

Fernando Malpica Cervantes MD

English

Hi, I also think it is a 1:1 atrial flutter, although the first thing to dismiss is TV, it is suggestive of atrial flutter because the QRS morphology and the tachycardia axis are similar to RS, and the heart rate is about 280 bpm.

Greetings and hear more opinions.

Fernando **Malpica Cervantes MD**

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Hola Amigos El eje eléctrico del QRS esta en - 150 grados consecuentemente en el cuadrante superior derecho o cardinal Noroeste En cuanto a la interpretación de los ECG hago una reflexión inversa comenzando por el ECG-2 bloqueo interauricular avanzado, BCRD asociado a bloqueo del fascículo anterosuperior izquierdo por lo que asumo que presenta una cardiopatía estructural (Chagas?)

En este contexto :

ECG#1 :taquicardia con QRS ancho FC 290 latidos por minuto con imagen de BRD Like en plano horizontal y en plano frontal eje máximo qrs en cuadrante superior derecho (noroeste) ,pienso en principio en TVMS originada en músculo papilar posteromedial o zona inferoapical de VI (aneurisma apical ?)

Otra posibilidad, de un ALETEO conducción 1/1 una maniobra vagal hubiese ayudado al diagnóstico pero me quedo con TVMS originada en VI zona inferolateral, aneurisma apical?

Abrazos

Juan José Sirena Santiago del Estero Argentina

English

Hi Friends The QRS axis is at - 150° consequently it is in the upper right quadrant or “cardinal Northwest”

Regarding the interpretation of the ECG I will make an inverse reflection-way beginning with the second one:

ECG-2 advanced interatrial block, RBBB and LAFB I assume that she carrier a structural heart disease (Chronic Chagasic myocarditis?)

In this context :

ECG -1: Broad regular complex QRS tachycardia, heart rate 290 beats per minute with RBBB- Like pattern in horizontal plane and in the frontal plane QRS axis in the upper right quadrant (Northwest), I think in principle it is a Monomorphic Sustained VT with focus in posteromedial papillary muscle or inferior zone of LV (apical aneurysm?)

Another possibility, is atrial flutter with 1:1conduction. A vagal maneuver would have helped the diagnosis but I will be with Monomorphic Sustained VT originated in VI inferolateral zone, apical aneurysm?

Hugs

Juan José Sirena MD Santiago del Estero Argentina



Spanish

Más probablemente es aleteo auricular con conducción 1:1. Los criterios diagnósticos de TV (p ej, QRS monofásico en V1) pierden especificidad en presencia de bloqueo de rama derecha basal. Una inyección de adenosina para provocar bloqueo AV transitorio antes de la cardioversión sería diagnóstica. Difícil obtener bloqueo AV con maniobras vagales en este escenario.

Cordialmente

Sergio Pinski, M.D.,

PINSKIS@ccf.org



English

More likely it is an atrial flutter with 1: 1 conduction. Diagnostic criteria for VT (eg, monophasic QRS in V₁) lose specificity in the presence of basal right bundle branch block. An injection of adenosine to cause transient AV block prior to cardioversion would be diagnostic. Difficult to obtain AV block with vagal maneuvers in this scenario.

Cordially

Sergio Pinski, M.D.,

Dr. Pinski graduated from the Univ De Buenos Aires, Fac De Cien Med, Buenos Aires, Argentina in 1984. He works in Weston, FL USA and 1 other location and specializes in Cardiovascular Disease. Dr. Pinski is affiliated with Cleveland Clinic Hospital.

Additional comments

Yo proponía inyectar la adenosina inmediatamente antes de la cardioversión, no en lugar de la misma. Hubiese tomado sólo un par de minutos y podría haber provisto información muy valiosa, que aún un EEF puede no brindar. Cordialmente. Sergio.

I would propose to inject adenosine immediately before cardioversion (CV), not substituting the CV procedure. It would have taken only a couple of minutes and could have provided very valuable information, which even an EPS may not provide. Cordially. Sergio

Spanish

Por supuesto que estaba indicada la CVE de urgencia, aun en un corazón normal. Esa frecuencia cardiaca, siendo persistente, es motivo de descompensación y muerte súbita.

Gerardo Juan Nau MD

Ex-jefe de Cardiología del Hospital Aleman de Bs As, miembro del legendario equipo del Dr Mauricio B. Rosenbaum.

English

Of course electrical cardioversion of urgency was indicated, even in a patient without structural heart disease. This heart rate, being persistent, is cause for decompensation and sudden cardiac death.

Gerardo Juan Nau MD

Former chief of cardiology at the Hospital Alemán de Bs As, member of the legendary team of Dr. Mauricio B. Rosenbaum.

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Gerardo Juan Nau



Mauricio B. Rosenbaum



Marcelo V. Elizari



Pablo A. Chiale – in memoriam

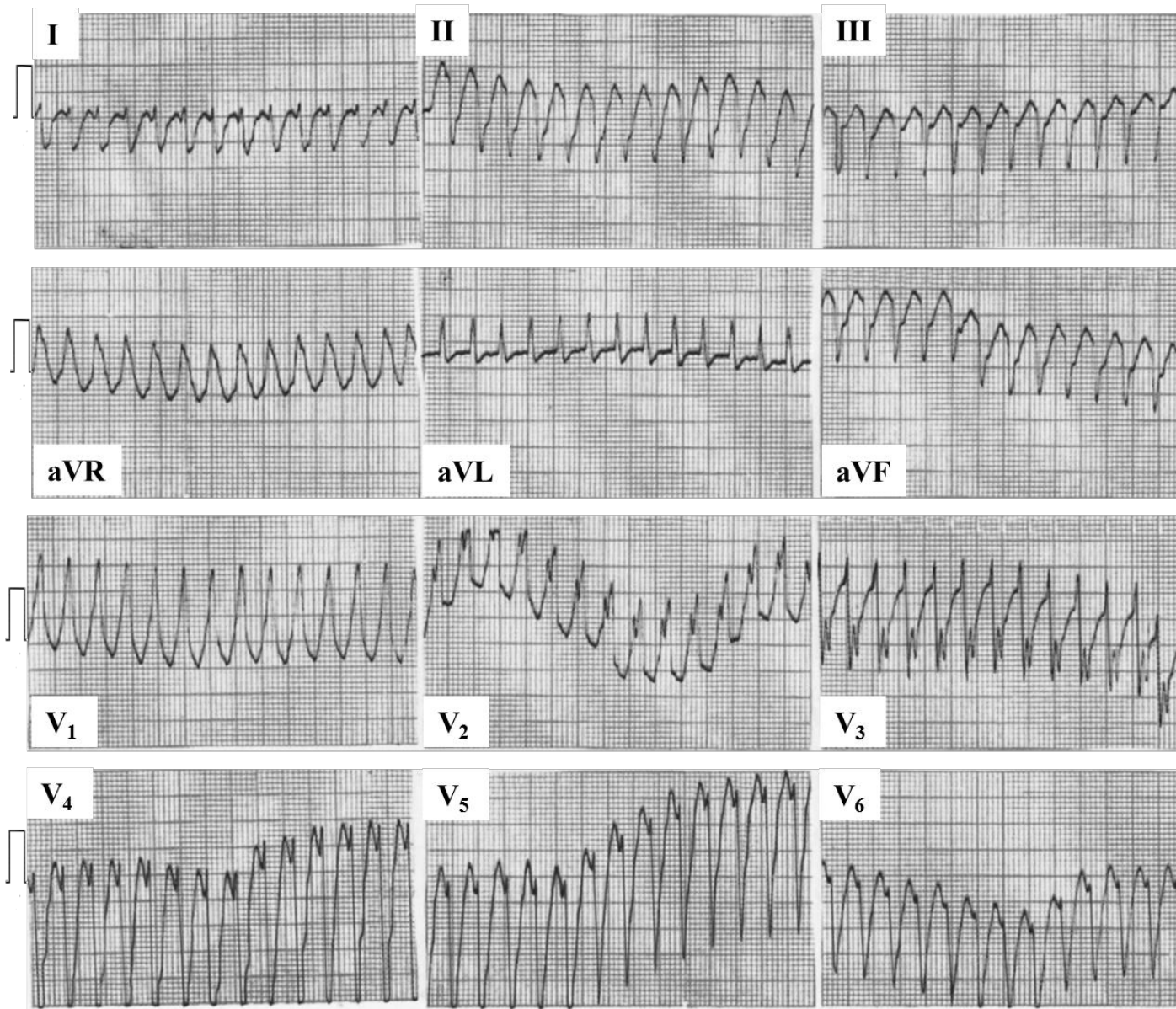
Final comments by Andrés Ricardo Pérez-Riera & Raimundo Barbosa-Barros



I am introducing my beloved ones: my son Andrés Vinicius, grandchildren Murilo, granddaughter Lucia and daughter-in-law Aldana, wife Helena, pet Evita, and best friend Raimundo.



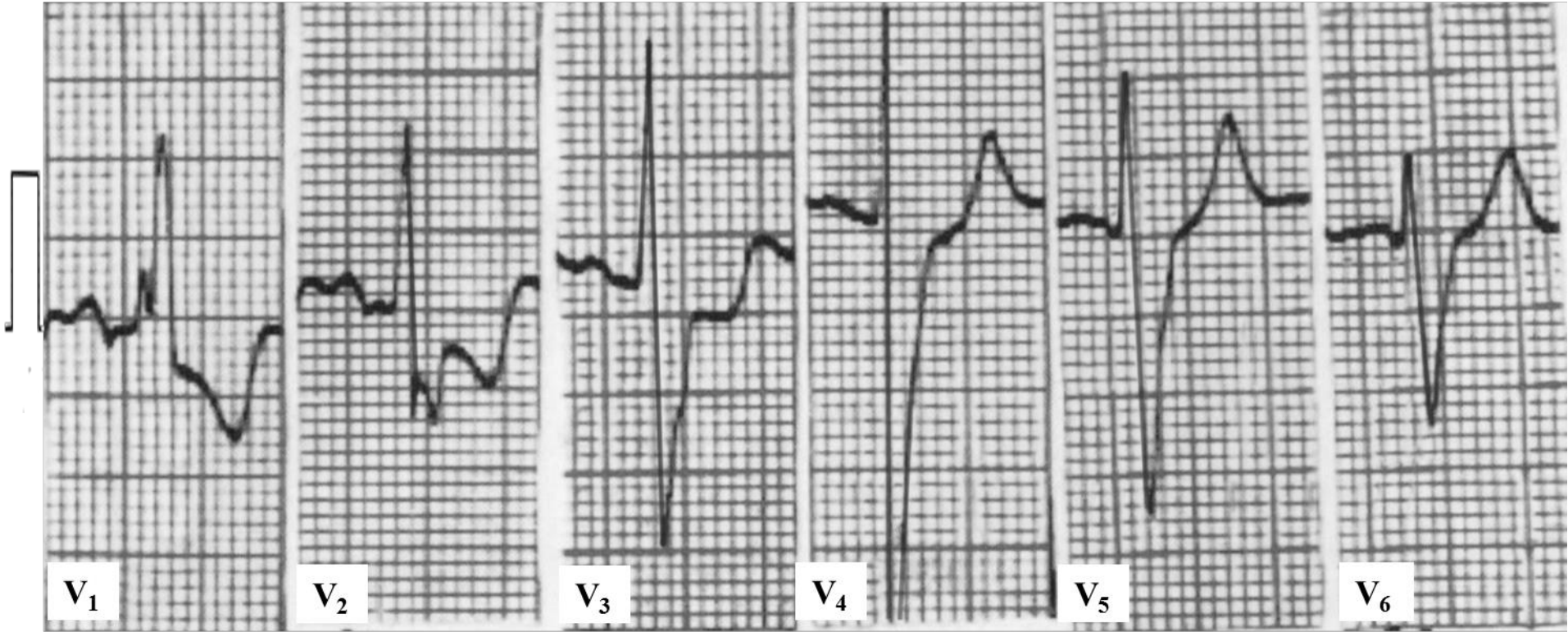
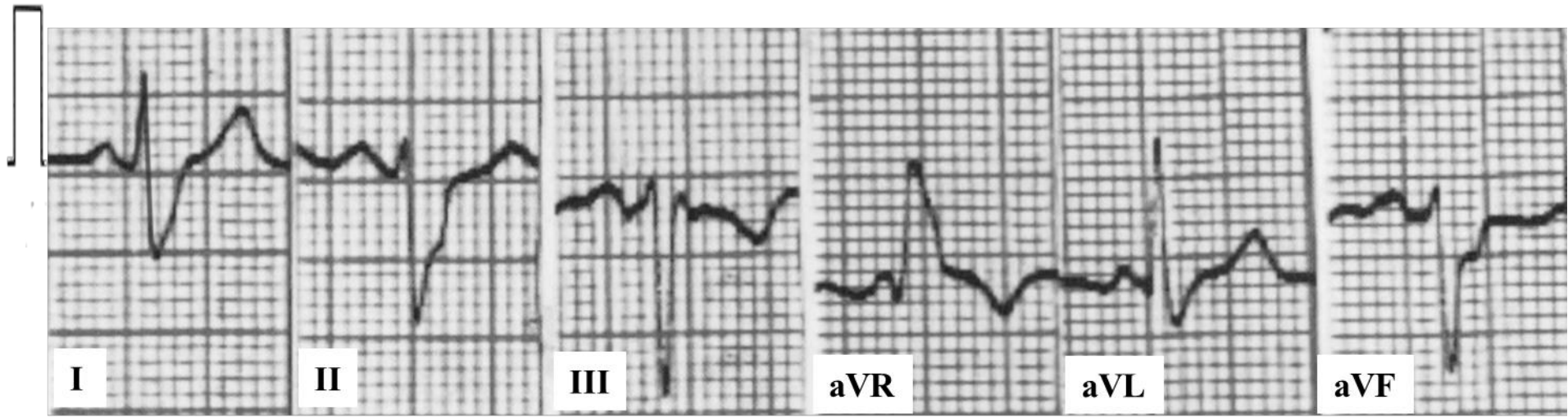
ECG-1



ECG diagnosis: Wide regular QRS tachycardia (≥ 120 ms), HR = 280 bpm, QRS axis in the superior right quadrant (-100°). Absence of AV dissociation. Positive QRS monophasic complexes in V1, biphasic in V2 and in V3 the ascending branch of the S wave is interrupted by a high voltage positive-negative or plus-minus.

Conclusion: 1:1 atrial flutter associated with right bundle branch block. **Clinical Diagnosis:** Toxic multinodular goiter or Plummer's disease.

