Unexplained cardiac hypertrophy with familial background

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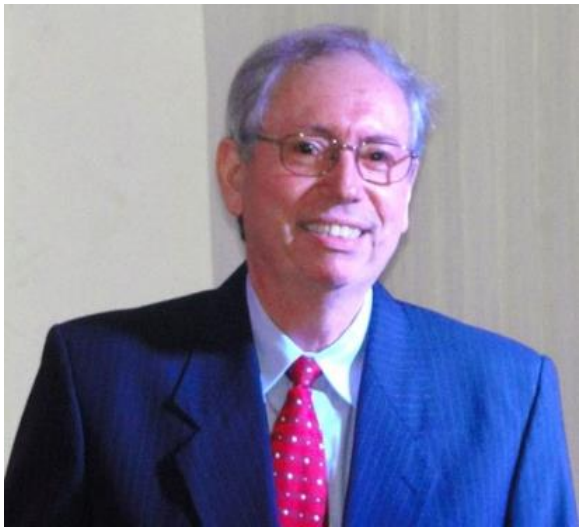


Raimundo **Barbosa-Barros, MD**
Chief of the Coronary Center of the Hospital de Messejana Dr. Carlos Alberto Studart Gomes. Fortaleza – CE- Brazil

English: Case report

MLSA, female, white, 46-year-old patient, born in Quixadá, from Fortaleza, Ceará, Brazil. Seamstress, Jehovah's witness, married. She was admitted into the Messejana Hospital, on December 2, 2011.

Main complaint: precordial discomfort, palpitations and dizziness.

History of the current disease: she tells that 4 years previously she presented episodes of palpitations, chest discomfort, dyspnea, sweating and general discomfort. Some episodes occurred momentarily after physical strain and others at rest, making her look for medical assistance at times. She denies suffering edema of lower limbs. The day before the admission she presented the same symptoms while she was sleeping, however more intense. She sought medical assistance in a secondary hospital, where an ECG was performed, and she was referred to the Messejana Hospital.

Previous pathological history: she mentions hypertension and type 2 diabetes for 2 years. Previous admission 6 years before for a hysterectomy. She mentions that 4 years before she discovered, because of a physician, that 2 brothers were carriers of genetic dialytic kidney disease (both had already died), and she was advised along with her remaining siblings to undergo the genetic test.

From the six siblings, five (including her) displayed the genetic mutation in the test.

Family history: her mother died by a stroke and two brothers due to neuropathy (both undergoing dialysis).

Habits: she denies consuming alcohol, illicit drugs or smoking.

Measurements in use: metformin 1 g/day; ASA 100 mg/day; enalapril 5 mg/day.

Physical examination: good general state. Height: 1.59 m; weight: 69 Kg, brevilineal, BP 135/85 mmHg, absence of jugular vein ingurgitation, with no shocks, ictus visible and palpable in the fifth left intercostal space at 2 cm outside the midclavicular line, with increased length (>2 cm), absence of fremitus, split regular heart rhythm, HR 80 bpm, fourth presystolic sound and mesosystolic murmur degree II in mitral focus of regurgitation radiated to the armpit. The rest of the physical examination showed nothing worth mentioning.

Cardiac MR (March 27, 2013): symmetrical myocardial hypertrophy of the LV, mild to moderate subaortic stenosis, preserved biventricular systolic function, increase in ventricular mass. LA=42 mm, LV of increased dimensions (LVDD=58 mm and LVSD=4 mm), diffuse fibrosis to late enhancement in lateral and inferior walls and right ventricular hypertrophy. Normal vessels of the base.

Transthoracic echo (March 2017): significant concentric hypertrophy of the LV (mass = 318 g/m2), end diastolic septum wall thickness of 37 mm, posterior wall diastolic thickness 18 mm, left atrium with significant dilatation (54 mm and volume of 56 ml/m2), outflow tracts of both ventricles unobstructed and stage II LV diastolic dysfunction (pseudo normal pattern). The Doppler revealed mild regurgitation flow of mitral valve insufficiency, normal left ventricular ejection fraction (66%), decreased volume/mass (0.18 ml/g).

Portuguese: Relato de caso

MLSA, feminino, branca, 46 anos, natural de Quixadá, procedente de Fortaleza, Ceará, Brasil, costureira, testemunha de Jeová, casada. Admitida no Hospital de Messejana no dia 02/12/11. **Queixa principal:** Desconforto precordial, palpitações e tonturas.

