MOSAIC TURNER SYNDROME IN YOUNG WOMAN WITH SEVERE RESTRICTIVE CARDIOMYOPATHY

MULHER JOVEM SINDRÓMICA (SINDROME DE TURNER- MOSAICO) COM CARDIOMIOPATIA RESTRITIVA SEVERA

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Case Report

Id: ACN, 28, female, born and raised in Fortaleza, Ceara, Brazil.

Main Complaint "shortness of breath and chest beater".

Patients with a history of "bone disease" since childhood. Three months ago presenting palpitations and dyspnea.

Sought assistance in our service because the doctor has prescribed an antiarrhythmic drug that could only be administered in the emergency room.

HPP: Accompanied by orthopedics service for suspected Escobar syndrome.

Patient with ectopic kidney and suspected hepatic hemangioma.

Also accompanied by a geneticist

Physical examination: webbed neck, difficulty opening mouth and limbs, keloid formation. TransThoracic Echo FE 44% important Increase biatrial size. Ventricular Myocardium: Granular appearance suggestive of myocardial infiltrative cardiomyopathy. Left and right ventricles with normal dimensions. Mild mitral and tricuspid regurgitation. Calculated Pulmonary artery systolic pressure = 40 mmHg. Normal pericardium.

Trans-esophageal echocardiography: thrombus in both left and right atria, carpeting and thrombus in the right atrium ceiling.

Karyotype: Mosaic Turner Syndrome.

Initially treated with beta-blockers, amiodarone and warfarin.

Readmitted to our service recently to endomyocardial biopsy (we are awaiting the results).

Questions:

1.ECGs diagnosis?

2.Wich is the posible cause of infiltrative cardiomyopathy?

Id: ACN, 28 anos, feminina, natural e procedente de Fortaleza, Ceará Brazil.

Queixa Principal: "falta de ar e batedeira no peito".

Paciente com histórico de "doença dos ossos" desde a infância. Há três meses apresentando palpitações e dispnéia.

Procurou assistência em nosso serviço porque o médico receitou-lhe uma medicação antiarritmica que só poderia ser administrada na sala de emergência.

HPP: paciente acompanhada na ortopedia por suspeita de Síndrome de Escobar.

Portadora de rim ectópico e suspeita de hemangioma hepático.

Acompanhada por geneticista –

Exame físico: pescoço alado, dificuldade de abertura bucal e dos membros, formação de quelóides.

ECO Transtorácico: FE 44% Aumento importante biatrial. Aspecto granuloso do miocárdio sugestivo de miocardiopatia infiltrativa. Ventrículos esquerdo e direito de dimensões normais. Insuficiência mitral e insuficiência tricúspide leves. Pressão sistólica da Artéria Pulmonar calculada = 40mmHg. Pericárdio normal

Ecocardiograma Trans-esofágico: trombos em ambas as aurículas esquerda e direita, e trombo atapetando no teto do átrio direito.

Cariótipo: Síndrome de Turner (Mosaico)

Inicialmente medicada com beta-bloqueadores, amiodarona e warfarina.

Reinternada no nosso serviço recentemente para realização de biopsia endomiocárdica (estamos aguardando o resultado). Qual os diagnósticos dos ECGs? Qual a possivel causa da cardiomiopatia?

ECG admissão 08 08 2011/Admission ECG 08 08 2011

Atrial HR: over 300 bpm
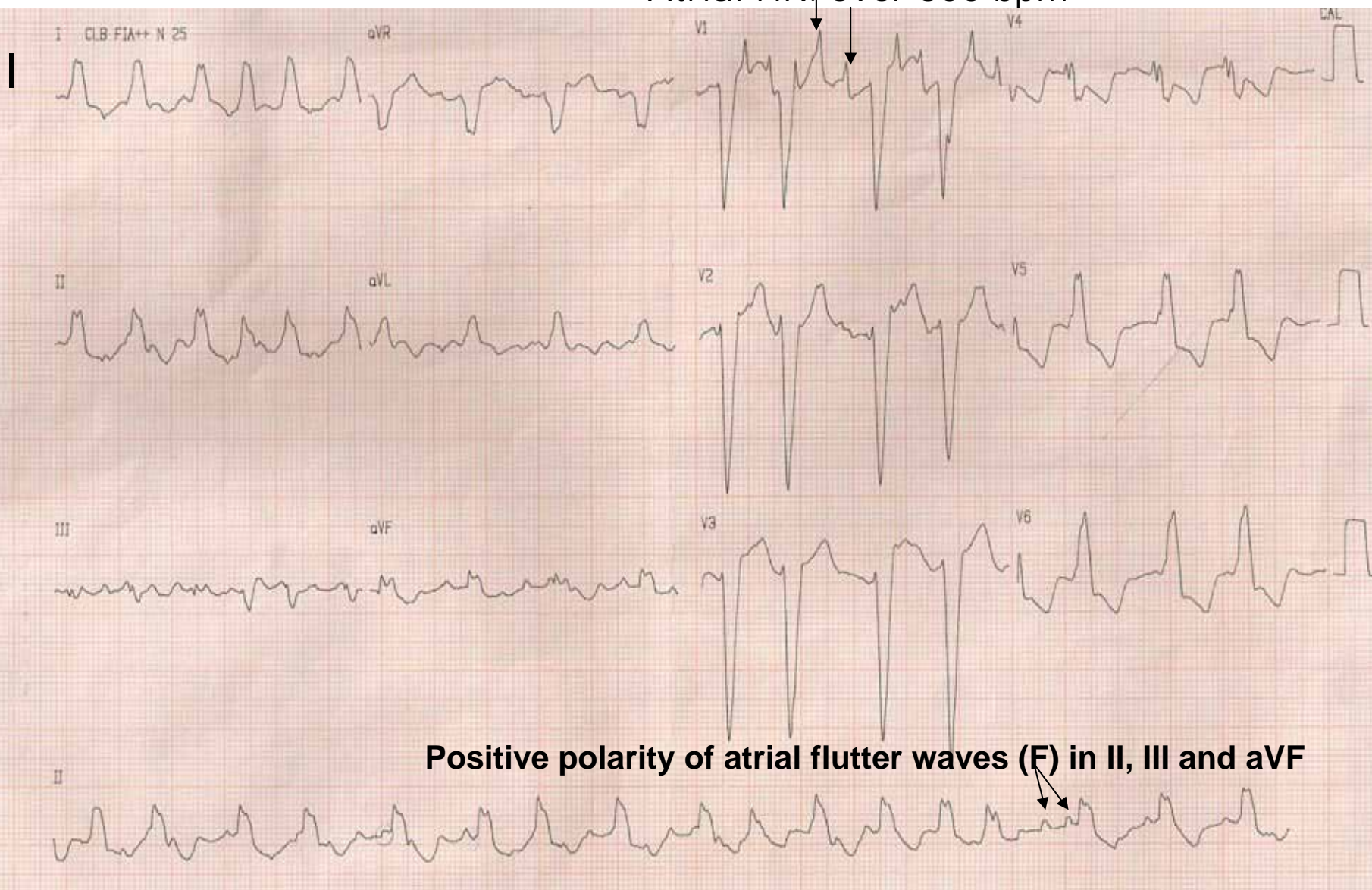
Positive polarity of atrial flutter waves (F) in II, III and aVF

Atrial flutter with variable AV block: irregular atrial flutter.

Atrial flutter with variable AV block (irregular flutter). Classical atrial flutter has a characteristic absence of isoelectric "plateau" between the F waves. In this case we observe an isoelectric plateau

DROMOTROPIC MECHANISMS BY MACRO-REENTRY IN ATRIAL FLUTTER

FLUTTER TYPE I OR CLASSICAL: intercaval macro-reentry: counterclockwise circular motion, descending by the RA free wall and ascending by the interatrial septum: "mother circus wave".

SVC

"MOTHER CIRCUS WAVE"

DAUGHTER WAVES

INTERCAVAL MACROREENTRY

COUNTER-CLOCKWISE

FREE WALL

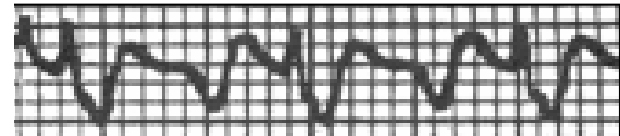INTERATRIAL SEPTUM

F

F

F

CRANEOCAUDAL

CAUDOCRANEAL

IVC

III

II

F waves of negative polarity in II, III and aVF without baseline

Outline of macro-reentry in atypical flutter.

DROMOTROPIC MECHANISMS BY MACRO-REENTRY IN ATRIAL FLUTTER

TYPE II FLUTTER OTHER NAMES:

Atypical, rare, antidromic, type B, rapid, left atrial. Macro-reentry in the junction of the right appendage with the RA near the atrioventricular sulcus.

Clockwise circular motion descending by the septum and ascending by the RA free wall.