ECG-2

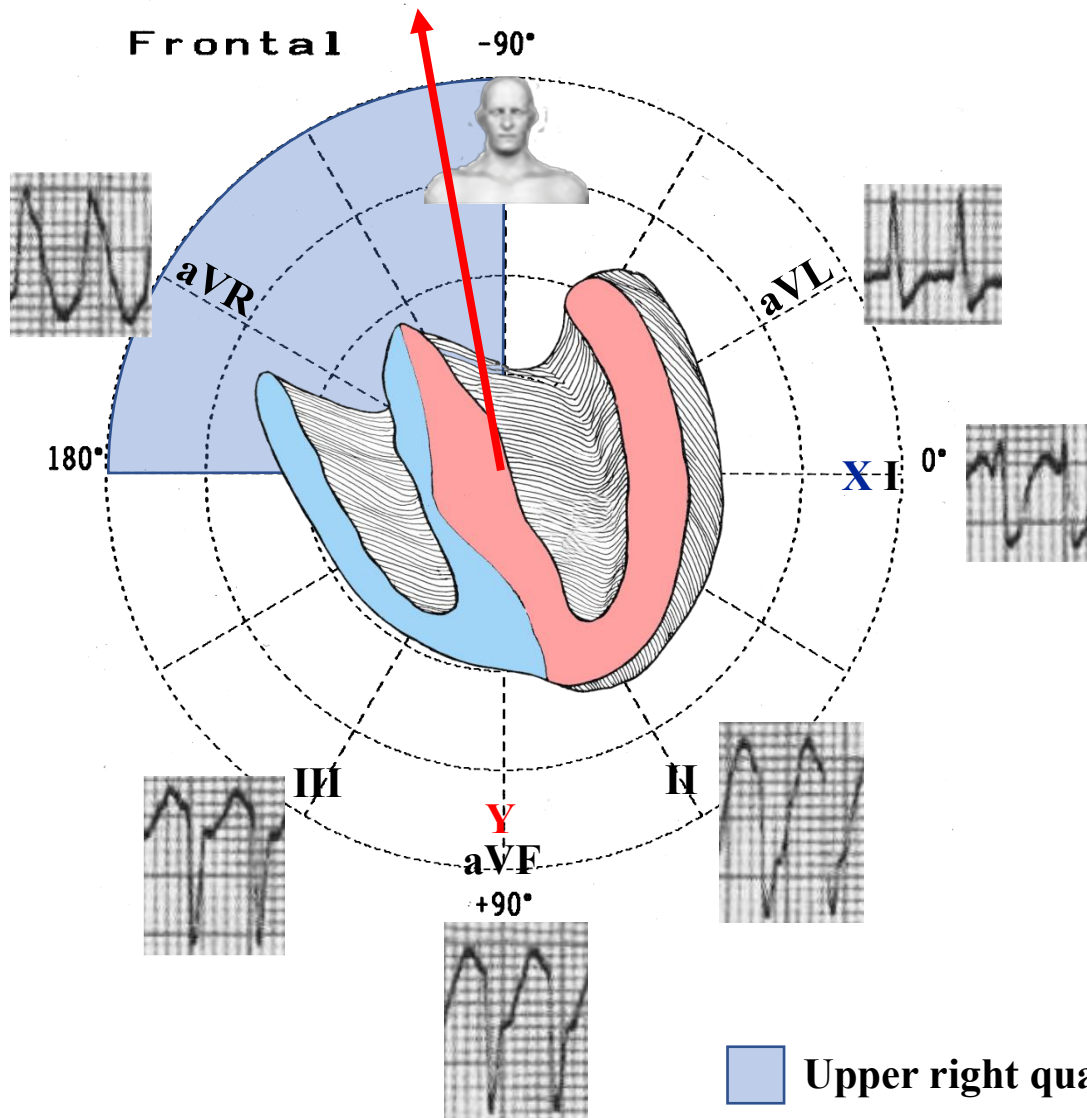


ECG-1

QRS axis -110°

Frontal

-90°

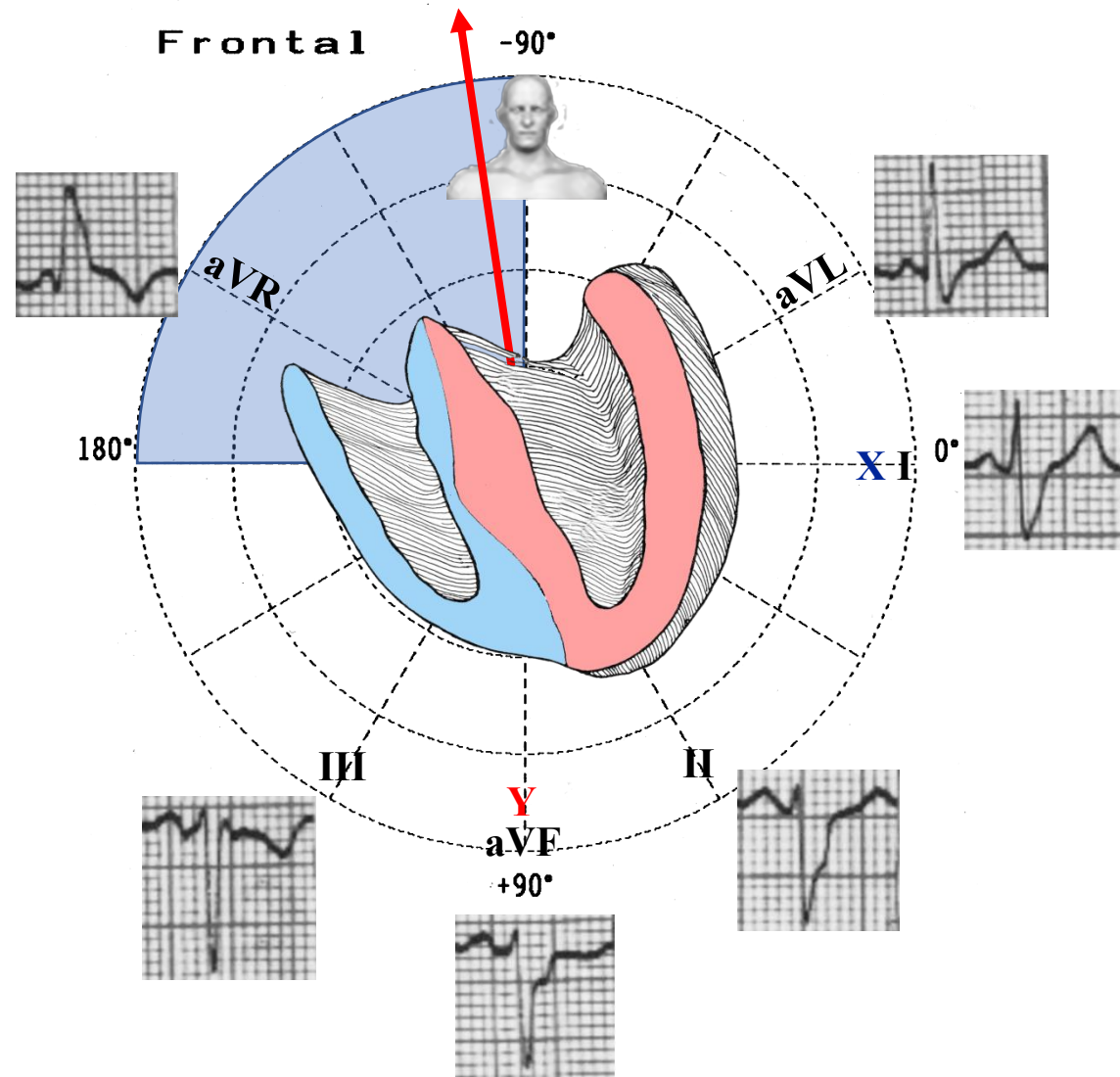


ECG-2

QRS axis -110°

Frontal

-90°



Upper right quadrant

ECG-2 shows RBBB pattern with QRS axis in the FP identical as ECG-1 (-100°), both located in the upper right quadrant. Consequently, the wide QRS during the event was caused by a pre-existing RBBB and the underlying cause is an atrial flutter with 1:1 AV conduction.

The existing criteria in both electrocardiograms that may lead us to think erroneously in monomorphic ventricular tachycardia

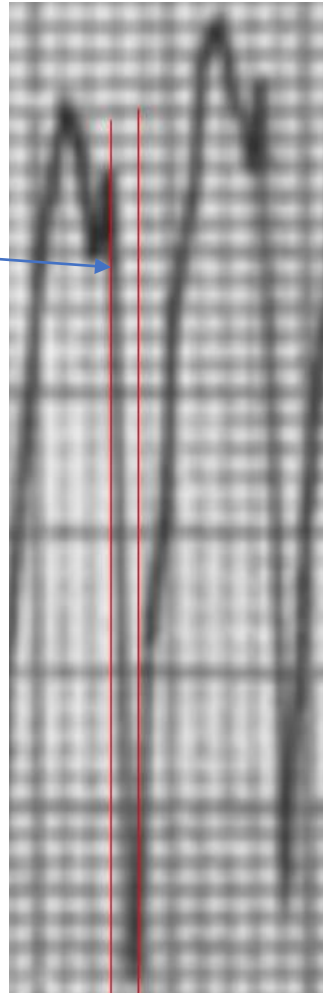
1. Wide QRS complexes (>120 ms) during the event
2. QRS axis on upper right quadrant: northwest quadrant axis No man's land axis VT is suggestive when $\hat{S}\hat{A}QRS$ is in the northwest quadrant between -90° and $\pm 180^\circ$
3. Right bundle branch block-like pattern with monophasic R wave in V1
4. Presence of an initial R wave in lead aVR
5. In lead V6, R wave height greater than S wave depth.

ECG-2 has not LAFB diagnosis because in this dromotropic disturbance the QRS axis is in left upper quadrant between -30° or higher until -90° . Additionally in LAFB $S_{III} > S_{II}$ In LAFB a shift of the main QRS forces superiorly and to the left, which elicits deep S waves in leads II, III, and aVF (S_{III} is deeper than S_{II} different of the present case) LAFB usually shifts the main forces of the $\hat{S}\hat{A}QRS$ to -45° , -60° , or even to -75° (complete LAFB). (**Elizari 2007**) Because the $\hat{S}\hat{A}QRS$ may be -45° in cases of incomplete LAFB, the degree of left axis deviation required for the accurate diagnosis of complete LAFB is -45° . (**Rosenbaum 1968; 1970**)



Characteristics of the case that reinforce the hypothesis of atrial flutter with conduction 1:1

1. Heart rate ≥ 100 beats per minute, Monomorphic VT usually have a HR between 150-200. In the present case, the HR is incompatible with monomorphic VT because the HR in the present case HR is equal 280bpm. Very high cardiac frequency incompatible with monomorphic VT
2. Absence of AV dissociation (capture or fusion beats)
3. Absence of R to S interval ≥ 100 ms in precordial leads
4. Absence of notching on the downstroke of a predominantly negative QRS complex
5. In lead V6, absence of R wave height greater than S wave depth.
6. Ventricular activation-velocity ratio The vertical excursion (in millivolts) recorded during the initial (Vi) and terminal (Vt) 40 ms of the QRS complex.
7. The QRS axis and morphology are similar in both ECG-1 and ECG-2 (Both ECGs with QRS axis -110°) +RBBB



Comments: A hard diagnostic problem is associated with preexcited tachycardia, the condition resulting whenever supraventricular tachycardia impulses are conducted to the ventricles over an accessory pathway. This situation is far more rare than ectopy and aberration, and can be ruled out in the presence of negative precordial concordance (QS complexes in all the precordial leads) or deep q waves in a precordial lead other than V1. A QRS morphology not consistent with any of the typical patterns observed in the various locations of the accessory pathways rules out a preexcited tachycardia, too. (Oreto 2009)

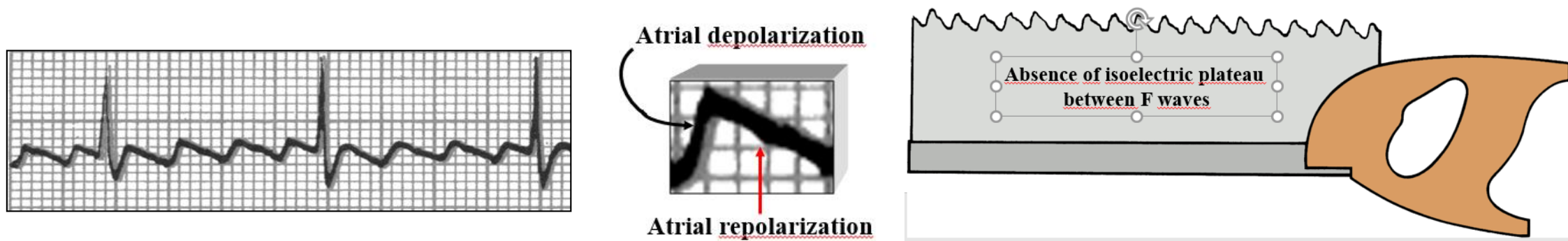
Atrial Flutter

Atrial flutter (AFL) is a common arrhythmia, which shares many clinical and therapeutic features with AF and coexists with AF in many patients. However, it has a distinct pathophysiology in that it occurs as a result of a macroreentrant circuit, which provides an opportunity to interrupt the circuit using currently available catheter ablation techniques. AFL is characterized by regular but rapid and organized atrial activity formed by a macroreentrant circuit, usually in the right atrium. It is the most common arrhythmia after AF. The epidemiology of AFL is poorly characterized because it has been studied in combination with AF. Its prevalence is difficult to estimate because it is unusual for patients to sustain AFL for long periods, because most patients either convert to sinus rhythm or may degenerate into AF as a result of shared risk factors between the 2 arrhythmias. (**Granada 2000**)

Epidemiology The incidence of AFL as assessed from data from a single-center study, derived from the Marshfield Epidemiologic Study Area (MESA) cohort, over a 4-year period was 88/100,000 person-years.⁶³ The risk of developing AFL is higher in men by a factor of 2.5. The risk in patients with heart failure and COPD is higher by a factor of 3.5 and 1.9 times, respectively.⁶³ The risk factors for development of AFL are identical to those for AF, and this arrhythmia affects a similar population of patients. In the analysis of the MESA subset, 58% of the patients with AFL had at least 1 episode of AF. (**Granada 2000**) One population group who have a unique predilection for AFL is the subset of patients with previous history of endocardial scarring either from previous ablation procedures or cardiac surgery causing block in a critical location, which serves as a substrate for development of reentry. Mortality risk in patients affected with AFL is 1.7 times that of the control group. (**Vidaillet 2002**)

Family with , autosomal dominant AFL Follow-up family-based genetic analysis identified Mendelian transmission. Three affected members were exome-sequenced for the identification of potential causative mutations, which were subsequently validated by direct sequencing in the other 3 affected members of sporadic lone AFL/AF cases. rs58238559 in ABCB4 is a rare missense variant with a significant effect on the development of AFL/AF. **Pathophysiology** AFL develops as a macroreentrant rhythm around a site of anatomic or functional block. The typical AFL (also called type 1 flutter) develops in the right atrium around the tricuspid annulus, with the crista terminalis and the opening of the inferior vena cava forming an anatomic-functional block. The narrow band of atrial tissue bound by the inferior vena cava posteriorly and the tricuspid annulus anteriorly, called the cavotricuspid isthmus, often forms the critical path of slow conduction, (**Tai 1997**) which is a suitable target for ablation. Usually, the direction of impulse propagation is counterclockwise around the tricuspid annulus, with impulses traveling up in the interatrial septum. 90% of typical AFL are counterclockwise, reflected as negative flutter waves in the inferior leads and positive atrial deflections in the anterior precordial leads. (**Cosio 1996**) The clockwise circuit propagates in the opposite direction, with opposite AFL wave direction on the ECG. The cycle length of a typical AFL is characteristically at 200 to 240 ms (corresponding to rates of 250–300 bpm). The ventricular rate is usually slower, with the atrial activity being variably blocked at the level of the AV node at a ratio of 2:1 to 4:1. The ventricular rates are usually a whole number factor of 300 bpm,