HDA: Relata que há 4 anos apresenta episódios de palpitações, desconforto torácico, dispneia, sudorese e mal estar. Alguns episódios ocorreram por momentos após o esforço físico e outros no repouso, fazendo-a procurar algumas vezes assistência médica. Nega edema de MMII. Há um dia da admissão apresentou o mesmo quadro durante o sono, porém de mais forte intensidade. Procurou atendimento médico em um hospital secundário, onde realizou um ECG e foi encaminhada ao Hospital de Messejana

História patológica pregressa: Refere ser hipertensa e diabética tipo 2 há 2 anos. Internamento prévio há 6 anos para histerectomia. Relata que há 4 anos descobriu, por intermédio de uma médica, que 2 irmãos, eram portadores de doença renal dialítica (ambos já falecidos), genética e a aconselhou que todos os seus irmãos deveriam realizar teste genético. Dos seis irmãos, cinco deles e inclusive ela, o exame mostrou mutação genética.

História familiar: Mãe faleceu por acidente vascular cerebral e dois irmãos por neuropatia (ambos faziam terapia dialítica).

Hábitos: Nega etilismo e tabagismo, bem como o uso de drogas ilícitas.

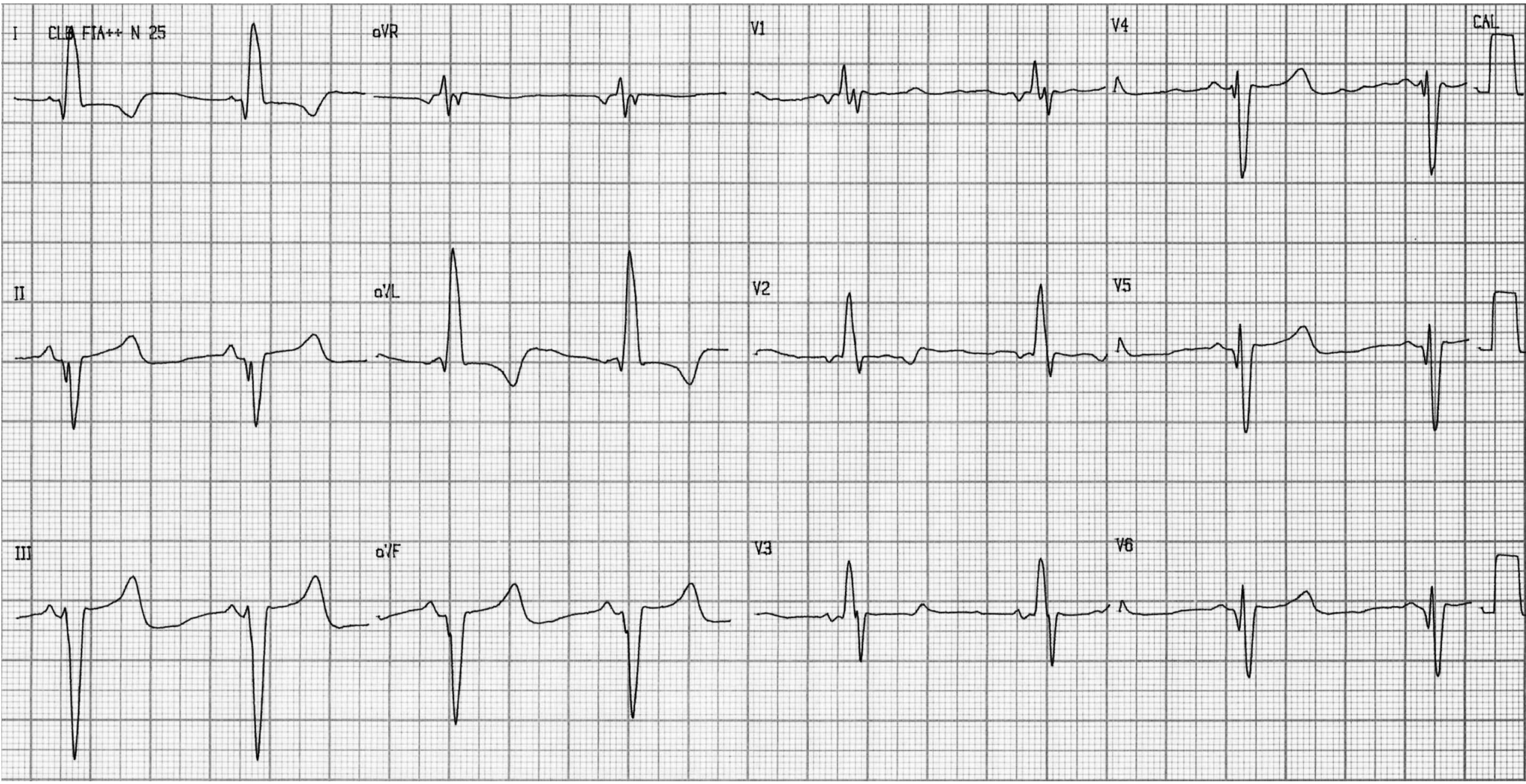
Medicações em uso: Metformina1g/dia; AAS 100mg/dia; enalapril 5mg/dia.