CW ROTATION

F

F

F

F WAVES OF POSITIVE POLARITY IN II, DII AND aVF AND WITH A MUCH GREATER RATE WITHOUT BASELINE
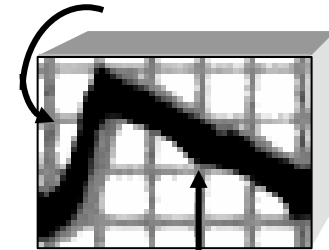
F F

Atrial rate of 345 bpm
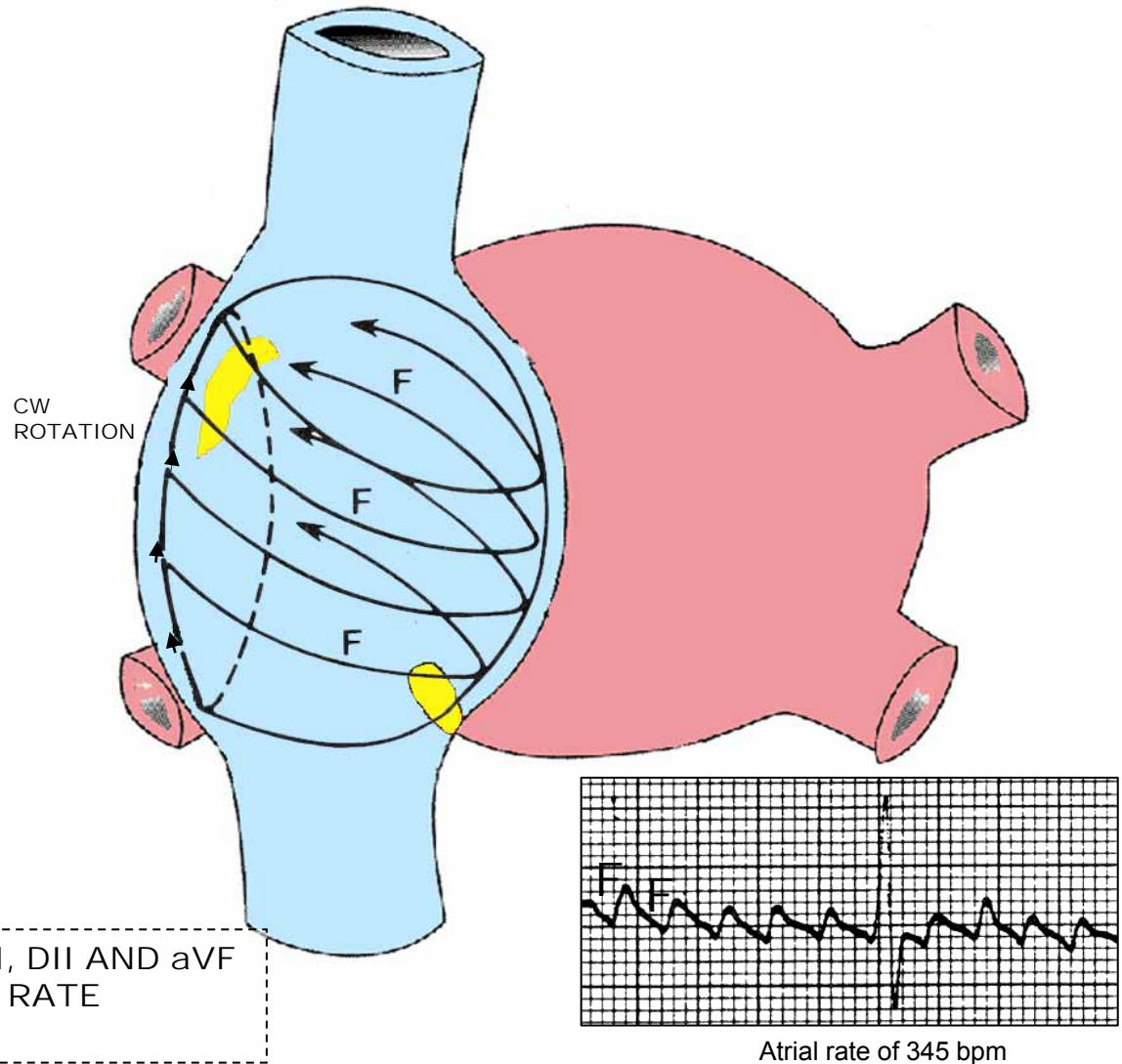
Differences between flutter type I and type II.

CHARACTERISTICS OF ATRIAL ACTIVATION IN ATRIAL FLUTTER
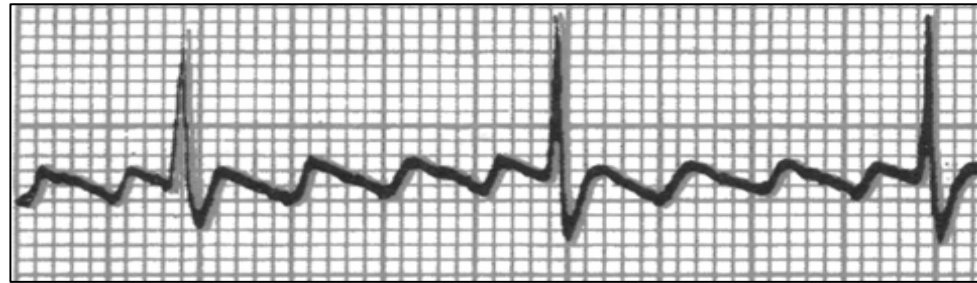
SAWTOOTH APPEARANCE

ATRIAL DEPOLARIZATION

ATRIAL REPOLARIZATION

**ABSENCE OF ISOELECTRICAL
"PLATEAU"
BETWEEN F WAVES**
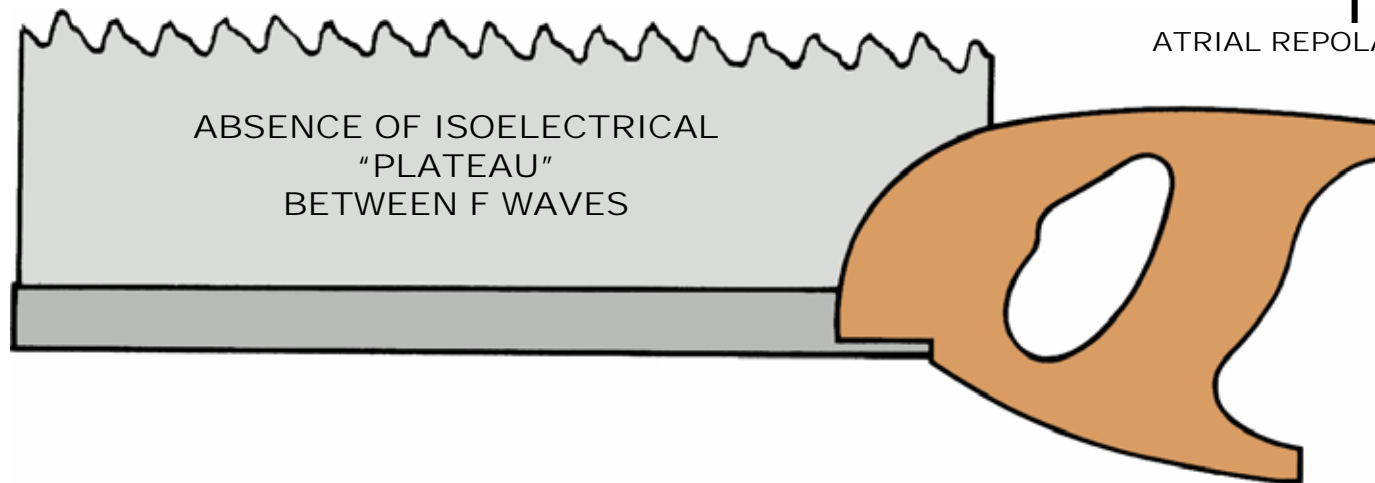
Waves with sawtooth or picket fence appearance called F waves, with a heart rate between 250 and 350 bpm, observed better in the inferior wall and V_1 with slowly descending and rapidly ascending ramp. These waves resemble an inverted P wave, followed by an ascending ramp: "Tp" waves.

Electrocardiographic characterization.