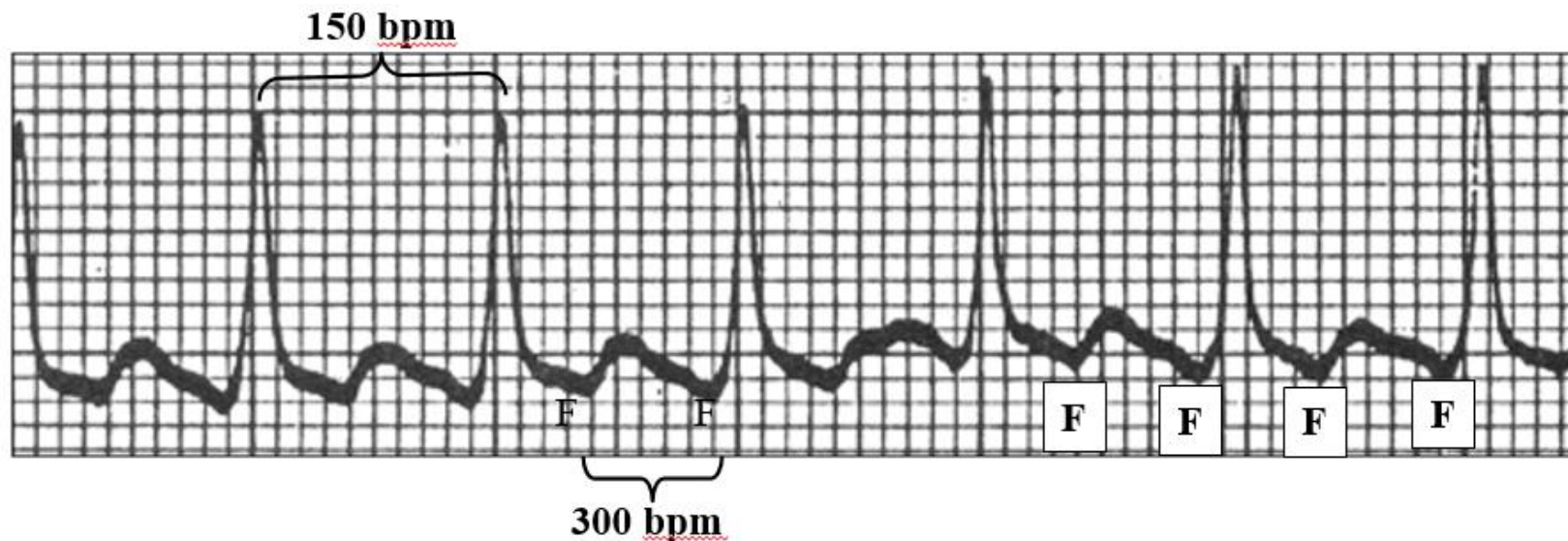
often providing a clue to the presence of underlying AFL when the flutter waves may not be clearly evident or are fused with the ventricular complexes. A conduction ratio of less than 4:1 is usually a sign of AV nodal disease. Atypical AFL, on the other hand, does not use these circuits, traveling through the cavotricuspid isthmus. The atypical AFLs are often scar-related from previous surgical incisions, such as right atriotomy scar formed after post cardiopulmonary bypass or from other cardiac surgeries involving atrial tissue, including congenital heart surgery. A narrow area of tissue between the scar and an anatomic barrier like tricuspid annulus or inferior vena cava then forms a critical slow zone in the atypical AFL circuit. Previous endocardial ablation procedures leaving behind areas of conduction block can also form substrates for atypical AFL formation and propagation. With AFL ablation procedures becoming more common, the development of left AFL as a result of incomplete scar lines around the pulmonary veins is also emerging as an important cause of atypical AFL. The clinical effects of AFL are similar to AF. Long-term presence of AFL can lead to tachycardia-induced cardiomyopathy. Long-term AFL also comes with thromboembolic risks, but the risk attributable to AFL alone is difficult to quantify because most patients have coexisting AF. (**Granada 2000**) The ACC/AHA recommend that chronic or recurrent AFL be treated identical to AF with regards to stroke prophylaxis. (**Fuster 2006**) The CHADS2 and CHADS2-VASc scores can be applied to patients with AFL when determining stroke risk. (**Parikh 2012**). **Clinical** The symptoms related to AFL include palpitations, shortness of breath, angina, and dizziness (occasionally, syncope). Hemodynamic effects of AFL can also lead to exercise intolerance and worsening of CHF. On examination, no specific feature points to a diagnosis of AFL. Tachycardia may be evident from rapid ventricular response rates. Features of underlying cardiac and noncardiac comorbidities may be noted. Cannon waves suggestive of atrial contraction during tricuspid valve closure may be present. The diagnosis of AFL is confirmed on ECG by the presence of repetitive fast atrial activity faster than 240 bpm (cycle length < 250ms) and no isoelectric line (some isoelectric line between discernible P waves may be seen in atypical AFLs and under the influence of antiarrhythmic medication if the slow zone occupies nearly 70% of the circuit and surface ECG does not record any activity when conduction occurs through this area) between the atrial complexes, because some part of the atrium is always being activated. The ECG shows atrial activity commonly as flutter waves (saw tooth pattern). Figure Investigations such as echocardiogram to diagnose associated cardiac conditions and other blood tests are similar to those for AF. **Sawtooth appearance**



Types of atrioventricular conduction in atrial flutter

A) Regular:

2:1 – $\frac{1}{2}$ The most frequent ratio in untreated patients is 2:1 with atrial and ventricular rate of 300/150 bpm respectively. This ratio is due to physiological interference in the junction. If the ventricular response rate is regular and constant (e.g. always 2:1) the FR interval will also be so, varying between 260 ms to 460 ms. If the ventricular rate of F is 240 bpm, in 2:1 flutter, ventricular rate will be 120 ppm in the arterial pulse.



1:1 – it suggests ventricular pre-excitation (anomalous accessory pathway). In these cases, regular and wide QRS complexes without apparent atrial activity may lead to the mistaken diagnosis of ventricular tachycardia, with atrial and ventricular rate close to 250 bpm.

3:1 – $\frac{1}{3}$ – rare and it means 3 F waves per each QRS

4:1 – $\frac{1}{4}$

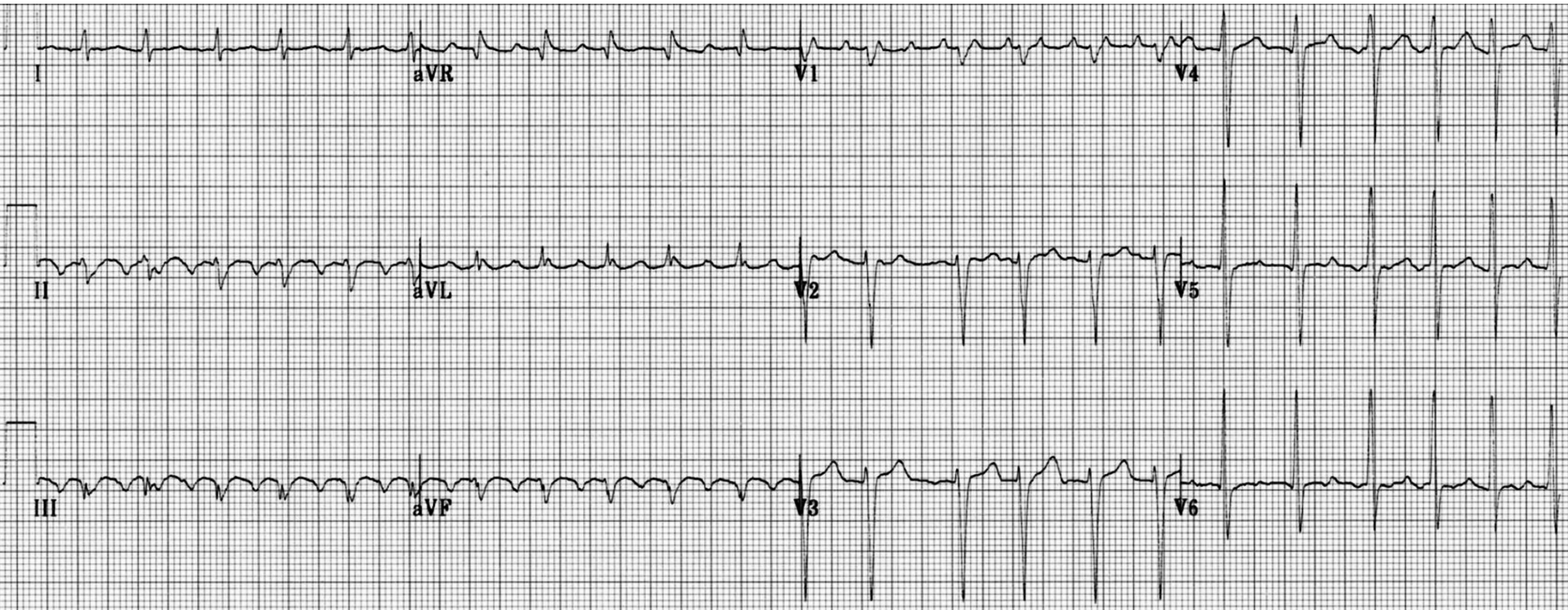
6:1 – observed in cases with marked AV block. The differential diagnosis of conduction with a high rate of ventricular response should be done with complete AV block. A constant ventricular rate with FR intervals is present in the first case with fixed FR, contrary to the third degree or complete block with constant RR intervals accompanied by FR interval variations.

B) Irregular

C) **Absent:** with complete AV block – ventricular rate is usually low and independent from atrial rate.

Commentaries: in flutter, ventricular rhythm could be regular or irregular, unlike AF where ventricular rhythm is nearly always irregular.

Atrial Flutter with 2:1 AV conduction example



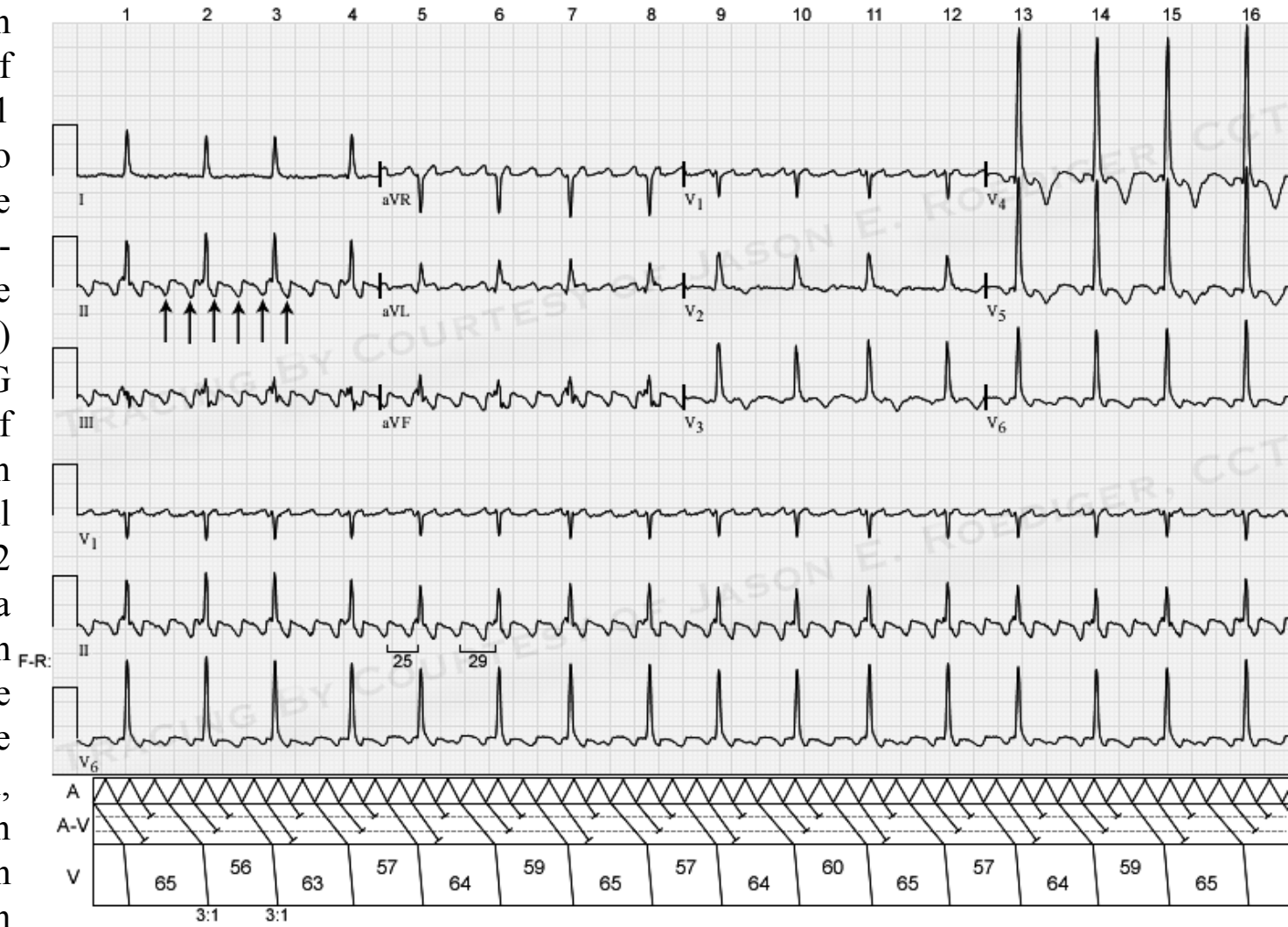
ECG diagnosis: typical counterclockwise, typical, common or classical AFL inverted F waves in inferior leads II, III and aVF with a rate of 300 bpm (one per big square), upright F waves in V1 simulating P waves. There is a 2:1 AV block resulting in a ventricular rate of 150 bpm. Occasional irregularity, with a 3:1 cycle seen in V1-3.

AFL is the second most common type of tachyarrhythmia in the fetus and neonate. An atrial rate of 240 to 360 bpm, 2:1 AV conduction, and a "saw tooth" appearance on ECG are characteristic. On echocardiogram, bilateral atrial enlargement is the most common finding. Treatment is dependent on the severity of symptoms; delivery is usually indicated in the case of fetal heart failure or hydrops fetalis, whereas postnatal AFL is most commonly treated with direct current cardioversion (**Woo 2015**).

The AFL itself is typical. Note the sawtooth (i.e., “picket fence”) appearance in the inferior leads. In V1, they appear as little, upright P-like waves and in V6 they appear as inverted P-like waves. As is usually the case, the flutter waves are barely discernible in lead AFL with 3:1 A-V conduction has an atrial rate of 300/min with a resulting ventricular rate of 100/min. Quite often I’ve noticed that people interpret 4:1 AFL as being 3:1 AFL because they don’t use their calipers to march out the F waves. Invariably, they overlook the F wave that is superimposed on the larger QRS complex. Even-numbered ratios (e.g., 2:1, 4:1, 6:1, etc.) are much more common than odd-numbered ratios (e.g., 1:1, 3:1, 5:1, etc.) The computer of the electrocardiograph interpreted this ECG as “**AFL with variable AV block**”. There are many causes of bigeminal patterns but this is one of the most uncommon forms. Usually when AFL with associated with bigeminal patterns, it is a result of alternating 2:1 and 4:1 ratios with 2 anatomic levels of conduction. There is a 2:1 “filtering” at a higher level in the A-V node and a 3:2 Wenckebach conduction at the level below that. The mechanism here involves 3 anatomic levels of conduction as illustrated in the A-V tier. Note the 3 levels separated by the grey horizontal, dashed lines. Typically in AFL, the F-R interval is between 0.26s and 0.46s. Here the F-R intervals alternate between about 0.25s and 0.29s but fall within an acceptable range. In hundredths of a second, the ventricular cycles alternate between a mean average of 58 and 64. (Pick 1979; Marriott 1998; Fisch 1989)

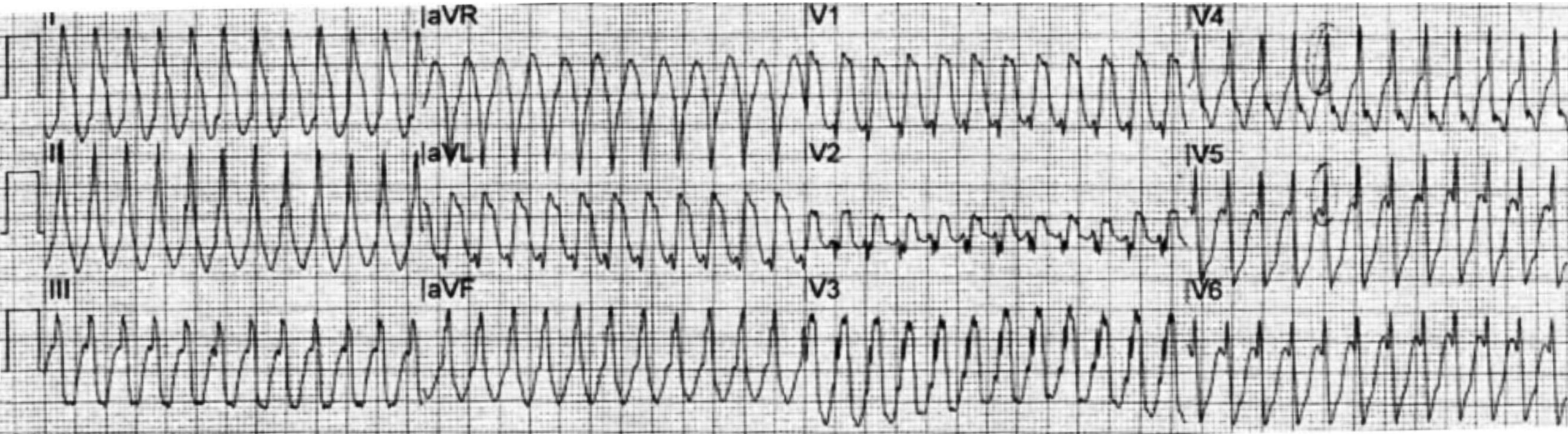
Regular Atrial Flutter with 3:1 AV conduction block example

Rare and it means 3 F waves per each QRS



Source: Jason's Blog

Atrial Flutter with 1:1 example



Electrocardiogram demonstrating Classic appearance of AFL with 1:1 conduction. This patient has AFL with 1:1 conduction and aberrant conduction, and this is confirmed during electrophysiological study. Initially, the treating personnel thought the rhythm to be VT.