E**xame físico:** Bom estado geral, altura 1,59m, peso: 69Kg; brevilínea, PA 135/85 mmHg, ausência de ingurgitamento jugular, sem abalamentos, ictus no quinto espaço intercostal esquerdo a 2 cm por fora da linha hemiclavicular, de extensão aumentada (> 2cm), ausência de frémitos, ritmo cardíaco regular em dos tempos, FC 80bpm, quarta bulha pré-sistólica, e sopro meso-telesistólico grau II em foco mitral de regurgitação irradiado a axila. Resto do exame físico nada digno de nota.

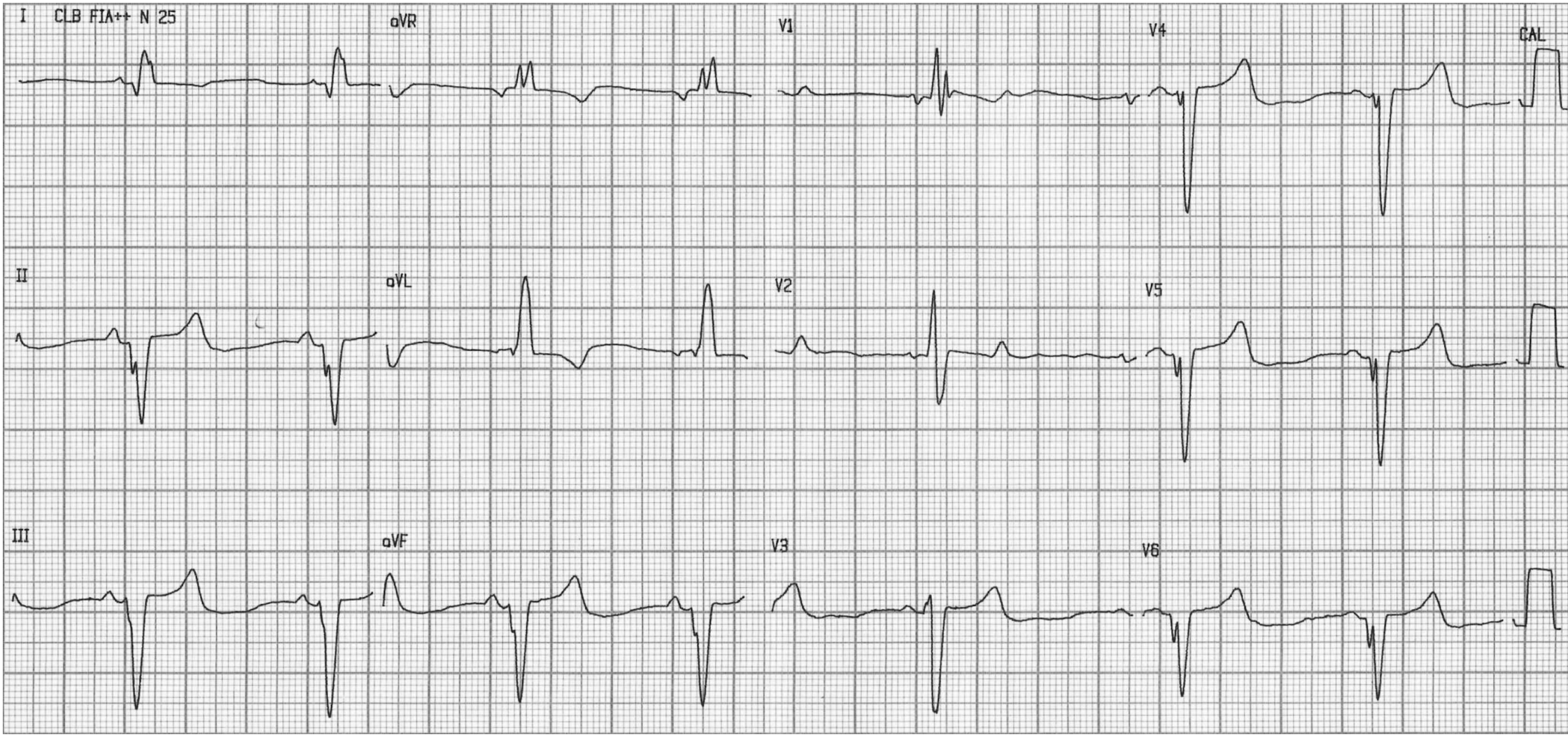
RM do coração (27/03/2013): hipertrofia miocárdica simétrica do ventrículo esquerdo, estenose subaórtica leve a moderada, função sistólica bi ventricular preservada, aumento da massa ventricular. AE 42mm, VE de dimensões aumentadas (DDVE 58mm e DS VE 4mm), fibrose difusa ao realce tardio em parede lateral e inferior e hipertrofia do ventrículo direito. Vasos da base normais.