22-08-2011

August 22-2011

V1

RA

LA

RA

LA

III

P axis: +55°
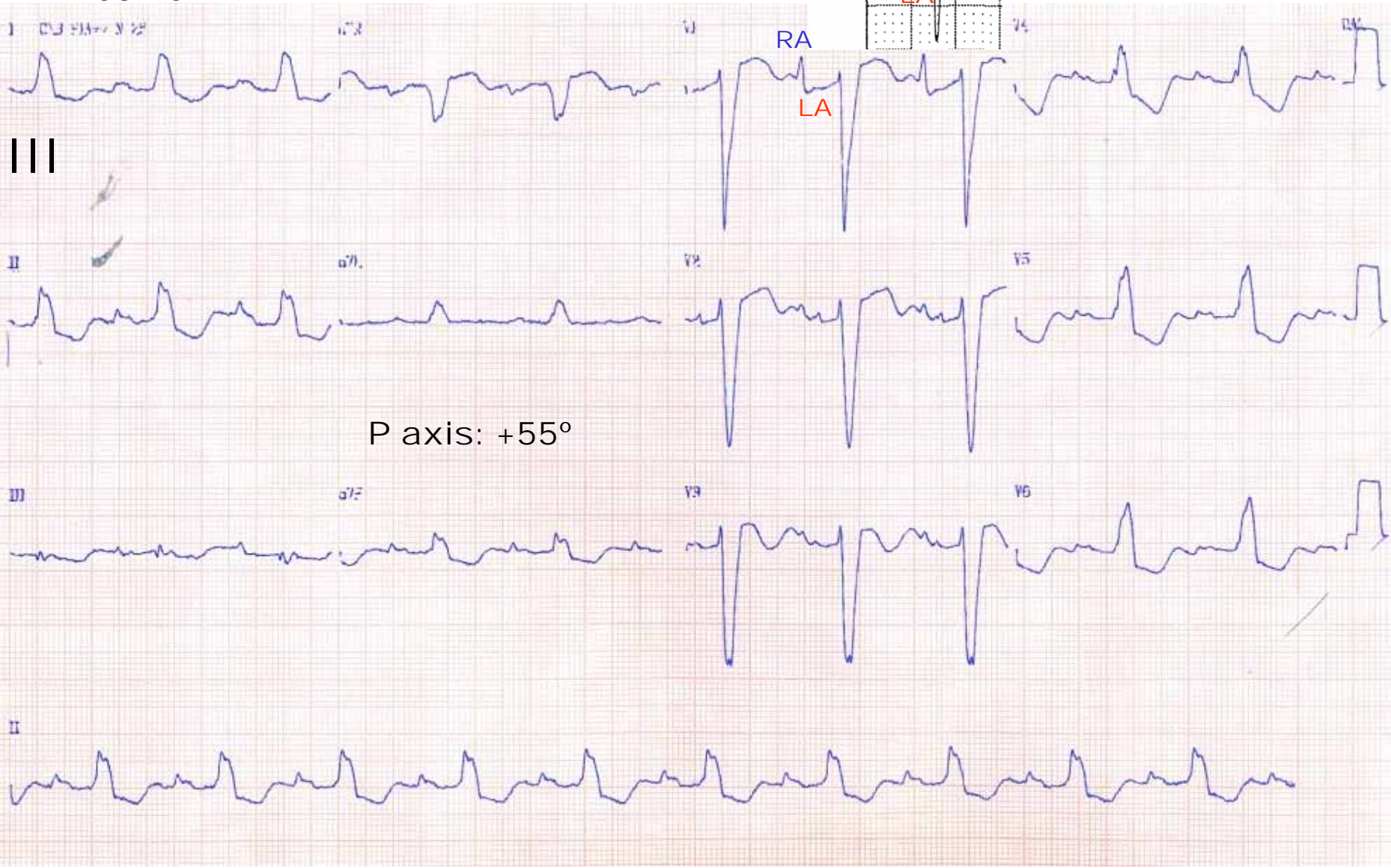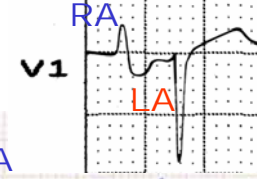
Biatrial enlargement + first degree AV block (PR interval 280ms) + LBBB

BIATRIAL ENLARGEMENT (BAE) ELETROCARDIOGRAPHIC CRITERIA

1. Initial component of P wave in V1 >1.5 mm and final slow and deep negative component > 1 mm in depth and 40 ms in duration

2. P waves of voltage >2.5 mm and duration ≥120 ms in II

3. P waves with initial component of voltage >1.5 mm in V_1 and V_2 associated to bimodal P and of increased duration with notches in II

4. P waves of duration ≥120 ms and bimodal with SAP deviated to the right

5. Atrial Fibrillation associated with initial q or Q wave in V_1 or V_1-V_2

6. QRS complexes of low voltage in V_1 in contrast to QRS of normal voltage or increased in V_2.

P LOOP IN BIATRIAL ENLARGEMENT
HORIZONTAL PLANE

NORMAL P LOOP

P LOOP IN BIATRIAL ENLARGEMENT

COUNTERCLOCKWISE ROTATION

INCREASE OF ANTERIOR AND POSTERIOR VOLTAGES OF P LOOP
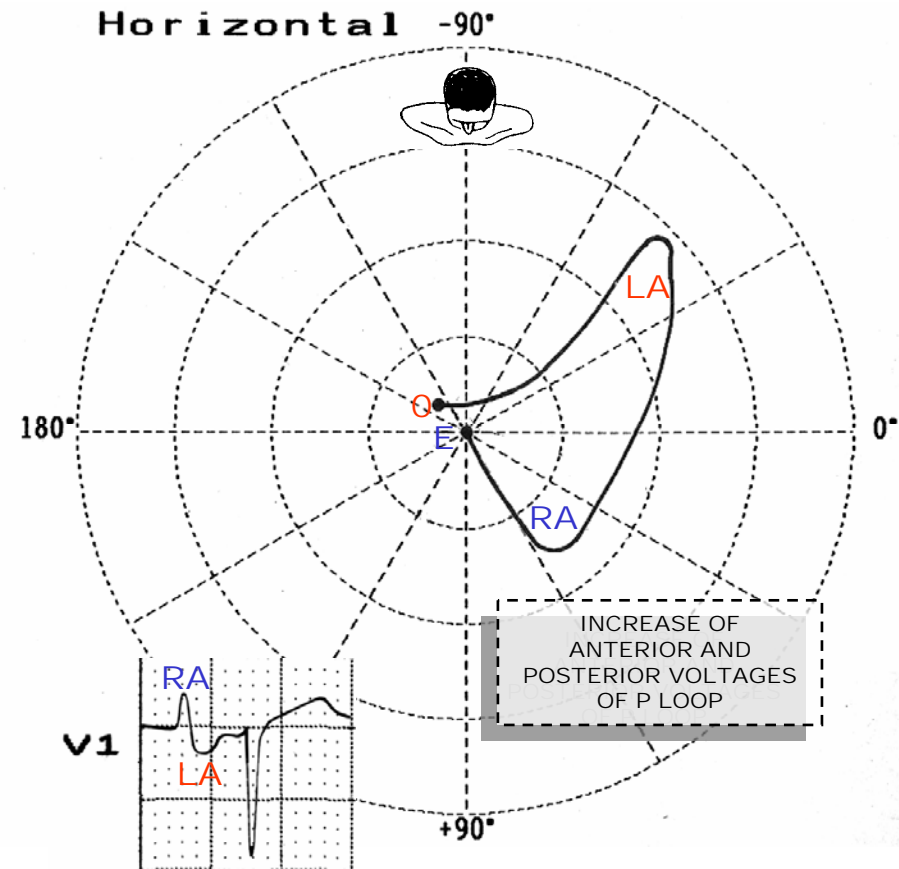
COLLEAGUES COMMETS

Case presented by Prof. Andrés and Dr. Raimundo: This poor woman received a single female sexual gene, that is to say an X from the mother but not the X from the father, which left her in the middle of her sexual evolution. The ECG shows atrial flutter with variable AV block, but it could also be variable RBBB, since in the second ECG it seems that there could be bilateral block, i.e. left block plus first degree block. Also, as the first degree block is persistent, it could be a left block plus His block. This left block is troncular, and P waves suggest a biatrial hypertrophy with predominance of the right atrium. Turner's syndrome presents only a toned down development of the female organs, but when shuffling the 44 fatherly genes, she received several mutations that affected several other organs, and in the heart, very rare conditions of the conduction and endocardial systems of the atria. The conditions of the kidneys, liver and heart should be around the same genetic locus. Warm regards,
And as I am an inveterate atheist, God willing see you on Thursday,
Samuel

Caso presentado por el Prof Andrés y Dr Raimundo: Esta pobre mujer que recibio un solo gen sexual femenino es decir una X de la madre, pero no la X del padre, y la dejo en el; medio de la evolución sexual El electro muestra flutter auricular con bloqueo A-V variable, pero tambien puede ser BRD variable, ya que el segundo electro parece que podria ser un bloqueo bilateral ,es decir BRI mas bloqueo de primer grado.Tambien como el bloqueo de primer grado es persistente podria ser un BRI mas un bloqueo hisiano, Este BRI es trocular, Las ondas P sugieren una hypertrofia biauricular con predominancia de la auricula derecha El sindrome de Turner presenta unicamente desarrollo atenuado de los organos femeninos, pero en el barajear los 44 genes paternos recibio varias mutaciones que afectaron varios otros organos, y en el corazon afectiones muy raras del sistema de conducción y endocardial de las auriculas Las afecciones de los riñones higado y corazon deben andar por el mismo locus genético Fraternal abrazo Y como soy ateo empedernido, dios mediante nos veremos el jueves   Samuel

Some explanations about Turner's syndrome. This is an enigma of the play of the sexual genes. As it happens that the cells instead of becoming deploid, as it usually happens in all vegetal and animal cells that reproduce sexually, a haploid phenomenon appears. As it is known in sexual reproduction, the ovule has 2 XX genes and from the father it receives another 2 XX, and thus it becomes a girl, and if it receives XY, it will be a boy as the grandchild of Prof. Edgardo. To produce a being, there should be only one from the mother and one from the father, so what happens with the other extra 2 XX? There is a mechanism that removes these extra 2 XX and turns them into Barr bubbles, that appear as 2 black dots within the nucleus. But in Turner, 3 X are erased, and the woman isleft as a monoploid, i.e. she is left with a single X in the ovule's cytoplasm. If there was an extra X, i.e. 2 XX and one Y, it will be a Klinefelter, with undeveloped and infertile male genitals.

Here I presented a very brief notion of the genetic sexual differentiation, and some of the disorders. I advise reading the fantastic book by BryanSykes, "Adam's Curse, a future without men", Prof. of genetics in Oxford.