Causes of AFL with 1:1 conduction

- AFL in children: average HR of 300 bpm with 1:1 conduction response.
 - AFL of ventricular preexcitation: it suggests ventricular pre-excitation (anomalous accessory pathway). In these cases, regular and wide QRS complexes without apparent atrial activity may lead to the mistaken diagnosis of ventricular tachycardia, with atrial and ventricular rate close to 250 bpm. AFL with 1:1 conduction can occur due to sympathetic stimulation or in the presence of an accessory pathway — especially if AV-nodal blocking agents are administered to a patient with WPW.
 - Type II AFL of Wells: rate of AFL between 340 and 433 bpm: cannot be interrupted by pacing
- AFL with 1:1 conduction is associated with severe hemodynamic instability and progression to VF.

In the present case a close inspection of the ECG shows several features to suggest that this may not be VT. Firstly, not all the QRS complexes in all 12 leads are broad (that is, > 120 ms), particularly in limb lead III (see later).



AFL with 1:1 AV conduction is a rare entity. Normally not all of the impulses can reach the His-Purkinje system based on the physiological properties of the AV node. In most of the cases, ventricular rate is lower than the atrial rate during AFL and AF. In AFL, classically, a 2:1 conduction occurs across the AV node; as a result, the ventricular HR is about one-half the flutter rate provided there is no AV node dysfunction, which produces the typical ventricular rate of 150 bpm.

Class I antiarrhythmic drugs are known to slow down the atrial rate, increasing the probability of 1:1 AV conduction during their use, especially in patients with rapid AV nodal conduction. (**Brembilla-Perrot 2001**) Accessory AV conduction pathways connecting the atria to the ventricles can cause fast conduction of impulses through AV node increasing the likelihood of 1:1 conduction in AFL. (**Moleiro 1981**) Conditions like hyperthyroidism that potentiates AV conduction may occasionally result in 1:1 AFL conduction. (**Moleiro 1981**) Exercise may also cause 1:1 AV conduction owing to both increased flutter cycle length and enhanced AV conduction. (**van den Berg 1995**)

In AFL with 1:1 conduction there is a very rapid, regular narrow-complex tachycardia at 250-300 bpm. In the present case the QRS complexes are wide because complete RBBB is present at baseline and flutter waves (F) are not clearly seen, but there is an undulation to the baseline in the inferior leads suggestive of AFL with a 1:1 block. AFL is possible with aberrant conducted beats. Conduction delay or block in the His-Purkinje system during antegrade conduction of impulses over the AV conduction system results in a wide, abnormal QRS. Features suggesting aberrant conduction are the presence of an initially narrow QRS portion

myocardial infarction and rapid HR arrhythmia. For further knowledge, the prospective observational survey evaluating landiolol efficacy on tachyarrhythmia is in progress. (**Yamashita 2015**) Recent reports say landiolol converted AF (**Yamamoto 20010**) and AFL (**Mayahara 2004**) to sinus rhythm, and it had been safely used in poor LV function patients with LVEF between 25–50 % and was more effective in controlling HR than digoxin. (**Nagai2013**) It has also been suggested that landiolol is effective for prevention of AF after heart valve surgery [**Sakaguchi 2012**]. Landiolol could be safely used without causing hypotension and worsening heart failure. Rapid decrease of HR could be detrimental for it might decrease cardiac output in patient with poor left ventricular ejection fraction. However, by carefully administrating landiolol from small dose, reduced ventricular response as well as HR and improved our patient's hemodynamics. Landiolol effect to the HR and rhythm exceeded its negative inotropic effect in an emergent AFL situation. It would have been more effective to use larger continuous intravenous infusion dose after first 1:1 AFL occurred. The exact reason why the second episode of 1:1 conducted AFL was followed by deteriorated hemodynamics although the first one was rather reserved is unknown. The constant high HR which is a compensation for the poor LV function might have made the LV possible to correspond and eject even in 1:1 conducted AFL in the first episode. In summary, a perioperative AFL with 1:1 ventricular response could be safely treated by landiolol. Landiolol is effective controlling the ventricular HR of AFL, but in a hemodynamically compromised situation, we should always consider synchronized cardioversion first. General anesthesia is useful for AFL patients to restrain the perioperative sympathetic stimulation which could lead to fatal 1:1 conduction and a RBBB pattern. Features suggesting ventricular tachycardia include:

- 1) the absence of an RS complex in the precordial leads and
- 2) AV dissociation. Other features of ventricular tachycardia outlined in a 1991 article by Brugada and colleagues are known as the Brugada Criteria (**Brugada 1991**).

Alternatively, this may just be rapid SVT (AVNRT / AVRT) with rate-related ST depression. Secondly, the QRS complexes in the anterior leads give a false impression of being broad because the up sloping portion of the ST segment can easily be mistaken as part of the QRS complexes. There is no evidence of atrioventricular dissociation. After DC cardioversion, the ECG remained in sinus rhythm with complete RBBB and the same QRS axis as the during the event. As survivors of congenital heart disease (CHD) continue to age, healthcare utilization by this population has increased. It is unknown how often these patients utilize the emergency department (ED) at children's hospitals and how arrhythmias play a role in their utilization of care. Using a retrospective cohort design, the Pediatric Hospital Information System database was investigated by Mohan et al. They studied adults (≥ 18 years) with CHD who presented to pediatric EDs from 2004 to 2014 in a tertiary care pediatric hospitals. Of the 6310 encounters to pediatric EDs, 1594 (25%) were for arrhythmias. The median age was 21 years. The most common tachyarrhythmia diagnoses during the study period were AFL (32%), atrial fibrillation (15%), and paroxysmal VT (10%). Bradyarrhythmias represented a minority of total arrhythmias (**Mohan 2017**).

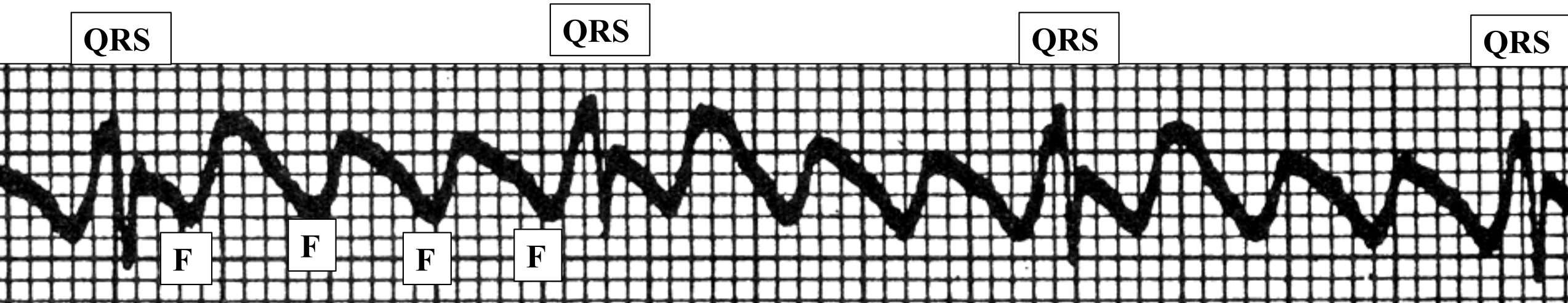
Learning points

- Spontaneous conduction of 1:1 AFL is a rare occurrence and it could be difficult to differentiate this arrhythmia from ventricular tachycardia or fibrillation.
- It is associated with significant symptoms and hemodynamic compromise.
- Common causes of facilitators of 1:1 conduction need to be ruled out.
- Treatment aims at ventricular rate control, anticoagulation and attempts at restoration of the normal sinus rhythm.

AFL with increased atrioventricular conduction ratio especially 1:1 conduction requires prompt treatment, for it exacerbates hemodynamics rapidly. According to ACC/AHA/HRS Guideline for the management of adult patients with Supraventricular Tachycardia (**Brandt 2013**), synchronized cardioversion is a Class I recommendation for acute treatment of patients with AFL who are hemodynamically unstable and do not respond to pharmacological therapies. In hemodynamically deteriorated situation, synchronized cardioversion is the first choice. Since perioperative sympathetic stimulation was thought to be the reason that led 1:1 atrioventricular conduction, β blockers was the initial choice for the pharmacological treatment. Landiolol is a short acting β_1 selective blocker with a short half-time of approximately 4 min in human blood, which its negative inotropic effect does not sustain. These features made it relatively safe use in a case with acute decompensated heart failure.

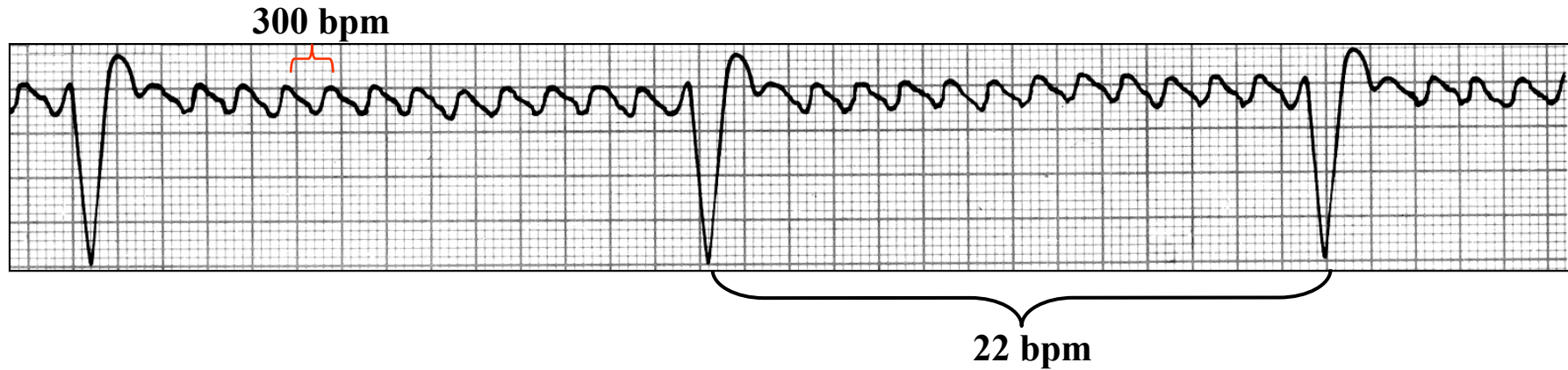
Others examples

Regular AFL with 4:1 AV block: 240/60 bpm



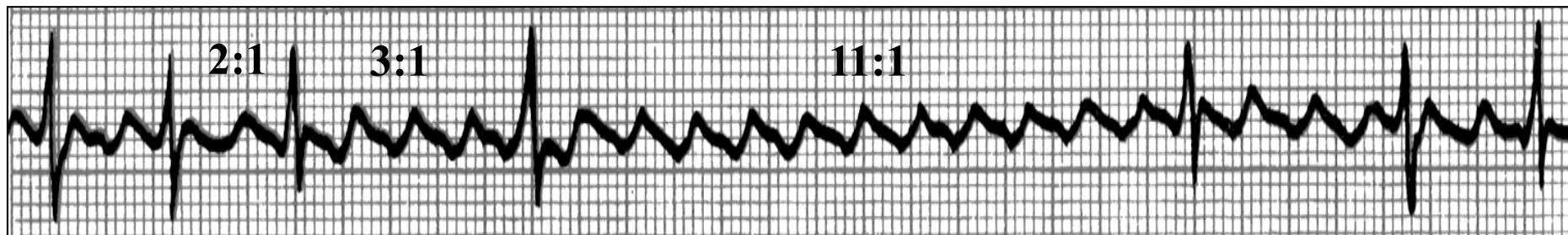
If the rate of F waves is 240 bpm in 4:1 AFL, the ventricular rate will be 60 bpm in arterial pulse; i.e. within what is considered a normal HR.

AFL with complete AV block

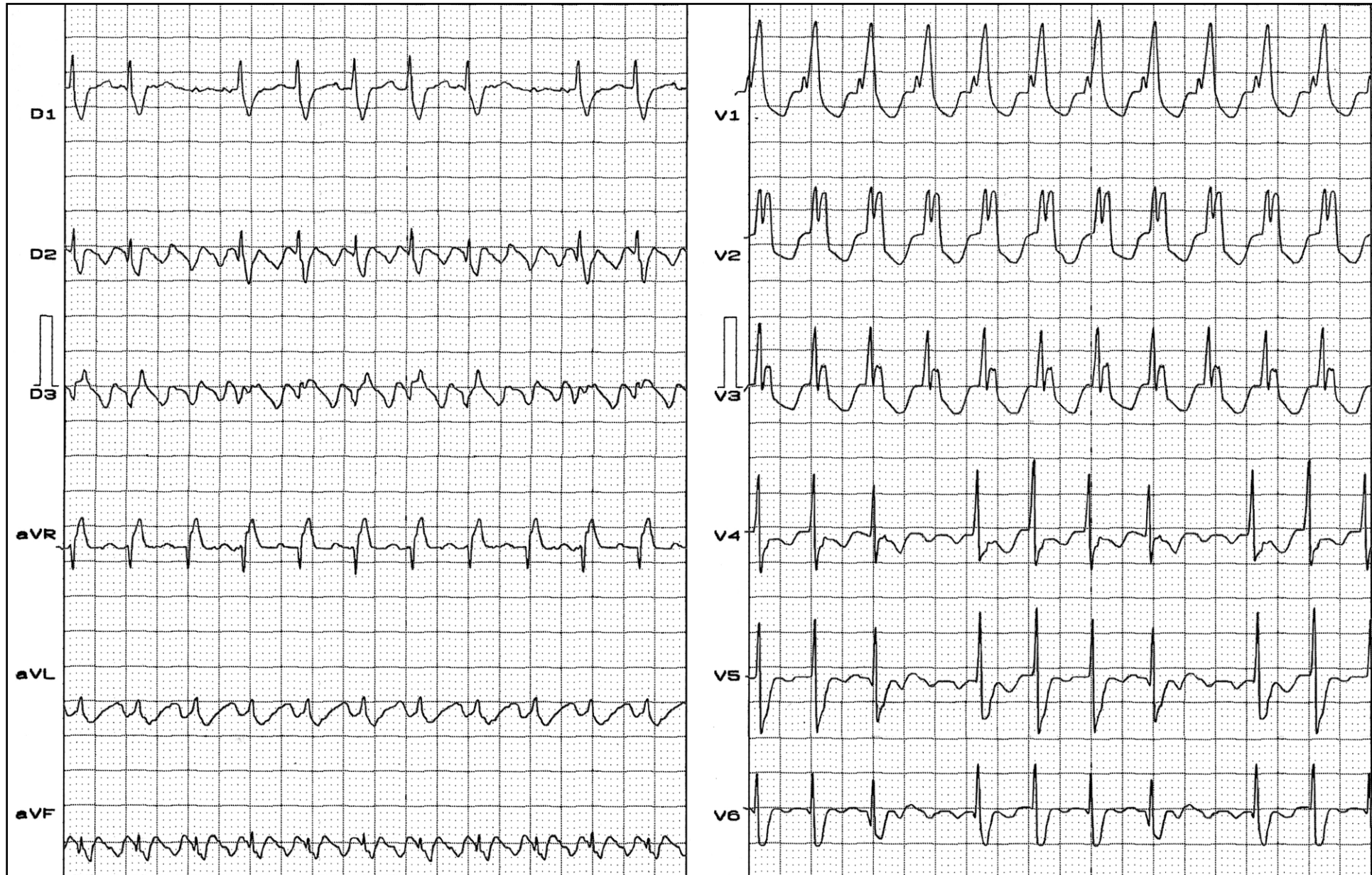


Atrial heart rate of 300 bpm. The stimulus does not conduct to the ventricles. Very low, regular ventricular heart rate, regardless of atrial activity.