I think that it is translated in all western languages.

Fraternal regards,

Samuel Sclarovsky Israel

Agunas disquisiciones sobre el sindrome de Turner. Este es un enigma de la jugada de los genes sexuales. Como ocurre que las celulas en vez de hacer biploides, como ocurre generalmente en todas las celulas vegetales y animales que se reproducen sexualmente, aparece un fenómeno de haploide. Como se sabe en la reproducción sexual el ovulo posee 2 genes XX y del padre recibe otras 2 XX y sera ninia, y se recibe XY sera un niño como el nieto del Profesor Edgardo. Para producir un ser deben existir unicamente uno de la madre y otro del padre, entonces que pasa con los otros 2 XX de sobra?. Existe un mecanismo que elimina estas 2 XX que sobran y las transforma enlos bubles (globito) de Barr, que aparecen como 2 manchas negras dentrodel nucleo. Pero en el Turner se borran 3 X,s y la mujer queda monoploide, es decirqueda una sola X en el citoplasma del óvulo Si quedan una X demasiada   decir   2 xx y una Y sera un Klinefelter, con genitales masculinos no desarrollados e infertiles

Aqui presento una concepción muy somera de la diferenciacion sexual genetica, y algunos de los transtornos.

   Recomiendo leer el fantástico libro de Bryan Sykes   Adam's Curse   "a future without men" Profesor de genética en Oxford.

   Me parece que esta traducido en todos los idiomas occidentales.

Un fraternal abrazo

Samuel Sclarovsky

Andres, I look forward to learning from the Master about this case and this entity. My knowledge of Turner Syndrome dates back to Medical School and I have never encountered a case in my clinical career. As such, I am really looking forward to the final discussion.

I am going to start with the ECG recorded on August 22, 2011. This shows sinus rhythm with a cycle length for 940 ms equivalent to a rate of 62 bpm. The P wave is broad (160 ms) consistent with an inter-atrial conduction delay best seen in Lead V2 where there appear to be two distinct P waves. There is also bi-atrial enlargement with the extremely tall initial P in V1 and the initial sharp upward deflection in II, III and aVF consistent with right atrial enlargement. The terminal portion of the broad dimpled P wave seen in leads V2 and V5-6 and the terminal negativity in V1 is consistent with left atrial enlargement. There is a first degree AV block with a PR interval of 280 ms and there is a LBBB pattern with a QRS duration of180 ms. The very deep S waves in the anterior precordial leads are also consistent with left ventricular hypertrophy in the setting of LBBB (perhaps the LBBB simply reflects the markedly thickened LV with increased time to conduct through the thickened muscle although I would favor both entities being present as the thickening is likely due to fibrosis and this should not be electrically active). About the only interval that is normal is the QT at 440 ms.

At this time, based on the above ECG, I would say bi-atrial and at least left ventricular hypertrophy, inter-atrial conduction delay, first degree AV block and left bundle branch block. This is all consistent with a diffuse infiltrative process throughout the entire heart (unlike, for example, Duchenne's Progressive Muscular Dystrophy where the fibrosis is usually limited to the posterior-inferior wall of the heart) including the atria and the ventricles. I suspect the RV is involved as well or perhaps the lungs for without this, one would not expect Right atrial enlargement/hypertrophy but I can make that diagnosis from the ECG alone (does the VCG help in this setting?). The bi-atrial hypertrophy is probably due to increased diastolic pressure associated with the stiffened ventricles while the inter-atrial conduction delay is probably associated with the infiltrative process in the atria.

The first ECG recorded on August 8, 2011 shows an irregularly irregular rhythm raising concerns about atrial fibrillation except for Lead VI which suggests atrial flutter with variable AV block. Dr. Barbosa kindly provided a continuous V1 rhythm strip from that initial hospital day and this shows what initially appears to be atrial flutter, commonly upright and pointed in lead V1 anyway but add the very prominent P wave shown on the 12 lead ECG from August 22, this is consistent. Flutter is usually absolutely regular, at least on the atrial channel, but the atrial tachyarrhythmia is not absolutely regular. When differences are minor, one can magnify these differences by setting the calipers to encompass a number of consecutive cycles (I arbitrarily chose 6) and then move the calipers to another location on the tracing. If the rate is absolutely regular, the compass points will align perfectly with comparable points on the measured wave (I chose the peak of the P wave as it was so discrete). They don't. As such, the atrial rate that looks to superficially be regular actually varies from about 250 bpm to 350 bpm. While it is taught that the atrial rate in flutter is absolutely regular, this is not the case and it can vary due to waxing and waning sympathetic and parasympathetic tone impacting conduction velocity but that occurs over a long period of time. I have not recognized (although I have not specifically looked for it) this degree of variation in such a short period of time with atrial flutter. Still, I am going to label the rhythm Atrial Flutter with variable block accounting for the irregular ventricular response due to various degrees of AV block or multilevel AV block.

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Andres: Estoy deseando aprender del Maestro sobre este caso y esta entidad. Mi conocimiento del Síndrome de Turner se remonta a la Facultad de Medicina y nunca encontré un caso en mi carrera clínica. Como tal, realmente estoy esperando la discusión final. Comenzaré con el ECG registrado el 22 de agosto de 2011. El mismo muestra ritmo sinusal con una longitud de ciclo de 940 ms equivalente a una frecuencia de 62 lpm. La onda P es ancha (160 ms) consistente con retardo de conducción interauricular, que se observa mejor en la derivación V2 dondeparece haber dos ondas P distintas. También hay sobrecarga biauricular con Pinicial extremadamente alta en V1 y deflexión aguda hacia arriba inicial enII, III y aVF consistente con sobrecarga de la AD. La porción terminal de laonda P ancha con muesca observada en las derivaciones V2 y V5-6 y lanegatividad terminal en V1 es consistente con sobrecarga de la AI. Hay un bloqueo AV de primer grado con intervalo PR de 280 ms y hay un patrón de BRIcon duración QRS de 180 ms. Las ondas S muy profundas en las derivacionesprecordiales anteriores también son consistentes con hipertrofia del VI en el contexto de BRI (talvez el BRI simplemente refleje el VI con marcadoengrosamiento con tiempo aumentado de conducción por el músculo engrosado aunque yo favorecería la idea de que ambas entidades están presentes, puesto que el engrosamiento probablemente se deba a fibrosis y no debería ser eléctricamente activo). Sobre el único intervalo que es normal, es el QT a 440 ms. En este momento, en base al ECG anterior, yo diría hipertrofia biauricular y como mínimo del VI, retardo de conducción interauricular, bloqueo AV de primer grado y bloqueo de rama izquierda. Todo esto es consistente con un proceso infiltrativo difuso a través de todo el corazón incluyendo las aurículas y los ventrículos.(a diferencia de,por ejemplo, la Distrofia Muscular Progresiva de Duchenne donde la fibrosisgeneralmente está limitada a la pared póstero-inferior del corazón). Sospecho que el VD está involucrado también, o talvez los pulmones, puesto que sin esto, uno no esperaría que hubiera sobrecarga/hipertrofia de la AD, pero puedo hacer el diagnóstico con el ECG solamente (¿el VCG ayuda en este contexto?).

La hipertrofia biauricular probablemente se deba a presión diastólica aumentada asociada con ventrículos rígidos, mientras que la conducción interauricular probablemente esté asociada al proceso infiltrativo en las aurículas. El primer ECG registrado el 8 de agosto de 2011, muestra un ritmo irregularmente irregular que causa preocupación sobre la fibrilación auricular, excepto por la derivación V1, que sugiere aleteo auricular con bloqueo AV variable. El Dr. Barbosa amablemente ofreció una tira de ritmo continuo de V1, de ese día inicial de internación y esto muestra lo queinicialmente parece ser aleteo auricular, comúnmente vertical y en punta en la derivación V1 de todos modos, pero si agregamos la onda P muy prominente mostrada en el ECG de 12 derivaciones del 22 de agosto, esto es consistente. El aleteo generalmente es absolutamente regular, al menos en el canal auricular, pero la taquiarritmia auricular no es absolutamente regular. Cuando las diferencias son menores, uno puede aumentar estas diferencias calibrando para incluir una cantidad de ciclos consecutivos (yo en forma arbitraria elijo 6) y luego cambio los calibres hasta otra ubicación en el trazado. Si la frecuencia es absolutamente regular, las puntas del compás se alinearán perfectamente con puntos comparables de la onda medida (yo elijoel pico de la onda P porque fue tan discreta). No lo hacen. De este modo la frecuencia auricular que superficialmente parece ser regular, en realidad varía desde aproximadamente 250 lpm a 350 lpm. Mientras se enseña que lafrecuencia auricular en el aleteo es absolutamente regular, éste no es el caso y puede variar por aumento y disminución del tono simpático y parasimpático que tiene un impacto sobre la velocidad de conducción, pero que ocurre en un período prolongado de tiempo. No reconocí (aunque no lo busqué específicamente) este grado de variación en un período tan corto de tiempo con aleteo auricular. Aun así voy a catalogar el ritmo como AleteoAuricular con bloqueo variable, siendo responsable de la respuestaventricular irregular por diversos grados de bloqueo AV o bloqueo AV de múltiples niveles.

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How is everything there? As to the tracing of this 28-year-old patient, the thrombus that she presents in both atria produces a morphology of ventricular tachycardia with wide QRS given the detail of the thrombi in both atria about the ectopic foci coming from there, about the P waves in D1, D2. At the level of the SA node and the AV node, the arrhythmia continues. What is the focus starting from there:

About the arrhythmogenic potential of amiodarone and the effect of warfarin, the T waves in D1, D2, V4, V5, V6 due to the thrombosis present in it, in the first tracing are remarkable.

The premature contractions present in V5 and V6, observed in the first tracing, are heading to ventricular tachycardia.

In the long DII of the following tracing, the three spikes within QRS observed in this tracing are remarkable.

About the tracing from August 22, I see the damage in both atria, about the QRS in this tracing in V1, V2, V3, V4, V5, V6, T wave inversion is remarkable there. The lesion at this level reflects severe ischemia. How is the EF of the RV and the LV after this, and the function of the mitral and tricuspid valves in this patient.

An infiltrative restrictive pathology proper of the mosaic form present in it, with connective tissue condition.

How is the aorta in its trajectory, from the origin to the chest.

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I remain at your disposal.

Como va todo por allá? en cuanto al trazo de esta paciente de 28 años el trombo que presenta en ambos atrios da la morfología de una taquicardia ventricular con QRS ancho dado al detalle de los trombos en ambas aurículas en cuanto a los focos ectópicos provenientes de allí en cuanto a las ondas P en D1,D2.

A nivel del nodo SA y del nodo AV continúa la arritmia. cual es el foco partiendo de allí.

En cuanto al potencial arritmogénico de la amiodarona y el efecto de la warfarina llama la atención las ondas T en D1,D2,V4,V5,V6 por causa de la trombosis presente en ella en el primer trazo. las estrasístoles presentes

V5 y V6 vistas en el primer trazo van rumbo a una taquicardia ventricular.

el DII largo del siguiente trazo llaman la atención las tres espigas dentro del QRS vista en este trazado.

En cuanto al trazado del 22 de agosto veo el daño de ambas auriculas, en cuanto al QRS de este trazado en V1,V2,V3,V4,V5,V6 llama la atención la inversión de la onda T allí. la lesión a este nivel refleja isquemia severa como quedo la fe del ventrículo derecho y el izquierdo posterior a esto y la función de la válvula mitral y tricuspide en esta paciente.

Una patología restrictiva infiltrativa propia del mosaisismo presente en el con afección del tejido conectivo.

Como sigue la aorta en su trayecto desde el origen hasta el tórax?

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Cualquier asesoria a la orden.

FINAL COMMENTARIES

Turner syndrome Bonnevie-Ullrich Syndrome / Gonadal Dysgenesis, 45,X / Gonadal Dysgenesis, XO / Status Bonnevie-Ullrich

A syndrome of defective gonadal development in phenotypic women with a karyotype of sex chromosome monosomy (45,X or 45,XO), associated with the loss of a sex chromosome X or Y. Patients generally are of short stature with undifferentiated (streak) gonads, sexual infantilism (HYPOGONADISM WITH elevated GONADOTROPINS), webbing of the neck, cubitus valgus, and decreased ESTRADIOL level in blood. Studies of Turner Syndrome and its variants have contributed significantly to the understanding of SEX DIFFERENTIATION. NOONAN SYNDROME bears similarity to this disorder; however, it also occurs in males, has normal karyotype, and is inherited as an autosomal dominant.(See differential diagnosis latter)

Described by Dr. Henry Turner (August 28, 1892 - August 4, 1970) in 1938(1), and manifested with short stature, webbed neck, cubitus valgus (arms turned out slightly at elbow), and sexual infantilism. He was an American endocrinologist, noted for his published description of Turner Syndrome in 1938 at the Association for the Study of Internal Secretions.

He served as chief of endocrinology and as associate dean of the University of Oklahoma College of Medicine. Turner was born in Harrisburg, Illinois.

He received his medical education at the University of Louisville School of Medicine, and graduated in 1921.

He died in Oklahoma City, Oklahoma in 1970.

1. Turner HH. "A Syndrome of infantilism, congenital webbed neck, and cubitus valgus." Endocrinology 1938;23:566-574.

Grumback used the term "Gonadal Dysgenesis" (abnormal development of the ovaries) to describe the syndrome. Many girls may have distinctive characteristics, while some girls show few.

The syndrome represents a wide spectrum of clinical presentation. The most common of which is the classic TS with 45XO (one X chromosome is missing completely). Less common, the mosaic TS with 45X/46XX,45X/46XY. Isochromosome happens when one chromosome is partially missing.

Short stature is almost a consistent finding in TS. Most children with TS show gradual decline in growth rate between 3 and 11 years of age, drifting considerably below the lower normal percentiles for age. Without treatment, the ultimate height range is between 4'7" to 4'10". Family height may play a role in determining the ultimate height in girls with TS.

Children with TS may have the following physical findings:

1) Congenital lymphedema (puffy hands and feet at birth),

1. .
2. **The most common feature of Turner syndrome is short stature, which becomes evident by about age 5.**
3. **Webbed neck About 30 percent of people with Turner syndrome have extra folds of skin on the neck (webbed neck),**

4. **Prone to keloid (excessive growth of scar tissue).**
5. **Low posterior hairline**
6. **Prominent ears**
7. **High arched palate**
8. **Micrognathia (small jaw)**
9. **Broad chest**
10. **Hypoplastic nipples**
11. **Cubitus valgus (arms turned out slightly at the elbow)**
12. **Multiple pigmented nevus (moles)**
13. **Abnormal fingernails (turned up at the end)**
14. **Intestinal telangiectasia (malformation of the intestinal blood vessels).**

15. Cardiovascular anomalies are common and the most clinically frequent coarctation of the aorta. Echocardiographic studies, however, show non stenotic bicuspid aorta might be the most common cardiovascular lesion in Turner syndrome. One third to one half of people with Turner syndrome are born with a heart defect.

MR Angiography (MRA) Showing aortic coartation in a patient with Turner syndrome

Risk for acute aortic dissection is increased by more than 100-fold in young and middle-aged women with Turner syndrome. Monitoring frequency and treatment modalities are decided on an individual basis until more information on outcomes becomes available(1). The incidence of aortic dissection is significantly increased in individuals with Turner syndrome at all ages, highest during young adult years and in pregnancy. Pediatric patients with dissection have known congenital cardiovascular defects, but adults often have aortic valve and arch abnormalities detected only by screening cardiac magnetic resonance. Thoracic aortic dilation in Turner syndrome must be evaluated in relation to body surface area.

Dilation is most prominent at the ascending aorta, similar to the pattern seen in nonsyndromic bicuspid aortic valve, is equally prevalent (20-30%) in children and adults, and does not seem to be rapidly progressive.

Cardiovascular anomalies and risk for aortic dissection in Turner syndrome are strongly linked to a history of fetal lymphedema, evidenced by the presence of neck webbing and shield chest.

Through oocyte donation, women with Turner syndrome may achieve motherhood. However, this population has a high prevalence of cardiac malformations and carry a risk for aortic dissection that is increased by pregnancy. Until recently, the necessity for a specialized cardiac evaluation before pregnancy was underestimated as was the need for follow-up through adulthood. Obstetric outcomes in women with a Turner syndrome karyotype were mostly favorable. Singletons of Turner syndrome women had shorter gestational age, but similar size at birth, adjusted for gestational age and sex. Birth defects did not differ between Turner syndrome and controls.(2)

Careful follow-up, including cardiac evaluation, should be recommended for women diagnosed with TS, before and after puberty. Moreover, assessment of cardiovascular parameters by a cardiologist familiar with TS should be routinely repeated before undertaking oocyte donation.(3)

1. Bondy CA. Aortic dissection in Turner syndrome. Curr Opin Cardiol. 2008 Nov;23(6):519-26.
2. Hagman A, Källén K, Barrenäs ML, et al. Obstetric Outcomes in Women with Turner Karyotype.J Clin Endocrinol Metab. 2011 Aug 24. [Epub ahead of print]
3. Chalas Boissonnas C, Davy C, Marszalek A, et al. Cardiovascular findings in women suffering from Turner syndrome requesting oocyte donation. Hum Reprod. 2011 Oct;26:2754-62.

Aortic rupture is a rare but potentially catastrophic complication following a balloon aortoplasty for recoarctation in Turner syndrome patients who experienced a life-threatening rupture in her aorta after a balloon aortoplasty for recoarctation. Prudent balloon aortoplasty for recoarctation in patients with Turner syndrome is important due to their inherent aortopathy and previous surgical repairs. Possible reasons for an aortic rupture are oversized ballooning and the choice of balloon diameter based only on an angiographic measurement. It is very important of keeping a commercially available stent graft available to treat this complication that has potentially fatal consequences(1).

A general aortopathy is present in Turner syndrome with enlargement of the ascending aorta, which is accelerated in the presence of a bicuspid aortic valve.(2).