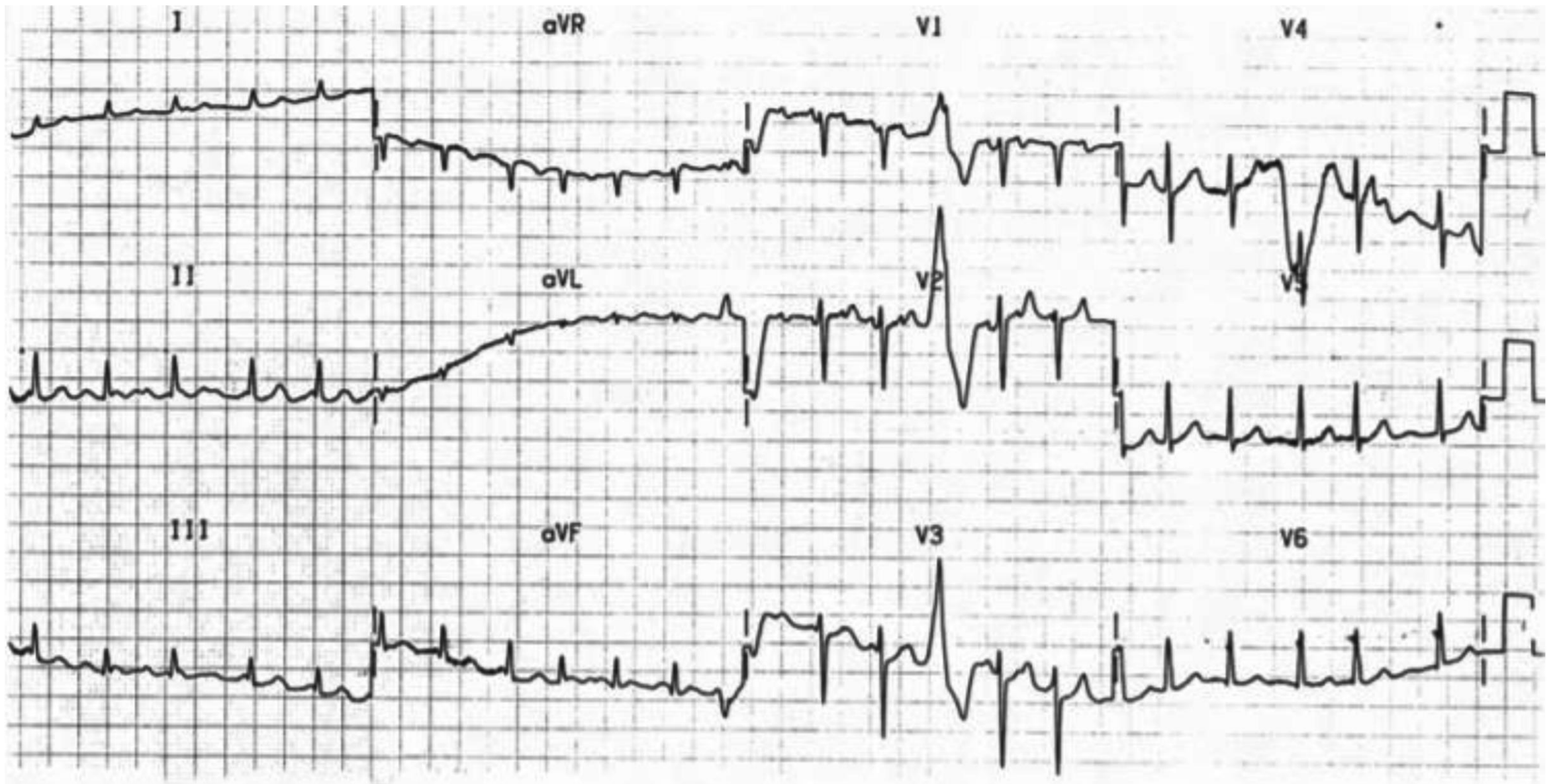
AFL with irregular variable AV block



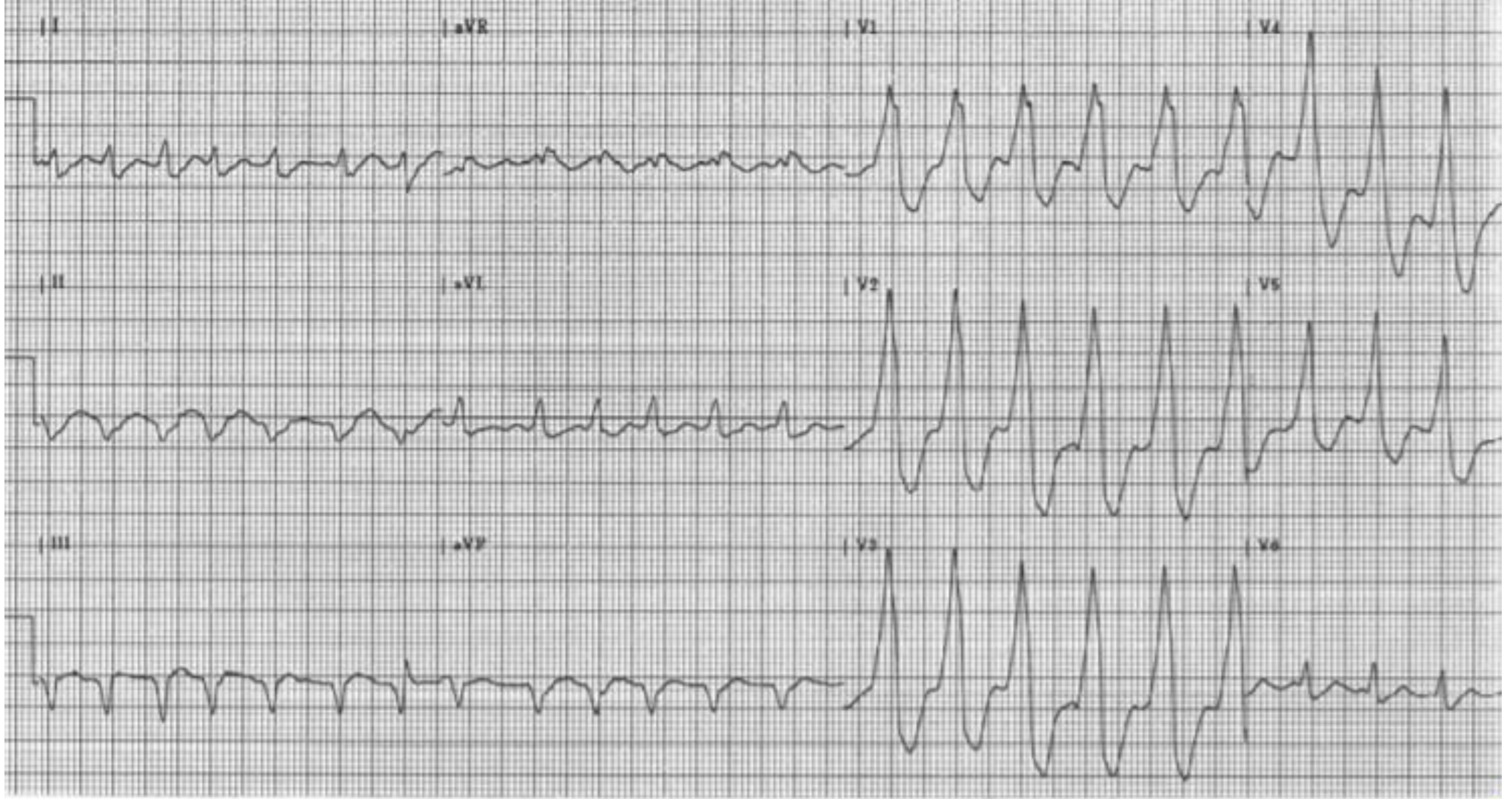
AFL with irregular AV block



AFL with 2:1 and 4:1 AV block. Atrial rate of 330 bpm. QRS complexes with complete RBBB pattern.



The ECG suggested AF with a rapid ventricular response. In leads V1 and V2, however, distinct atrial depolarizations at a rate of 300/minute were noted indicating that at least part of the time the patient had AFL with variable AV block. Except for a premature complex with wide QRSs in leads V1-V3, the QRSs were narrow because ventricular depolarization was exclusively, or nearly so, via the AV node, His bundle, and bundle branches.



The sustained wide complex QRS tachycardia superficially resembles VT, but ventricular tachycardia is virtually never this irregular. Because ventricular depolarization begins away from the normal conduction system, the wide QRS is not characteristic of RBBB or LBBB, and thus the rhythm also can be distinguished from AF with aberrant ventricular conduction due to block in one of those structures.

Relevant Terms and Definitions for AFL (Page 2016)

<p>I. • Cavotricuspid isthmus–dependent AFL: Counterclockwise (common form) typical flutter</p> <p>I.A) Type I atrial flutter with CCW rotation: In this case, F waves are positive in II, III and aVF.</p>	<p>The ECG is very helpful in establishing a diagnosis of right atrial cavo-tricuspid isthmus (CTI)-dependent AFL, mainly the common form due to counterclockwise (CCW) re-entry in the right atrium(RA). This is the most common type of AFL (90% of cases). It is sustained by macro-re-entrant circuits in the RA supported by endocardial structures such as crista terminalis, eustachian ridge/valve (posteriorly) and tricuspid annulus (anteriorly). The activation wave front proceeds in a cranial direction over the RA septum, reaches the top of the RA , then descends on the RA free wall in a caudal direction, and finally reaches the space located between the low part of the RA and the atrial septum. The inferior area, called cavotricuspid isthmus, is the critical link of the circuit and it is the target of the RFCA procedure. RFCA energy applied in the isthmus between inferior vena cava and tricuspid valve isthmus is effective in eliminating the AFL.</p>
<p>I.B) Cavotricuspid isthmus–dependent AFL: reverse typical</p> <p>I.B) Type I AFL with CW rotation (reverse): In both subtypes RFCA of the isthmus is the right procedure for treatment. The removal of conduction through the isthmus prevents the perpetuation of the circular motion, preventing AFL recurrence.</p>	<p>Macroreentrant AT that propagates around in the direction reverse that of typical AFL. Flutter waves typically appear positive in the inferior leads and negative in V1. This type of AFL is also referred to as “reverse typical” AFL or “clockwise typical AFL”</p>
<p>II. Atypical or non–cavotricuspid isthmus– dependent AFL</p>	<p>Macroreentrant ATs that do not involve the cavotricuspid isthmus. A variety of reentrant circuits may include reentry around the mitral valve annulus or scar tissue within the left or right atrium. A variety of terms have been applied to these arrhythmias according to the re-entry circuit location, including particular forms, such as “LA flutter” and “LA macroreentrant tachycardia” or incisional atrial re-entrant tachycardia due to re-entry around surgical scars.</p>

New classification of Electrophysiological Mechanisms of AFL (Scheinman 2004; Pedrinazzi 2006)

- 1) Right atrial CTI-dependent flutter
 - Counterclockwise flutter (common)
 - Clockwise flutter (uncommon)
 - Double-wave reentry
 - Lower loop reentry
 - Intra-isthmus reentry
- 2) Right atrial non CTI-dependent flutter
 - Scar-related flutter: Surgical atrial scars, especially due to cardiac surgery in congenital heart disease, are the anato-mopathological substrate of scar related circuits in RA non CTI dependent flutter
 - Upper loop flutter: The upper loop flutter is characterized by a critical circuit confined in the superior portion of the right atrium, and this circuit is non-CTI dependent

Scar-related flutter and upper loop reentry flutter are macro-re-entrant circuits due to anatomic obstacles located outside the cavo-tricuspid isthmus.

- 3) Left AFL The CARTO electroanatomic 3D mapping system provides important information to completely map and characterize left AFL as well as providing precise localization of the ablation catheter and the graphical presentation of the ablation line.
 - Mitral annulus flutter or perimitral annulus flutter: The ECG findings of mitral annulus flutter present low amplitude flutter waves (F) in the inferior leads II, III, aVF, and positive F waves in V1 and V2. Ablation at the anterior mitral isthmus shows the same success rate as the posterior mitral isthmus does. RFCA at the anterior mitral isthmus is associated with significantly shorter procedure durations without the need of a coronary sinus ablation.(Huemer 2015)
 - Scar and pulmonary vein-related flutter The re-entry circuit in this form involves one or more pulmonary veins in the posterior wall of the LA, especially in patients with mitral valve disease and sometimes after RFCA procedure in the LA to cure AF.
 - Coronary sinus flutter
 - Left septal flutter: circuit rotating around the fossa ovalis in counterclockwise or clockwise sequence. The ECG show prominent positive F waves only in V1 or V2 and diminished amplitude in the other leads.

Additionally, recently Yuichi Hori et al presented an atypical LA variant in an older woman called **Roof-dependent AFL** after a 28 mm second-generation cryoballoon ablation. A 73-year-old woman underwent a 28 mm 2nd generation cryoballoon ablation, and a roof-dependent AFL was induced just after the pulmonary vein isolation and LA voltage mapping. Ablation of the PV antrum was performed with two applications per vein, one for 180s followed by another for 150s. The voltage map during sinus rhythm revealed an overlap of the cryoablation lesion on the LA posterior wall, and the overlapping lesion created slow conduction during the AFL. The AFL terminated after a **roof linear ablation**, and no further atrial arrhythmias were documented during 1-year of follow-up. The occurrence of AFL after cryoablation is rare during the follow-up period, however, investigating the mechanism of the AFL after the cryoablation may contribute to an improved clinical outcome.(**Hori 2017**)

Typical AFL

Typical AFL is an organized atrial tachycardia. It can also be defined as a macroreentrant tachycardia confined to the RA. This arrhythmia has a 200-260 ms cycle length, although it may fluctuate depending on patient's previous treatment or ablation, congenital heart disease, etc (**Saoudi 2001**). Ventricular rate response will be limited by the AV node conduction, usually presenting a 2:1 response, during AFL.

Typical AFL originates in a well-known circuit around the tricuspid annulus limited by anatomical barriers such as both the superior and inferior cava veins, the coronary sinus and crista terminalis. The wave front may rotate around this circuit counterclockwise (most frequently) or clockwise (CW), resulting in the CCW common AFL or the CW AFL, respectively (**Saoudi 2001; Wellens 2002**). This condition produces continuous electrical activity around the atrial circuit and consequently in the ECG (F waves).

The ECG shows a saw tooth's pattern in inferior leads, with a slow downward slope followed by a fast upward slope explained by electrical forces going through the cavotricuspid isthmus and the septum, and then approaching the inferior leads through the lateral wall (**Saoudi 2001; Wellens 2002**). This saw tooth's appearance could be easily registered when the ventricular rate response is controlled.