Adult patients with Turner syndrome under under chronic hormonal replacement therapy are connoted by higher frequency of central obesity, insulin resistance, hypercholesterolemia, and hypertension. (3)

Turner syndrome patient have high risk of cardiovascular complications, atherosclerosis and thrombo-embolic events. Turner syndrome females have high levels of von Willebrand factor, factor VIII, fibrinogen and the C-Reactive Protein (15-40%) and an increased frequency of the Leiden mutation, with important associations to carotid intima thickness and blood pressure, suggesting that a subset of Turner syndrome may have an unfavourable haemostatic balance, which may contribute to the increased risk of premature ischemic heart disease and possibly increase the risk of deep venous and portal vein thrombosis. (4)

1. Wu IH, Wu MH, Chen SJ, et al. Successful deployment of an iliac limb graft to repair acute aortic rupture after balloon aortoplasty of recoarctation in a child with Turner syndrome. Heart Vessels. 2011 Jun 17. [Epub ahead of print]
2. Mortensen KH, Hjerrild BE, Stochholm K,et al. Dilation of the ascending aorta in Turner syndrome - a prospective cardiovascular magnetic resonance study. J Cardiovasc Magn Reson. 2011 Apr 28;13:24.
3. Gravholt CH, Mortensen KH, Andersen NH, et al. Coagulation and fibrinolytic disturbances are related to carotid intima thickness and arterial blood pressure in Turner syndrome. Clin Endocrinol (Oxf). 2011 Aug 17. doi: 10.1111/j.1365-2265.2011.04190.x. [Epub ahead of print]
4. Giordano R, Forno D, Lanfranco F, et al. Metabolic and cardiovascular outcomes in a group of adult patients with Turner's syndrome under hormonal replacement therapy. Eur J Endocrinol. 2011 May;164:819-826.

16. Kidney problems: Kidney anomalies occur in 1/3 to 1/2 of girls with TS, with monosomic (one chromosome is missing). The most common anomaly is a horseshoe kidney.

17. Endocrinophaties: The principal features of Turner syndrome are short stature and ovarian dysgenesis accompanied by estrogen deficit. Increased frequency of chronic lymphocytic thyroiditis and diabetes mellitus. An early loss of ovarian function (premature ovarian failure) is also very common. The ovaries develop normally at first, but egg cells (oocytes) usually die prematurely and most ovarian tissue degenerates before birth. Many affected girls do not undergo puberty unless they are treated with the hormone estrogen. A small percentage of females with Turner syndrome retain normal ovarian function through young adulthood.

18. Mental status: Specific deficit in spatial ability and frequently exhibit gross and fine motor dysfunction. Most girls and women with Turner syndrome have normal intelligence. Developmental delays, nonverbal learning disabilities, and behavioral problems are possible, although these characteristics vary among affected individuals. Studies show that many women with Turner syndrome have higher-than-average educational achievements.

19. Skeletal abnormalities The bone age is delayed. Osteoporosis may also be seen.

The genetic changes related to Turner syndrome

Turner syndrome is related to the X chromosome, which is one of the two sex chromosomes. People typically have two sex chromosomes in each cell: females have two X chromosomes, while males have one X chromosome and one Y chromosome. Turner syndrome results when one normal X chromosome is present in a female's cells and the other sex chromosome is missing or structurally altered. The missing genetic material affects development before and after birth, leading to the characteristic features of the condition.

This condition occurs in about 1 in 2,500 newborn girls worldwide, but it is much more common among pregnancies that do not survive to term (miscarriages and stillbirths). Turner Syndrome (TS) occurs in approximately 1 in 2500 live female births. Approximately 98% of pregnancies with TS abort spontaneously.   Approximately 10% of fetuses from pregnancies that have spontaneously aborted have TS.

About half of individuals with Turner syndrome have monosomy X, which means each cell in the individual's body has only one copy of the X chromosome instead of the usual two sex chromosomes. Turner syndrome can also occur if one of the sex chromosomes is partially missing or rearranged rather than completely absent. Some women with Turner syndrome have a chromosomal change in only some of their cells, which is known as mosaicism. Women with Turner syndrome caused by X chromosome mosaicism are said to have mosaic Turner syndrome.

Researchers have not determined which genes on the X chromosome are responsible for most of the features of Turner syndrome. They have, however, identified one gene called SHOX that is important for bone development and growth. Missing one copy of this gene likely causes short stature and skeletal abnormalities in women with Turner syndrome

Most cases of Turner syndrome are not inherited. When this condition results from monosomy X, the chromosomal abnormality occurs as a random event during the formation of reproductive cells (eggs and sperm). An error in cell division called nondisjunction can result in reproductive cells with an abnormal number of chromosomes. For example, an egg or sperm cell may lose a sex chromosome as a result of nondisjunction. If one of these atypical reproductive cells contributes to the genetic makeup of a child, the child will have a single X chromosome in each cell and will be missing the other sex chromosome.

Mosaic Turner syndrome is also not inherited. It occurs as a random event during cell division in early fetal development. As a result, some of an affected person's cells have the usual two sex chromosomes (either two X chromosomes or one X chromosome and one Y chromosome), and other cells have only one copy of the X chromosome. Other sex chromosome abnormalities are also possible in females with X chromosome mosaicism.

Noonan Syndrome

Definition: A multifaceted disorder characterized by short stature, webbed neck, ptosis, skeletal malformations, hypertelorism, hormonal imbalance, CRYPTORCHIDISM, multiple cardiac abnormalities (most commonly including PULMONARY VALVE STENOSIS), and some degree of MENTAL RETARDATION. The phenotype bears similarities to that of TURNER SYNDROME that occurs only in females and has its basis in a 45, X karyotype abnormality. However, Noonan syndrome occurs in both males and females with a normal sex chromosome constitution (46,XX and 46,XY). NS1 is due to mutations at chromosome location 12q24.1, in PTPN11, a gene encoding the non-receptor type 11 PROTEIN TYROSINE PHOSPHATASE. LEOPARD SYNDROME, a disorder that has clinical features overlapping those of Noonan Syndrome, is also due to mutations in PTPN11. In addition, there is a syndrome called neurofibromatosis-Noonan syndrome. Both the PTPN11 and NF1 gene products are involved in the SIGNAL TRANSDUCTION pathway of Ras (RAS PROTEINS).

	TURNER SYNDROME	**NOONAN SYNDROME**
MAYOR CARDIAC MANIFESTATIONS:	Coarctation of the aorta. Non stenotic bicuspid aorta	Pulmonic valve dysplasia with pulmonary valve stenosis. Cardiomyopathy usually hypertrprophic(1) Of all patients with Noonan **syndrome, 50-90% have one or more congenital heart defects. The most frequent occurring are pulmonary stenosis and** **hypertrophic** cardiomyopathy**.** **Septal defects: atrial —***(10%)* **or ventricular —***(less common)*
MAYOR NON CARDIAC ABNORMALITIES:	Short stature Weebed neck,	Short stature, Weebed neck, hypertelorism, down-slanting eyes, pectus excavatum, chryptorchydism
KARYOTYPE	One normal X chromosome is present in a female's cells and the other sex chromosome is missing or structurally altered.	With a normal sex chromosome constitution. Normal karyotypes
SEX	Only women.	Occurs in both males and females equally in either a sporadic or autosomal dominant fashion.
INCIDENCE	Is estimated to be 1 case per 1000 to 1 case per 2500 live births.	Approximately 1 in 1,000 and 1 in 2,500 children worldwide

1. Sánchez Andrés A, Moriano Gutiérrez A, Carrasco Moreno JI. Prenatal hypertrophic cardiomyopathy and neonatal noonan syndrome: an association to remember].Rev Esp Cardiol. 2011 Jun;64:537-8.

CARDIOMYOPATHIES

The first classifications of cardiomyopathies from 1980 and 1996 described them as heart muscle diseases, with dilated (DCM), hypertrophic (HCM), restrictive (RCM), arrhythmogenic right ventricular (ARVC), and nonclassifiable cardiomyopathies. Furthermore, the World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) classification from 1996 listed among the specific cardiomyopathies inflammatory cardiomyopathy as a new and distinct entity, which was defined histologically as myocarditis in association with cardiac dysfunction. Infectious and autoimmune forms of inflammatory cardiomyopathy were recognized. Viral cardiomyopathy was defined as viral persistence in a dilated heart without ongoing inflammation. If it was accompanied by myocardial inflammation, it was termed inflammatory viral cardiomyopathy (or viral myocarditis with cardiomegaly). This entity was further elucidated in a World Heart Federation consensus meeting in 1999 by quantitative immunohistological criteria (< 14 infiltrating cells/mm(2)) and the etiology by molecular biological methods, e.g., polymerase chain reaction, as viral, bacterial, or autoimmune (= nonmicrobial). The development of molecular genetics, with the discovery of a genetic background in several forms of cardiomyopathies previously alluded to as "of unknown origin", was the origin of a debate on a new classification based on genomics. A genomic/postgenomic classification was postulated taking the underlying gene mutations and the cellular level of expression of encoded proteins into account, thus distinguishing cytoskeleton (cytoskeletalopathies, e.g., DCM or ARVC), sarcomeric (sarcomyopathies as in HCM and RCM) and ion channel (channelopathies, e.g., long or short QT syndrome and Brugada's syndrome) cardiomyopathies.