Some conditions may make the ECG diagnosis difficult:

- 1) Scarred atria with low areas of voltage could mimic isoelectric baseline despite atrial continuous electrical activity.
- 2) Concomitant circuits could also change the typical atrial appearance.
- 3) Both high and irregular ventricular rate responses may make the diagnosis difficult. In the first case, vagal maneuvers or AV node blocking drugs, such as adenosine, may be useful. In the second case, a regular irregularity has to be always ruled out (**Irie 2011; Hoffmayer 2011**).

Electrophysiological studies (EPs) are indicated:

In AFL -I recurrences despite medical treatment (Class I indication)

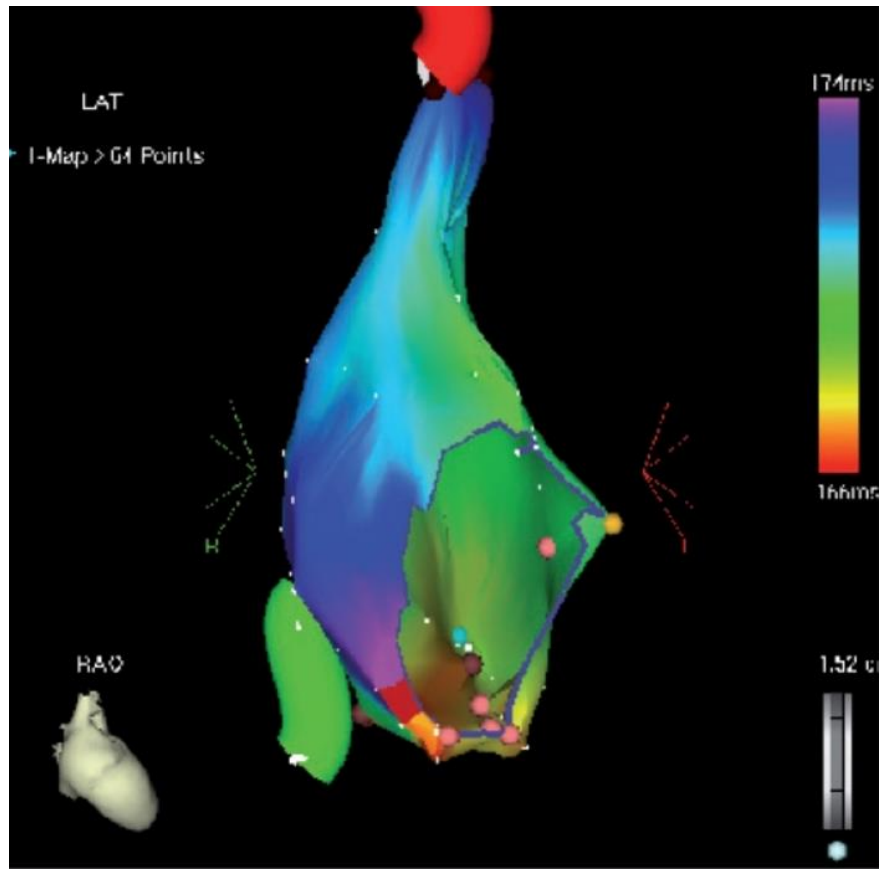
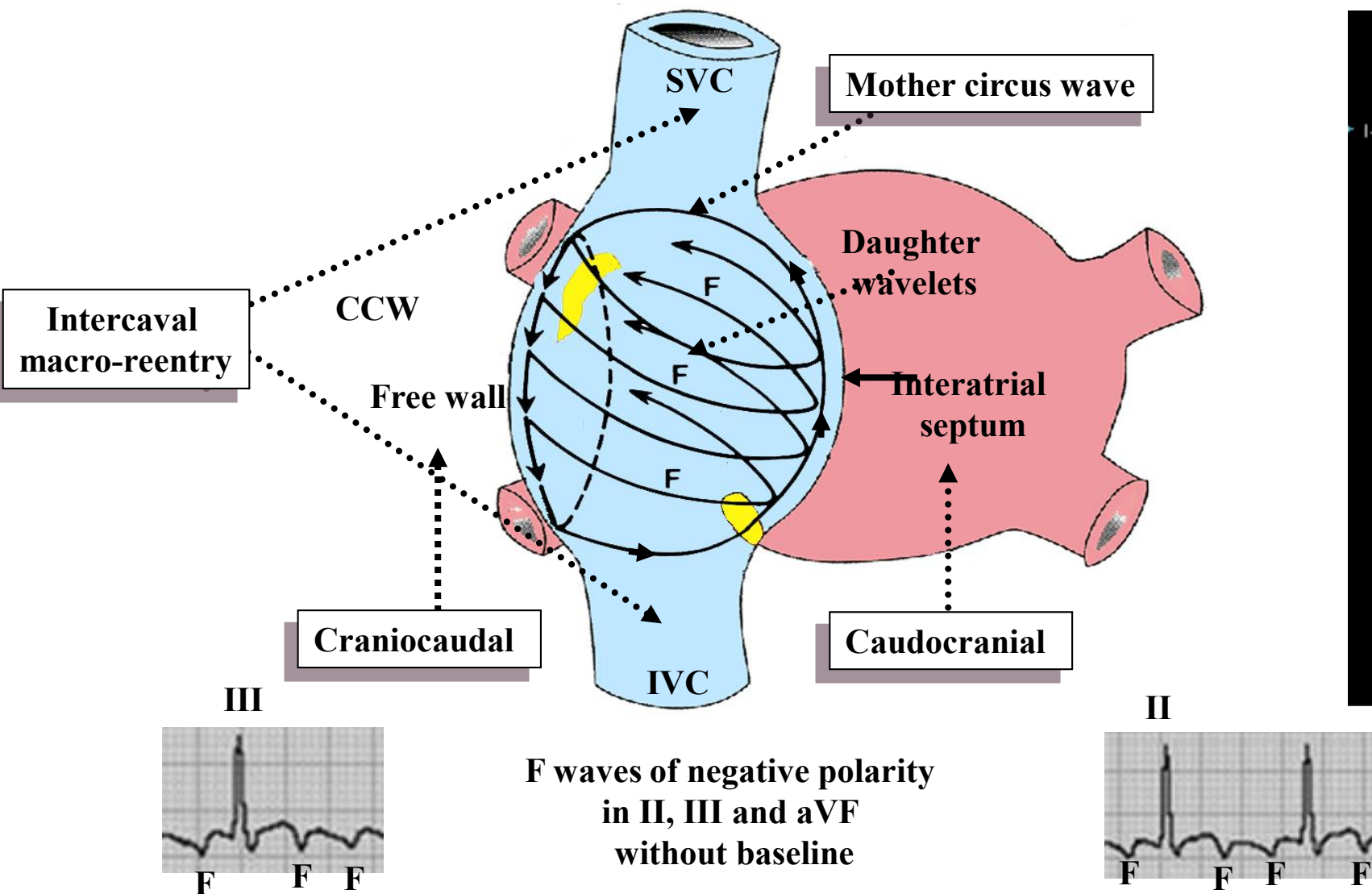
After the first episode of AFL I (Class IIa indication), especially in those presenting with poor hemodynamic tolerance or tachycardiomyopathy (**Luchsinger 1998**).

The ablation procedure's main target is to achieve bidirectional block through the cavotricuspid isthmus (CTI). Acute success rate is almost 95% in the registries (**Díaz 2010**). However, at 5 year follow-up almost 70% of these patients might develop AF or atypical AFL, which is probably related to the baseline characteristics, structural heart disease and uncontrolled risk factors (**Gilligan 2003; Tai 1998; Bandini 2011**).

Dromotropic mechanisms by macro-reentry in typical counterclockwise, common or classical AFL

Type I A counterclockwise, typical, common or classical AFL: intercaval macro-reentry: CCW circular motion descending by the RA free wall going through the cavo-tricuspid isthmus and ascending by the interatrial septum: mother circus wave. The typical saw-toothed pattern of inverted F waves in the inferior leads II,III, aVF.

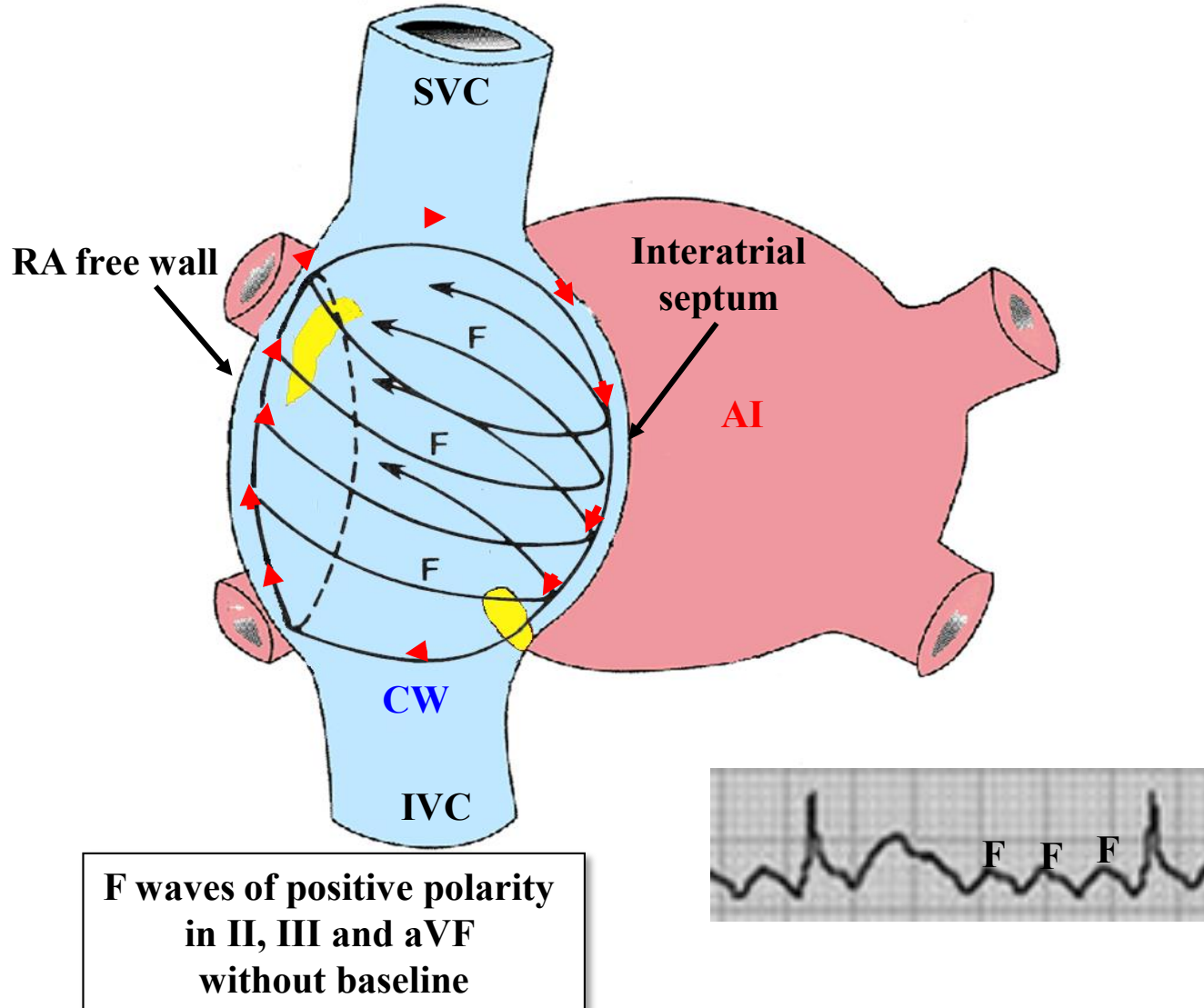
Counterclockwise right AFL is also characterized by flat to biphasic F waves in I and aVL, an upright F wave in V1 and an inverted F in V6.



Electroanatomical map of RA showing the CCW activation during AFL. The activation sequence proceeds from red to purple.

Dromotropic mechanisms by macro-reentry in typical AFL Type IB CW, “reverse typical” AFL or “CW typical AFL”

- **Type IB CW typical AFL, “reverse typical” AFL:** intercaval macro-reentry, with CW motion descending through the septum, going through the cavo-tricuspid isthmus and ascending through the RA free wall. In contrast, in the uncommon form of the right atrial CTI-dependent AFL the F wave pattern on the 12-lead ECG is less specific and variable. The activation sequence of this “reverse” version of flutter proceeds superiorly over the right atrial anterior and lateral walls and inferiorly over the right atrial posterior and septal walls.

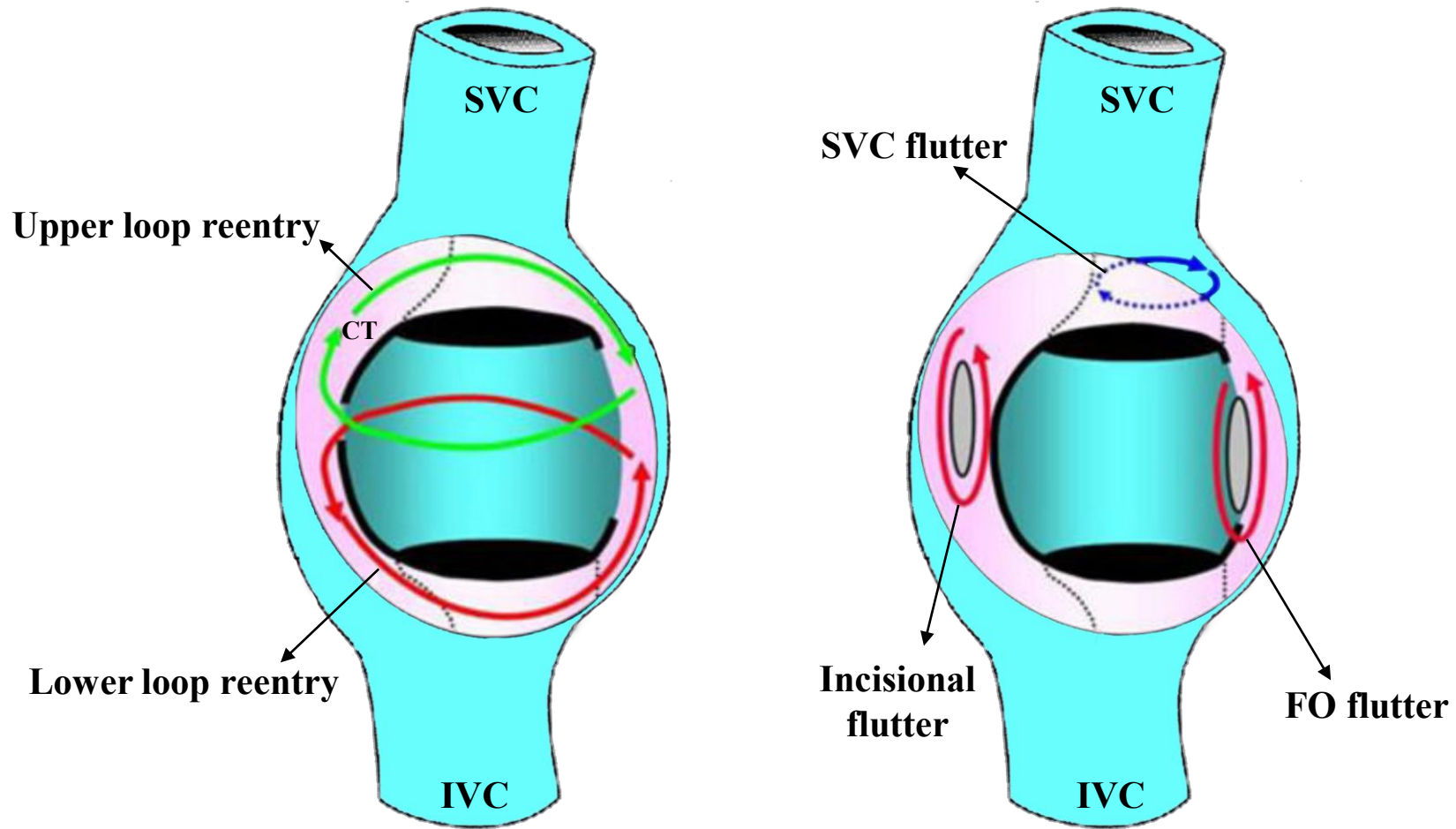


CW AFL makes up about 10% of clinical cases and has ECG findings that include positive F waves in the inferior leads II, III, aVF, and negative deflection in V₁. During electrophysiological study the diagnosis of common or uncommon form of RA CTI-dependent AFL is suggested by observing a CCW or CW activation pattern in the RA and around the tricuspid valve annulus.

The uncommon form of the RA CTI-dependent AFL is diagnosed electrophysiologically by demonstrating CW activation sequence around the RA and tricuspid valve annulus, with cranial to caudal activation in the interatrial septum and caudal to cranial activation in the RA free wall, the opposite sequence of that seen in the CCW RA CTI-dependent AFL. Confirmation that the reentry circuit involves the inferior isthmus requires the demonstration, for the common and uncommon forms, of the classic criteria for entrainment, including concealed entrainment with tachycardia acceleration to the pacing cycle length without a change in the F wave pattern on the ECG (**Cheng 1999; Zhang 2004**).

Atypical or non-cavotricuspid isthmus– dependent AFL

The definition of atypical AFL includes a broad spectrum of other macroreentrant tachycardias in which the wave front does not travel around the tricuspid annulus. Atypical right AFL other than reverse typical AFL, includes the following: lower loop reentry, fosa ovalis flutter, superior vena cava flutter and upper loop reentry (**Yang 2001; Bochoeyer 2003; Merino 2005; Kall 2000**).



Right atypical AFL's circuits. SVC: superior vena cava; IVC: inferior vena cava; CT: crista terminalis; FO: Foramen ovale.

Lower loop reentry **AFL** uses a circuit that includes the CTI, as common **AFL**, but it shortens the circuit through a gap in the crista terminalis. The mean cycle length is usually from 170 to 250 ms. Positive forces in inferior leads and V1 will be underpowered as a consequence of the change in the typical up-down depolarisation of the lateral wall. Upper loop reentry was also described using a circuit through a gap in the crista terminalis and then in the posterior right atrium wall. The ECG pattern mimics a clockwise typical flutter but the cycle length is usually shorter, as in lower loop reentry (**Yang 2001; Bochoeyer 2003**).

An infrequent form of right atrial atypical flutter is confined within the superior vena cava and from it the atria are passively activated (**Merino 2005**).

A second group could be called incisional flutters which includes those where the circuit uses previous surgery related scars, frequently seen in patients with history of surgical correction of congenital heart diseases (**Wellens 2002; Kall 2000**).

Finally, atypical flutter may originate in the left atrium. In this case, the leading wave front is confined to the left atrium. The most frequent left AFLs are perimitral, peripulmonary veins, septal, roof and posterior wall macroreentries. The surface ECG usually presents isoelectric baseline or low amplitude and positive regular F waves best in V1 (**Bochoeyer 2003; Shah 2009**).

Eletrophysiological studies are indicated in AFL-II recurrences despite optimized medical treatment. During EPs, the diagnosis and an accurate characterization of the circuit may be performed by activation and postpacing interval maps, which requires 3D navigation systems (**Jaïs 2000; Ouyang 2002**).

The acute ablation success is inferior to common AFL ablation, probably due to multifactorial issues such as worse clinical baseline characteristics, multiple concomitant atypical AFLs, and the instability of the clinical flutter during the procedure (**Castrejón 2011; Deisenhofer 2006**).

Management

The management issues with AFL are similar to AF and involve addressing the rate, rhythm, and anticoagulation both acutely and over the long-term. The important differences are mentioned in the following sections. Rate control agents slow down conduction at the AV node to decrease ventricular rate response to AFL. AV node ablation for pure AFL is rarely recommended for patients refractory to or intolerant of such agents. In elderly patients with multiple comorbidities and concurrent AF, AV node ablation may be the best clinical option. Electrical cardioversion, indicated for unstable patients, is successful in almost 100% of patients and usually requires less energy than is required for AF (50–100 J vs 120–200 J). AFL in the short-term is a stable rhythm and difficult to convert pharmacologically. IV-administered class III agents such as ibutilide and dofetilide prolong the action potential and increase the refractory period of the tissue in the slow zone, which can interrupt the reentrant circuit. Pharmacologic control of AF over the long-term involves administration of antiarrhythmic agents to prevent AFL. The success rates for various agents are in the range of 50% and are affected by issues of drug-related toxicity. Rhythm control and conversion to sinus rhythm are different by virtue of the relative ease and efficacy of catheter ablation for AFL. Catheter ablation of typical AFL has a success rate of more than 90%, with a major complication rate of less than 0.5%. The latter includes inadvertent heart block, tamponade, and phrenic nerve paralysis. Catheter ablation in typical AFL involves ensuring a bidirectional block across the cavotricuspid isthmus, which, as mentioned earlier, forms the narrowest area of the circuit for arrhythmia sustenance. Catheter ablation when feasible is the definitive treatment choice for typical AFL.

RFCA was effective and safe for pediatric AFL. There is no difference on the acute success rate, the follow-up AFL recurrence rate, as well as occurrence of sick sinus syndrome between the groups with and without CHD. AFL patients with CHD included the cavotricuspid isthmus-dependent AFL, atrial scars-dependent AFL or both. (**Jiang 2017**)

Toxic nodular goiter (TNG), toxic multinodular goiter, toxic nodular struma, toxic thyroid adenoma (TA) or Plummer's disease

Hyperthyroidism types

1. **Graves' disease:** It is the first most common cause of hyperthyroidism in the Western world. Graves disease accounts for 40% of cases of hyperthyroidism.
2. **Toxic multinodular goiter** In patients older than 55 years, toxic multinodular goiter is the most frequent etiology of spontaneous hyperthyroidism (**Diez 2003**) This entity correspond to the present case.
3. **Autonomously functioning thyroid adenoma**
4. **Rare causes:** pituitary adenoma, autoimmune thyroiditis (Hashitoxicosis), levothyroxine overdose, inadequate iodine supplementation (including amiodaron induced hyperthyroidism, iodine-based contrast media), hCG excess (pregnancy, gestational trophoblastic disease, germ-cell tumors), drug induced hyperthyroidism (e.i. amiodarone use), differentiated thyroid carcinomas and/or their metastases, struma ovarii, and familial nonautoimmune hyperthyroidism.

Toxic nodular goiter (TNG), toxic multinodular goiter, toxic nodular struma, toxic thyroid adenoma (TA) or Plummer's disease

A TNG is a thyroid gland that contains autonomously functioning thyroid nodules, with resulting hyperthyroidism. There are distinct considerations if the patient has a single solitary toxic nodule. TNG, or Plummer's disease, was first described by Henry Plummer in 1913. TNG is the second most common cause of hyperthyroidism in the Western world, after Graves disease. In elderly individuals and in areas of endemic iodine deficiency, TNG is the most common cause of hyperthyroidism. (**Diez 2003**)

Pathophysiology

TNG represents a spectrum of disease ranging from a single hyperfunctioning nodule (toxic adenoma) within a multinodular thyroid to a gland with multiple areas of hyperfunction. The natural history of a multinodular goiter involves variable growth of individual nodules; this may progress to hemorrhage and degeneration, followed by healing and fibrosis. Calcification may be found in areas of previous hemorrhage. Some nodules may develop autonomous function. Autonomous hyperactivity is conferred by somatic mutations of the thyrotropin, or thyroid-stimulating hormone (TSH), receptor in 20-80% of toxic adenomas and some nodules of multinodular goiters. (**Palos-Paz 2008**) Autonomously functioning nodules may become toxic in 10% of patients. Hyperthyroidism predominantly occurs when single nodules are larger than 2.5 cm in diameter. Signs and symptoms of TNG are similar to those of other types of hyperthyroidism.

Epidemiology

TNG accounts for approximately 15-30% of cases of hyperthyroidism in the United States, second only to Graves disease.

In areas of endemic iodine deficiency, TNG accounts for approximately 58% of cases of hyperthyroidism, 10% of which are from solitary toxic nodules. Graves disease accounts for 40% of cases of hyperthyroidism. In patients with underlying nontoxic multinodular goiter, initial iodine supplementation (or iodinated contrast agents) can lead to hyperthyroidism (Jod-Basedow effect). Iodinated drugs, such as amiodarone, may also induce hyperthyroidism in patients with underlying nontoxic multinodular goiter. Roughly 3% of patients treated with amiodarone in the United States (more in areas of iodine deficiency) develop amiodarone-induced hyperthyroidism. **(Abraham-Nordling 2008)**

Morbidity and mortality from TNG may be divided into problems related to hyperthyroidism and problems related to growth of the nodules and gland. Both TNG and Graves disease have increased mortality but for different reasons. **(Brandt 2013)**

TNG is more common in elderly adults; therefore, complications due to comorbidities, such as coronary artery disease, are significant in the management of hyperthyroidism.

Sex: Toxic nodular goiter occurs more commonly in women than in men. In women and men older than 40 years, the prevalence rate of palpable nodules is 5-7% and 1-2%, respectively.

Age: Most patients with TNG are older than 50 years.

Thyrotoxicosis often occurs in patients with a history of longstanding goiter. Toxicity occurs in a subset of patients who develop autonomous function. This toxicity usually peaks in the sixth and seventh decades of life, especially in persons with a family history of multinodular goiter or TNG, suggesting a genetic component.

Symptoms: Most patients with TNG present with symptoms typical of hyperthyroidism, including heat intolerance, palpitations, tremor, weight loss, hunger, and frequent bowel movements. Local compression problems due to nodule growth, although unusual, include dyspnea, hoarseness, and dysphagia. Elderly patients may have more atypical symptoms, including: Weight loss is the most common complaint in elderly patients with hyperthyroidism. Anorexia and constipation may occur, in contrast to frequent bowel movements often reported by younger patients. Dyspnea or palpitations may be a common occurrence. Tremor also occurs but can be confused with essential senile tremor. Cardiovascular complications occur commonly in elderly patients, and a history of atrial fibrillation, congestive heart failure, or angina may be present. F Lahey, MD, first described apathetic hyperthyroidism in 1931; this is characterized by blunted affect, lack of hyperkinetic motor activity, and slowed mentation in a patient who is thyrotoxic. Obstructive symptoms - A significantly enlarged goiter can cause symptoms related to mechanical obstruction. A large substernal goiter may cause dysphagia, dyspnea, or frank stridor. Rarely, this goiter results in a surgical emergency. Involvement of the recurrent or superior laryngeal nerve may result in complaints of hoarseness or voice change.

Asymptomatics: Many patients are asymptomatic or have minimal symptoms and are incidentally found to have hyperthyroidism during routine screening. The most common laboratory finding is a suppressed TSH with normal free thyroxine (T4) levels.

Physical Findings of TNG hyperthyroidism may be more subtle than those of Graves disease. Features may include widened, palpebral fissures; tachycardia; hyperkinesis; moist, smooth skin; tremor; proximal muscle weakness; and brisk deep tendon reflexes. The size of the thyroid gland is variable. Large substernal glands may not be appreciable upon physical examination. A dominant nodule or multiple irregular, variably sized nodules are typically present. In a small gland, multinodularity may be apparent only on an ultrasonogram. Chronic Graves disease may present with some nodularity; therefore, establishing the diagnosis is sometimes difficult. Hoarseness or tracheal deviation may be present upon examination. Mechanical obstruction may result in superior vena cava syndrome, with engorgement of facial and neck veins (Pemberton sign).(**Basaria 2004**) Stigmata of Graves disease (eg, orbitopathy, pretibial myxedema, acropachy) are not observed.

Causes: Functional autonomy of the thyroid gland appears to be related to iodine deficiency. Various mechanisms have been implicated, but the molecular pathogenesis is poorly understood. The sequence of events leading to toxic multinodular goiter is as follows: Iodine deficiency leads to low levels of T₄; this induces thyroid cell hyperplasia to compensate for the low levels of T₄. Increased thyroid cell replication predisposes single cells to somatic mutations of the TSH receptor. Constitutive activation of the TSH receptor may generate autocrine factors that promote further growth, resulting in clonal proliferation. Cell clones then produce multiple nodules. Somatic mutations of the TSH receptors and G α protein confer constitutive activation to the cyclic adenosine monophosphate (cAMP) cascade of the inositol phosphate pathways. These mutations may be responsible for functional autonomy of the thyroid in 20-80% of cases.(**Lado-Abeal 2008**) These mutations are found in autonomously

functioning thyroid nodules, solitary and within a multinodular gland. Nonfunctioning thyroid nodules within the same gland lack these mutations. The reported frequency of these mutations varies widely, ranging from 10-80%. Higher incidence is reported in patients with iodine deficiency. In addition to somatic mutations, polymorphisms of the TSH receptor have been studied in patients with TNG; notably, polymorphisms involving the carboxyl-terminal tail of the human TSH receptor have been found in nodular and genomic deoxyribonucleic acid (DNA). Unlike the somatic mutations found in autonomously functioning nodules, these mutations have also been found in other cell lines, indicating a germline mutation. One of these, *D727E*, was present with greater frequency in patients with TNG than in healthy individuals; this suggests that this polymorphism may be associated with the disease (**Gabriel 1999; Muhlberg 2000**). The presence of the heterozygous state for the *D727E* variant of the human TSH receptor alone is not sufficient for the development of the TNG. Approximately 10% of healthy individuals have this polymorphism.

Possible mediators in growth include the following:

Endothelin-1 (ET-1) production is increased in rat thyroid glands that have undergone hyperplasia; this suggests that ET-1 production may be involved in thyroid gland growth and vascularity. In contrast to normal thyroid tissue and papillary thyroid cancer, thyroid tissue in patients with TNG shows markedly positive staining of the stroma but absent staining of the follicular cells. The significance of this finding is unclear, but ET-1 is, in addition to being a vasoconstrictor, a mitogen for vascular endothelium, smooth muscle cells, and thyroid follicular cells.

In vitro systems have shown stimulation of thyroid follicular cell proliferation with insulinlike growth factor-1, epidermal growth factor, and fibroblast growth factor. Reduced concentrations of transforming growth factor- β 1 or resistance to transforming growth factor- β have also been associated with follicular cell growth. The role of these multiple factors in the growth and secretory function of TNG needs further investigation.

Cardiovascular involvement in patients with different causes of hyperthyroidism

The etiology of hyperthyroidism must be established to enable the correct treatment of hyperthyroidism and its associated cardiovascular complications

1. Patients with Graves disease or TNG are at increased cardiovascular risk; however, their cardiovascular complications are influenced by their age, comorbidities, and the cause of hyperthyroidism
2. Patients with TNG have an increased prevalence of AF and atrial enlargement, as well as an increased risk of cerebrovascular embolism
3. Graves disease is associated with dilated cardiomyopathy, antiphospholipid syndrome and a high prevalence of pulmonary arterial hypertension
4. AF is an independent predictor of chronic heart failure in patients with hyperthyroidism
5. Autoimmunity underpins both autoimmune thyroid disease and myxoid degeneration of the mitral valves
6. Among patients younger than 65 years of age with AF related to hyperthyroidism, pulmonary hypertension and thrombogenic milieu detected

6. Cont..... using transesophageal echocardiography (TEE) were highly prevalent. There was no association between CHA₂DS₂-VASc with TEE markers of thrombogenic milieu. Thyroid status, especially longer duration of hyperthyroidism might influence thrombogenic abnormalities. TEE adds useful information that may change antithrombotic therapy if otherwise guided solely by clinical risk classification.(**de Souza 2017**)
7. AFL was a risk factor for all arterial and venous outcomes during the first year of follow-up, but only for peripheral embolism, ischemic stroke, and hemorrhagic stroke thereafter.(**Sundbøll 2017**)

Cardiovascular effects of hyperthyroidism thyroid hormones affect the respiratory system, skeletal muscles and cardiac function. Patients with thyrotoxicosis consequently have impaired cardiopulmonary function, which is reversible after normalization of thyroid function.