Such a classification of cardiomyopathies was proposed in 2006 by the American Heart Association (AHA), which took the rapid evolution of molecular genetics in cardiology into account. It also introduced several recently described diseases, and is unique in that it incorporated ion channelopathies even without hemodynamic dysfunction as a "primary" cardiomyopathy.
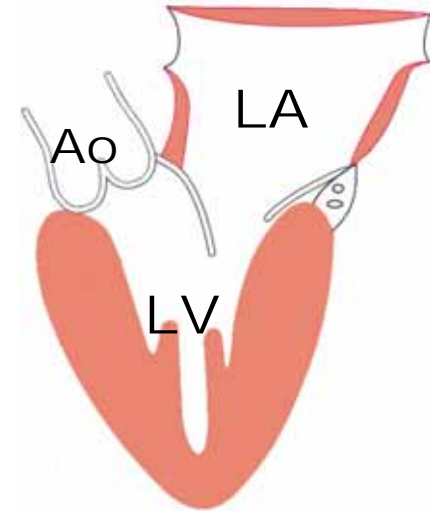
CLASSIFICATION OF CARDIOMYOPATHIES
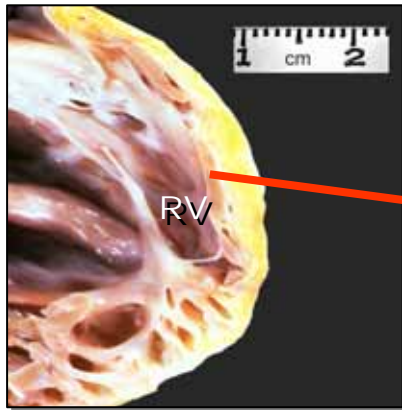
I) DILATED OR CONGESTIVE

Ao · LA

LV

II) HYPERTROPHIC

Ao · LA

LV

III) RESTRICTIVE

Ao · LA

LV
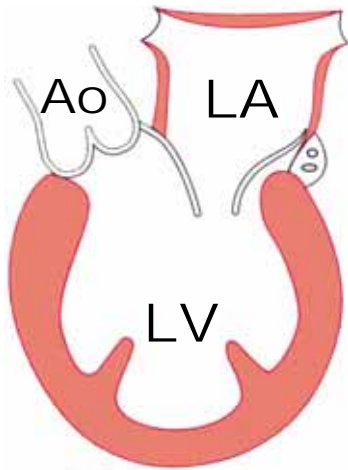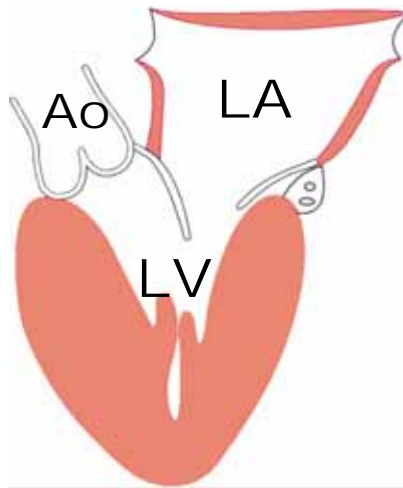
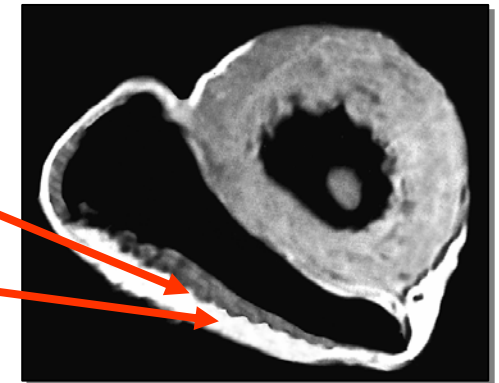## IV) ARRHYTHMOGENIC OR ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA

RV

THE CHARACTERISTIC FOUND IS FIBRO-FATTY REPLACEMENT OF RIGHT VENTRICULAR MYOCARDIUM

Richardson P, et al. Circulation. 1996;93:841-842.

The four main types of cardiomyopathy.

The ESC (European Society of Cardiology) Working Group on Myocardial and Pericardial Diseases has deliberately taken a different approach based on a clinically oriented classification in which heart muscle disorders were grouped according to morphology and function. This obviously remains the clinically most useful approach for the diagnosis and management of patients and families with heart muscle disease. In the ESC position statement published in 2008, cardiomyopathies were defined as *myocardial disorders in which the heart muscle is structurally and functionally abnormal, and in which coronary artery disease, hypertension, valvular and congenital heart disease are absent or do not sufficiently explain the observed myocardial abnormality*.

The aim was to help clinicians look beyond generic diagnostic labels in order to reach more specific diagnoses. In parallel, a scientific statement on the role of endomyocardial biopsy in the management of cardiovascular disease was published at the end of 2007 making useful recommendations for clinical practice and providing an understanding for the use of endomyocardial biopsy in an individual patient.

Taking the classification of cardiomyopathies and the statement on the role of endomyocardial biopsies in different clinical scenarios together, the clinician is now able to identify genetic, autoimmune and viral causative factors by using a thorough and logical approach to reach a diagnosis in patients with familial and nonfamilial forms of the underlying structural heart muscle diseases.

Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) also known as Intermediate Cardiomyopathy is a specific group of heart muscle disorders characterized by inadequate ventricular relaxation during diastole Although opinion varies as to the prevalence and certainty of the cardiac changes present. While debate continues as to what pathology exactly must be present to make this diagnosis, some consensus has it that a decrease in size of the left ventricle caused by heavy fibrosis of connective bands within the heart will be present. Combined with other abnormalities additionally possible, the condition results in poor pumping action by the heart. The cause of this condition is also unknown. This leads to diastolic dysfunction with relative preservation of systolic function. Although short axis systolic function is usually preserved in RCM, the long axis systolic function may be severely impaired. Heart failure with normal ejection fraction (HFNEF), previously referred to as diastolic heart failure, has increased in prevalence as a cause of heart failure, now accounting for up to 50% of all cases. Contrary to initial evidence, the prognostic outlook in HFNEF may be similar to that of heart failure with reduced ejection fraction. According to current consensus statements, the diagnosis of HFNEF requires the demonstration of relatively preserved systolic left ventricular function and evidence of diastolic dysfunction. Some people with earlier forms of restrictive cardiomyopathy have no symptoms or only minor symptoms, and live a normal life. Other people develop symptoms, which progress and worsen as heart function worsens.

Symptoms occur at any age and may include: Shortness of breath (at first with exercise; but over time it occurs at rest), fatigue (feeling overly tired), inability to exercise, swelling of the legs and feet, weight gain, nausea, bloating, and poor appetite (related to fluid retention), palpitations (fluttering in the chest due to abnormal heart rhythms).Less common symptoms: Fainting (caused by irregular heart rhythms, abnormal responses of the blood vessels during exercise, or no cause may be found), chest pain or pressure (occurs usually with exercise or physical activity, but can also occur with rest or after meals)

Diagnosis is based on history, physical examination,(jugular veous distension, an S3 , S4 or both.) an inspiratory increase in venous pressure ECG testing, X-rays, echocardiograms, Cardiac magnetic resonance (CMR) Cardiac catheterization, and endomiocardial byopsy (EMB). Although EMB plays a crucial role in the final diagnosis in patients with heart failure of unknown etiology, the invasive nature of this technique limits its clinical application

When diagnosing a restrictive hypertrophied cardiomyopathy, most echocardiographist consider cardiac amyloidosis as a possible cause, especially after the appearance of 'granular' sparkling echoes on a transthoracic echocardiography like this case. However, other infiltrative diseases (i.e. metabolic myopathies, Gaucher, Hunter's, and Hurler's diseases) or storage cardiomyopathies (haemochromatosis, Fabry's disease, glycogen storage, and Niemann-Pick disease) should be considered.

RCM is probably the least common of all cardiomyopathies, with a nonspecific clinical presentation and a frequently unknown cause. The concept of RCM has changed tremendously over time. Today it includes a large panel of disorders characterized by a non-hypertrophied, non-dilated cardiac phenotype and a restrictive ventricular filling pattern.Several unsuccessful attempts to define and classify cardiomyopathies have been made, but they all proved problematic due to the contradiction in terms and the overlap between classical patterns. Advances in disease pathology, genomics and molecular biology are emerging as the framework of a new revolutionary classification system, focused on the dynamic interaction between genotype and phenotype..

Most diagnostic procedures are unable to detect the relevant pathophysiological changes that generally occur at the cellular and molecular level of myocardial tissue or individual cells. Therefore, often only additional biopsy-based tissue analyses can provide the necessary basis for causal treatment options.Confirmation of diagnosis and information regarding etiology, extent of myocardial damage, and response to treatment requires imaging. Importantly, differentiation from constrictive pericarditis is needed, as only the latter is managed surgically.

Echocardiography is the initial cardiac imaging technique but cannot reliably suggest a tissue diagnosis; although recent advances, especially tissue Doppler imaging and spectral tracking, have improved its ability to differentiate RCM from constrictive pericarditis.

CMR is a versatile technique providing anatomical, morphological and functional information. In recent years, it has been shown to provide important information regarding disease mechanisms, and also been found useful to guide treatment, assess its outcome and predict patient prognosis. its overall role in patient management, and how it compares with other imaging techniques. Cardiac catheterization is the reference standard, but is invasive, two-dimensional, and does not aid myocardial characterization. Enlargement of the atria in concert with normal dimensions of the ventricles and almost normal systolic contractility as well as the dip-plateau phenomenon are characteristic findings in RCM. Specific treatment modalities for distinct cardiomyopathies, demand detailed diagnostic procedures in addition to the routine diagnostic workup. Quality analyses for causal treatment strategies of different cardiomyopathies are missing.

CLASSIFICATION OF TYPES OF RESTRICTIVE CARDIOMYOPATHY ACCORDING TO CAUSE

A) Infiltrative:

1. Cardiac amyloidosis
2. Sarcoidosis
3. Gaucher disease
4. Hurler disease
5. Fatty infiltration

B) Myocardial non-infiltrative

1. Scleroderma
2. Pseudoxantoma elasticum
3. Familial cardiomyopathy
4. Idiopathyc cardomyopathy

C) Storage Disease

Hemocromatosis
Fabry disease
Glycogen storage disease

D) Endomyocardial

1. Endomyocardial fibrosis (EMF)
2. Hypereosinophilic syndrome
3. Carcinoid Heart disease
4. Metastatic cancers
5. Radiation
6. Toxic effects of anthracile
7. Drugs causing fibrous endocarditis: serotonin, methysergide, ergotamine, mercurial agents, busulfan

A) Infiltrative:

1) **Cardiac amyloidosis** is a myocardial disease characterized by extracellular amyloid infiltration throughout the heart. Cardiac amyloidosis has a wide spectrum of clinical manifestations but the most frequent presentation is heart failure. Differential diagnoses from other restrictive cardiomyopathies is important. A combination of clinical, ECG and imaging methods is commonly used to diagnose this disease. Definite diagnosis is based on endomyocardial biopsy and treatment of cardiac amyloidosis is a challenge. Heart transplantation, although controversial, has demonstrated survival benefit.

2) **Sarcoidosis**: it is a multisystem, granulomatous disease. of unknown atiology and cardiac involvement can occur. Echocardiographic abnormalities, such as left ventricular dysfunction, segmental wall thinning, ventricular aneurysm, or valvular abnormalities are often subtle until the later stages of the disease. However, sarcoid has a predilection to cause ventricular arrhythmias or conduction system abnormalities in the early stages and hence may develop palpitations, syncope, or SD before structural abnormalities are detected. If patients with early cardiac sarcoid are identified, they respond well to corticosteroid therapy, and defibrillator implantation may reduce the risk of SD from malignant arrhythmias. Cardiac sarcoidosis with RCMIt is a progressive disorder that, if left untreated, can lead to early mortality.

3) **Gaucher disease:** is a disorder of glycosphingolipid metabolism caused by deficiency of lysosomal acid β-glucosidase (GC) activity, due to conformationally or functionally defective variants, resulting in progressive deposition of glycosylceramide in macrophages.

4) **Hurler disease Mucopolysaccharidosis I (MPS I)** is a lysosomal storage disease due to an α-L-iduronidase deficiency, which leads to an accumulation of glycosaminoglycans in the lysosomes of most cells, resulting in tissue and organ dysfunction. MPS I is inherited in an autosomal-recessive manner. This disorder has a chronic, progressive course and is characterized by mental retardation, dysmorphy, organomegaly, multisystem involvement, and multiple dysostosis. Early disease recognition is important for a prompt start of specific treatment, which improves many aspects of MPS I, and for the patient's overall management.

5) Fatty infiltration of the heart ("adipositas cordis"). Fatty infiltration of the heart is usually an incidental finding at post-mortem, but may have clinical significance at times of physiologic stress. Whether fatty infiltration of the right ventricle has to be considered "per se" a sufficient morphologic hallmark of arrhythmogenic right ventricular cardiomyopathy (ARVC) is still a source of controversy; ARVC should be kept distinct from both fatty infiltration of the right ventricle and adipositas cordis. In fact, it is well known that a certain amount of intramyocardial fat is present in the right ventricular antero-lateral and apical regions even in the normal heart and that the epicardial fat increases with increasing body weight. However, both the fibro-fatty and fatty variants of ARVC show, besides fatty replacement of the right ventricular myocardium, degenerative changes of the myocytes and interstitial fibrosis, with or without extensive replacement-type fibrosis. The need to adopt strict diagnostic criteria is warranted not only in the clinical setting but also in the forensic and general pathology arena.

6) Niemann-Pick disease refers to a group of fatal inherited metabolic disorders that are included in the larger family of lysosomal storage diseases (LSDs). Mutations in the SMPD1 gene cause Niemann–Pick disease types A and B, and mutations in NPC1 and NPC2 cause Niemann-Pick disease, type C (NPC). Type D was originally separated from Type C to delineate a group of patients with otherwise identical disorders who shared a common Nova Scotian ancestry. Patients in this group are now known to share a specific mutation in the NPC 1 gene, and NPC is now used to embrace both groups. The terms "Niemann-Pick type I" and "Niemann-Pick type II" were proposed to separate the high and low sphingomyelin forms of the disease in the early 1980s, before the molecular defects were described.

In 1961, the following classification was introduced:type A: classic infantile, type B: visceral, type C: subacute/juvenile and type D: Nova Scotian

Now that the genetics are better understood, the condition can be classified as follows:Niemann-Pick disease, SMPD1-associated, which includes types A and B Niemann-Pick disease, type C, which includes types C1 and C2. (Type D is caused by the same gene as type C1.)

B) Myocardial non-infiltrative

1) Diabetic cardiomyopathy: Although cardiovascular disease is the leading cause of diabetes-related death, its etiology is still not understood. The immediate change that occurs in the diabetic heart is altered energy metabolism where in the presence of impaired glucose uptake, glycolysis, and pyruvate oxidation, the heart switches to exclusively using fatty acids for energy supply. It does this by rapidly amplifying its lipoprotein lipase (LPL-a key enzyme, which hydrolyzes circulating lipoprotein-triglyceride to release fatty acids) activity at the coronary lumen. An abnormally high capillary LPL could provide excess fats to the heart, leading to a number of metabolic, morphological, and mechanical changes, and eventually to cardiac disease. Unlike the initial response, chronic severe diabetes "turns off" LPL, this is also detrimental to cardiac function.

2) Scleroderma is a chronic systemic autoimmune disease (primarily of the skin) characterized by fibrosis (or hardening), vascular alterations, and autoantibodies. There are two major forms:

Limited systemic sclerosis/scleroderma involves cutaneous manifestations that mainly affect the hands, arms and face. Previously called CREST syndrome in reference to the following complications: Calcinosis, Raynaud's phenomenon, Esophageal dysfunction, Sclerodactyly, and Telangiectasias. Additionally, pulmonary arterial hypertension may occur in up to one third of patients and is the most serious complication for this form of scleroderma.

Diffuse systemic sclerosis/scleroderma is rapidly progressing and affects a large area of the skin and one or more internal organs, frequently the kidneys, esophagus, heart and lungs. This form of scleroderma can be quite disabling. There are no treatments for scleroderma itself, but individual organ system complications are treated.

3) Pseudoxantoma elasticum
4) Familial cardiomyopathy
5) Idiopathyc cardomyopathy

C) Storage Disease

Hemocromatosis is the abnormal accumulation of iron in parenchymal organs, leading to organ toxicity. This is the most common inherited liver disease in white persons and the most common autosomal recessive genetic disorder.

Two mutations in the *HFE* gene have been described. The first, C282Y, comprises the substitution of tyrosine for cysteine at amino acid position 282. In the second, H63D, aspartic acid is substituted for histidine in position 63. C282Y homozygosity or compound heterozygosity C282Y/H63D is found in most patients with hereditary hemochromatosis. The discovery of the C282Y mutation in the *HFE* gene has altered the diagnostic approach to hereditary hemochromatosis. Cases of homozygotic C282Y without hepatic iron overload may occur, but the clinical outcome of some of these cases requires further study and adds to the controversy on whether systematic population screening should be made available.

Hereditary hemochromatosis, a very common genetic defect in the Caucasian population, is characterized by progressive tissue iron overload which leads to irreversible organ damage if it is not treated in a timely manner. Recent developments in the field of molecular medicine have radically improved the understanding of the physiopathology and diagnosis of this disease. However, transferrin saturation and serum ferritin are still the most reliable tests for identifying subjects with hereditary hemochromatosis. Therapeutic phlebotomy is the mainstay of the treatment of this disease and the life expectancy of these patients is similar to that of the normal population if phlebotomy is started before the onset of irreversible organ damage.

Fabry disease
Glycogen storage disease

D) Endomyocardial

Endomyocardial fibrosis (EMF) is a tropical restrictive cardiomyopathy of unknown etiology with high prevalence in Sub-Saharan Africa, Brazil for which it is unclear whether the primary target of injury is the endocardial endothelium, the subendocardial fibroblast, the coronary microcirculation or the myocyte. The presence of antibodies against myocardial proteins was demonstrated in a subset of EMF patients. These immune markers seem to be related with activity and might provide an adjunct tool for diagnosis and classification of EMF, therefore improving its management by identifying patients who may benefit from immunosuppressive therapy. Further research is needed to clarify the role of autoimmunity in the pathogenesis of EMF.

Hypereosinophilic syndrome

Carcinoid Heart disease

Metastatic cancers

Radiation

Toxic effects of anthracile

Drugs causing fibrous endocarditis: serotonin, methysergide, ergotamine, mercurial agents, busulfan

We are waiting the EMB