Sinus tachycardia is frequent in patients with overt and subclinical hyperthyroidism and is responsible for palpitations, which represent the most frequent symptom of thyroid hormone excess in young patients. 24 h Holter monitoring shows that the HR is constantly increased during the day (although its circadian rhythm is preserved) in hyperthyroid patients. HR variability is decreased in patients with overt and subclinical hyperthyroidism, which supports the concept that an imbalance between sympathetic and vagal activity is associated with thyroid hormone excess.

Hyperdynamic circulation the cardiovascular effects of hyperthyroidism are characterized by increased preload with low systemic vascular resistance, a high HR and increased myocardial oxygen consumption. The hyperdynamic circulation associated with short-term hyperthyroidism results from the raised HR and increased stroke volume, which lead to a high cardiac output state.

Decreased exercise capacity in spite of their high cardiac output state, hyperthyroid patients have reduced exercise tolerance. this phenomenon is caused by their reduced cardiovascular reserve, which leads to an inadequate increase in cardiac output during physical exercise. in fact, cardiac output reserve directly correlates with exercise capacity, and the mechanisms used by the cardiovascular system during exercise (the increase in HR, blood volume, venous return, myocardial contractility and myocardial oxygen consumption and the decrease in systemic vascular resistance) are already at almost maximal capacity in hyperthyroid patients who are at rest stress induced changes in cardiovascular and respiratory function have been studied noninvasively in previously untreated hyperthyroid patients with Graves disease (age range 19–49 years) or TNG (age range 50–71 years) who were free of cardiovascular disease and were not taking any cardiac or other interacting drugs. Researches showed substantial differences with respect to the cardiovascular and respiratory exercise capacities of hyperthyroid patients with Graves disease and those with TNG. The maximal work rate was significantly reduced in untreated patients with hyperthyroidism.

Cardiovascular complications

Cardiac arrhythmias: hyperthyroidism is associated with atrial arrhythmias, dysfunction of the sinus node and supraventricular ectopic activity. The prevalence of premature supraventricular contractions is higher in untreated patients with either Graves disease or TNG than in controls. Toxic adenoma and TNG develop in middleaged (age 50–60 years) and elderly people (aged 60 years and over), respectively. Both conditions are frequently associated with acute or chronic illness, especially heart disease. Patients may have subclinical or overt thyrotoxicosis depending on their iodine intake and the amount of autonomously hyperfunctioning thyroid tissue. Diagnosis of hyperthyroidism in these patients is important because the thyroid hormone excess associated with thyroid autonomy can have serious cardiovascular consequences, even though the symptoms are often milder than those of Graves disease. AF is an important cardiac complication in elderly patients with thyroid autonomy—those over 50 years of age with overt hyperthyroidism and those over 60 years with subclinical hyperthyroidism—and might not revert when euthyroidism is restored, if it has been present for a long time and is coexistent with heart disease. Patients aged over 65 years with TNG and AF or AFL are also at an increased risk of stroke. moreover, AF and AFL are independent predictors of congestive heart failure in patients with hyperthyroidism. For these reasons, the etiology of hyperthyroidism must be established to enable the correct treatment of the disease and of the associated cardiovascular complications. Dekkers et al studied 85 856 hyperthyroid patients and 847 057 matched population-based controls. Mean follow-up time was 9.2 years. The HR for mortality was highest in the first 3 months after diagnosis of hyperthyroidism, and remained elevated during long-term follow-up (>3 years). The risk for all examined cardiovascular events was increased, with the highest risk in the first 3 months after hyperthyroidism diagnosis. The 3-month post-diagnosis risk was highest for AF and arterial embolism, but the risks of venous thromboembolism, AMI, ischemic and non-ischemic stroke and percutaneous coronary intervention were increased also 2- to 3-fold. The authors concluded that an increased risk for all-cause mortality and acute cardiovascular events in patients with hyperthyroidism. (**Dekkers 2017**).

Long-term or untreated overt and subclinical hyperthyroidism is associated with cardiovascular risk factors that lead to increased morbidity and mortality

Long-term or untreated subclinical and overt hyperthyroidism

Risk factors

- ↑ Cardiac arrhythmias
- ↑ Oxygen consumption
- ↑ Heart rate
- ↑ Cardiac workload
- ↑ Pulse pressure

- ↑ Left ventricular mass
- Impaired diastolic filling
- ↑ Arterial stiffness
- ↑ Atrial size
- Persistent AF- AFL
- Pulmonary arterial hypertension

Increased cardiovascular morbidity and mortality

- Stroke
- Angina
- Myocardial infarction
- Heart failure
- Sudden death

Clinical characteristics of different causes of persistent hyperthyroidism

Feature	Graves disease	Toxic adenoma	Toxic multinodular goiter
Age of presentation	Usually young (peak age 40 years, although the disease can start at any age)	40-50 years in iodine-deficient areas	≥50 years in patients with multinodular goiter in iodine-deficient areas
Prevalence (% of cases of hyperthyroidism)	0.5-2.7 in areas of iodine sufficiency	~10 in iodine-deficient areas (increases with advancing age)	~50 in iodine-deficient areas (increases with advancing age)
Etiology	Autoimmune	Nonautoimmune	Nonautoimmune
Pathophysiological mechanism	Thyroid-stimulating immunoglobulins	Activating mutations in thyrotropin receptor or G protein	Activating mutations in thyrotropin receptor or G protein
Thyroid function	Subclinical hyperthyroidism is of short duration Severe clinical manifestations of thyrotoxicosis TSH may be persistently suppressed during antithyroid treatment Frequent T ₃ and T ₄ toxicosis	Thyroid autonomy Subclinical hyperthyroidism can last years History of slow thyroid nodule growth with a progressive increase in thyroid hormone levels and TSH suppression Frequent T ₃ toxicosis	Thyroid autonomy Subclinical hyperthyroidism is frequently prolonged Overt hyperthyroidism is uncommon but may develop, especially in patients with undetectable serum TSH after exposure to iodinated contrast agents, amiodarone, etc. Overproduction of thyroid hormone is usually less severe than in patients with Graves disease Frequent T ₃ toxicosis
Cardiovascular manifestations	Symptoms of adrenergic overactivity are common Potential association with autoimmune cardiovascular disease	Generally milder than in Graves disease Cardiovascular manifestations dominate the clinical presentation	Patients are less symptomatic than those with Graves disease for adrenergic overactivity Many patients have underlying cardiac disease AF is frequently the first manifestation of subclinical or overt hyperthyroidism

Treatment	Remission of the disease is possible with antithyroid drugs	Hyperthyroidism is reversible with antithyroid drugs (but treatment should not be lifelong) Antithyroid drugs are used for pretreatment before definitive therapy The cardiovascular risk should not be assessed before definitive treatment Definitive treatment with radioiodine or surgery is administered in relation to the size of the goiter and underlying cardiac conditions	Hyperthyroidism is reversible with antithyroid drugs (but treatment should not be lifelong) Antithyroid drugs are used for pretreatment before definitive therapy Cardiovascular risk should be assessed before definitive treatment Definitive treatment with radioiodine or surgery is advisable, in relation to the size of the goiter and underlying cardiac conditions Radioiodine is preferred in elderly patients with underlying heart disease and in patients with AF The risk of thromboembolic events should be assessed in patients with AF and underlying heart disease
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Medical Care

The optimal therapy for treatment of TNG remains controversial and differs slightly between a single dominant nodule and multiple toxic nodules. Unlike Graves disease, TNG is not an autoimmune disease and rarely, if ever, remits. (**van Soestbergen 1992**) Therefore, patients who have autonomously functioning nodules should be treated definitely with radioactive iodine or surgery. The American Thyroid Association has released guidelines for the management of hyperthyroid and other causes of thyrotoxicosis, including the use of radioactive iodine or surgery to treat toxic multinodular goiter. (**Ross 2016**) Patients with subclinical hyperthyroidism should be monitored closely for overt disease. Some suggest that elderly patients, women with osteopenia, and patients with risk factors for atrial fibrillation should be treated, even those who have subclinical disease.

Na¹³¹ I treatment - In the United States and Europe, radioactive iodine is considered the treatment of choice for TNG. Except for pregnancy, there are no absolute contraindications to radioiodine therapy. (**Grubeck-Loebenstein 1985**) Much debate exists regarding optimal dosing of radioactive iodine. Patients with TNG tend to have less uptake than do patients with Graves disease; therefore, they are generally considered to need higher doses of Na¹³¹ I. However, studies by Allahabadia and colleagues suggest that fixed doses of radioiodine do not demonstrate any difference in response in these 2 groups of patients (using a fixed dose of 370 megabecquerels). (**Allahabadia 2001**) A recent study proposes the use of a personalized dose calculation algorithm rather than fixed doses of radioiodine. (**Schiavo 2015**) A single dose of radioiodine therapy has a success rate of 85-100% in patients with TNG. Radioiodine therapy may reduce the size of the goiter by up to 40%. (**Zingrillo 2007; Erkan 2012**) Failure of initial treatment with radioactive iodine has been associated with increased goiter size and higher T3 and free T4 levels, which suggests that these factors may present a need for higher doses of Na¹³¹ I. A positive correlation exists between radiation dose to the thyroid and decrease in thyroid volume. In patients with uptake of less than 20%, pretreatment with lithium, PTU, or recombinant TSH can increase the effectiveness of iodine uptake and treatment. (**Lee 2015; Adamali 2007**) This treatment may be valuable in elderly patients in whom surgery is considered high risk and volume reduction is needed. Complications Hypothyroidism occurs in 10-20% of patients; this is similar to the incidence rate after surgery and is substantially less than in the treatment of Graves disease. (**Adamali 2007**) Tracheal compression due to thyroid swelling after radiation therapy is no longer thought to be a risk. (**Bonnema 1999**) Mild thyrotoxic symptoms after radioiodine occur in about one-third of patients, and about 4% of patients develop a clinically significant radiation-induced thyroiditis. These patients should be treated symptomatically with β -blockers. Elderly patients may have exacerbation of congestive heart failure and AF. Pretreat elderly patients with antithyroid drugs. Thyroid storm is a rare complication, particularly in patients with rapidly enlarging goiters or high total T3 levels. Patients with these conditions should receive pretreatment with antithyroid drugs. Pharmacotherapy: Antithyroid drugs and β -blockers are used for short courses in the treatment of TNG; they are important in rendering patients euthyroid in preparation for radioiodine or surgery and in treating hyperthyroidism while awaiting full clinical response to radioiodine.

with subclinical disease at high risk of complications (eg, atrial fibrillation, osteopenia) may be given a trial of low dose methimazole (5-15 mg/d) or beta blockers and should be monitored for a change in symptoms or for disease progression that requires definitive treatment.

- Thioamides - The role of therapy with thioamides (eg, PTU, methimazole) is to achieve euthyroidism prior to definitive treatment with either surgery or radioiodine therapy. Data suggest that pretreated patients have decreased response to radioiodine. The general recommendation is to stop antithyroid agents at least 4 days prior to radioiodine therapy in order to maximize the radioiodine effect. Antithyroid drugs are often administered for 2-8 weeks before radioiodine therapy in order to avoid the risk of precipitating thyroid storm. Although many physicians no longer consider this treatment necessary, the general consensus is that elderly patients or patients with high risk of cardiac complications should receive this treatment. Antithyroid drugs have side effects, the most common being pruritic rash, fever, gastrointestinal upset, and arthralgias. More serious potential side effects include agranulocytosis, drug-induced lupus and other forms of vasculitis, and liver damage. Methimazole is more likely to cause a cholestatic picture while PTU is more likely to cause a transaminitis. Beta blockers should be used with caution in those patients that have contraindications such as pulmonary or cardiac disorders. The US Food and Drug Administration (FDA) added a boxed warning, the strongest warning issued by the FDA, to the prescribing information for PTU. The boxed warning emphasizes the risk for severe liver injury and acute liver failure, some of which have been fatal. The boxed warning also states that PTU should be reserved for use in patients who cannot tolerate other treatments, such as methimazole, radioactive iodine, or surgery. The decision to include a boxed warning was based on the FDA's review of postmarketing safety reports and on meetings held with the American Thyroid Association, the National Institute of Child Health and Human Development, and the pediatric endocrine clinical community. The FDA has identified 32 cases (22 adult and 10 pediatric) of serious liver injury associated with PTU. Of the adults, 12 deaths and 5 liver transplants occurred, and among the pediatric patients, 1 death and 6 liver transplants occurred. PTU is indicated for hyperthyroidism due to Graves disease. These reports suggest an increased risk for liver toxicity with PTU compared with methimazole. Serious liver injury has been identified with methimazole in 5 cases (3 resulting in death). PTU is considered to be a second-line drug therapy, except in patients who are allergic to or intolerant of methimazole, or in women who are in the first trimester of pregnancy. Rare cases of embryopathy, including aplasia cutis, have been reported with methimazole during pregnancy. The FDA recommends the following criteria be considered for prescribing PTU.
 - Reserve PTU use during first trimester of pregnancy, or in patients who are allergic to or intolerant of methimazole.
 - Closely monitor PTU therapy for signs and symptoms of liver injury, especially during the first 6 months after initiation of therapy.
 - For suspected liver injury, promptly discontinue PTU therapy, evaluate the patient for evidence of liver injury, and provide supportive care.
 - PTU should not be used in pediatric patients unless the patient is allergic to or intolerant of methimazole and no other treatment options

are available.

- Counsel patients to promptly contact their health care provider for the following signs or symptoms: fatigue, weakness, vague abdominal pain, loss of appetite, itching, easy bruising, or yellowing of the eyes or skin.

- Beta-adrenergic receptor antagonists - These drugs remain useful in the treatment of symptoms of thyrotoxicosis; they may be used alone in patients with mild thyrotoxicosis or in conjunction with thioamides for treatment of more severe disease. Propranolol, a nonselective beta blocker, may help to lower the heart rate, control tremor, reduce excessive sweating, and alleviate anxiety. Propranolol is also known to reduce the conversion of T4 to T3.

- In patients with underlying asthma, beta-1 selective antagonists, such as atenolol or metoprolol, would be safer options.

- In patients with contraindications to beta blockers (eg, moderate to severe asthma), calcium channel antagonists (eg, diltiazem) may be used to help control the heart rate.

Surgical Care

Surgical therapy is usually reserved for young individuals, patients with 1 or more large nodules or with obstructive symptoms, patients with dominant nonfunctioning or suspicious nodules, patients who are pregnant, patients in whom radioiodine therapy has failed, or patients who require a rapid resolution of the thyrotoxic state.

Total or near-total thyroidectomy results in rapid cure of hyperthyroidism in 90% of patients and allows for rapid relief of compressive symptoms.

(**Smith 2013**) Goiter recurrence is lower patients who undergo total or near-total thyroidectomy compared to subtotal thyroidectomy. (**Cirocchi 2015**)

Restoring euthyroidism prior to surgery is preferable.

Complications of surgery include the following:

In patients who are treated surgically, the frequency of hypothyroidism is similar to that found in patients treated with radioiodine (15-25%), and is strongly dependent on the extent of the surgery.

Complications include permanent vocal cord paralysis (2.3%), permanent hypoparathyroidism (0.5%), temporary hypoparathyroidism (2.5%), and significant postoperative bleeding (1.4%).

Other postoperative complications include tracheostomy, wound infection, wound hematoma, myocardial infarction, atrial fibrillation, and stroke.

In experienced hands the mortality rate is almost zero.

When radioactive iodine, surgery or long-term antithyroidal drugs are inappropriate or contraindicated, radiofrequency ablation can be considered in select patients. (**Sung 2015**)

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