Ecocardiograma transtorácico (**março de 2017**): hipertrofia concêntrica importante do ventrículo esquerdo (massa= 318g/m^2) espessura diastólica final do septo de 37mm, espessura diastólica da parede posterior 18mm, átrio esquerdo com importante dilatação (54mm e volume de 56ml/m^2), vias de saídas de ambos os ventrículos sem obstruções e disfunção diastólica do ventrículo esquerdo estagio II (padrão pseud. normal). O Doppler revelou fluxo regurgitante leve de insuficiência mitral, fração de ejeção do ventrículo esquerdo normal (66%), relação volume/massa diminuída (0,18ml/g).

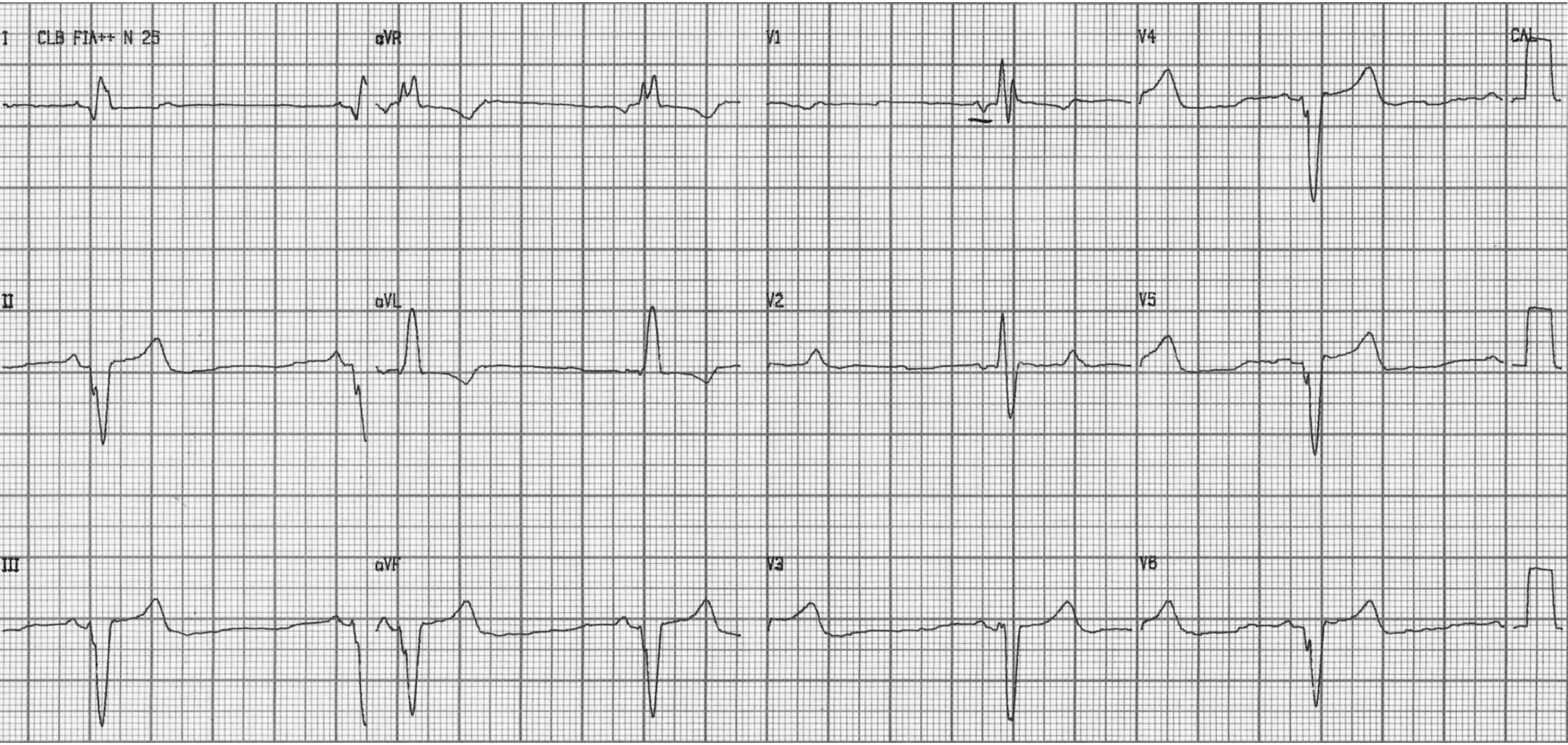
ECG1 - 2014



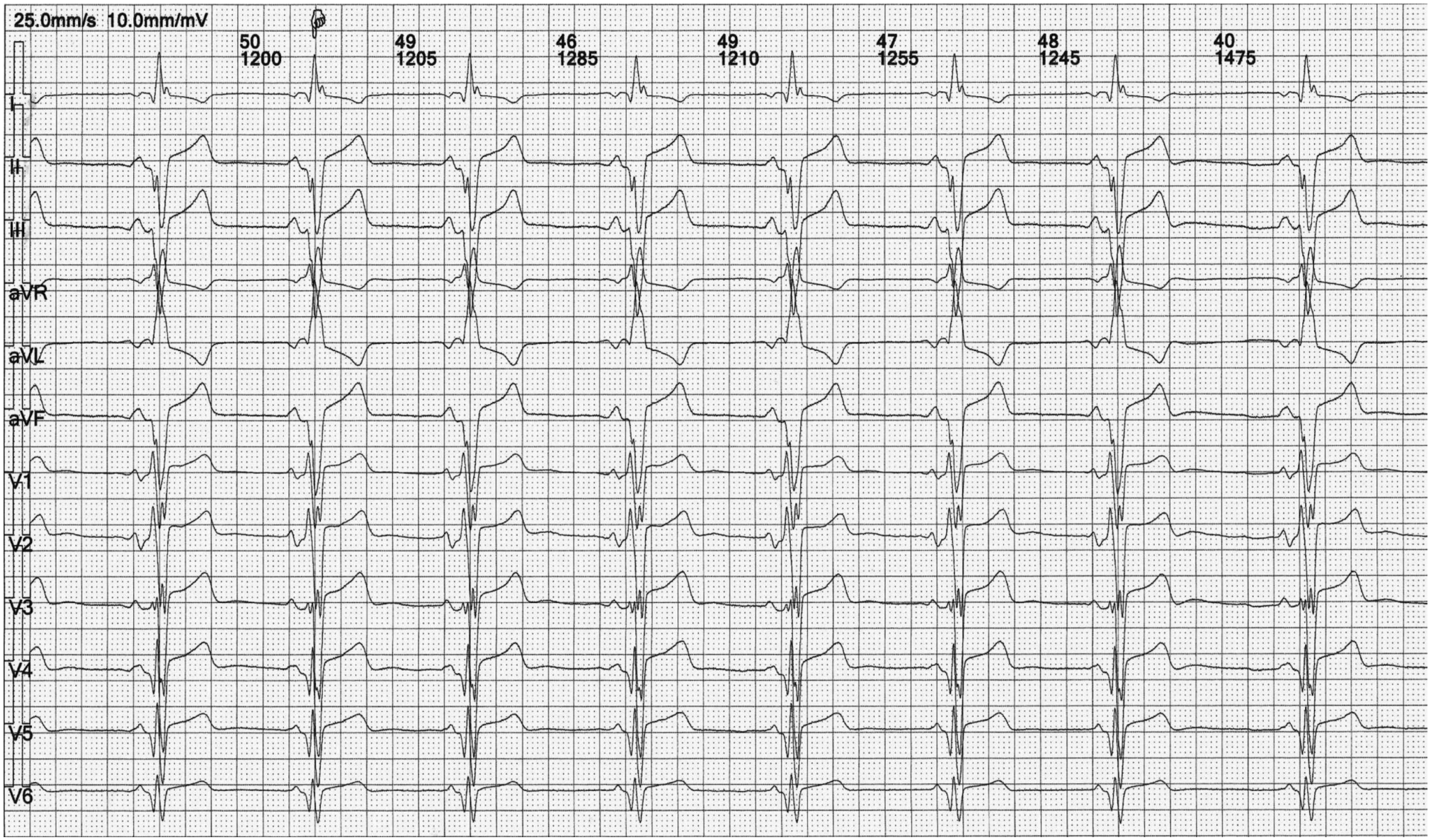
ECG2 - 2015



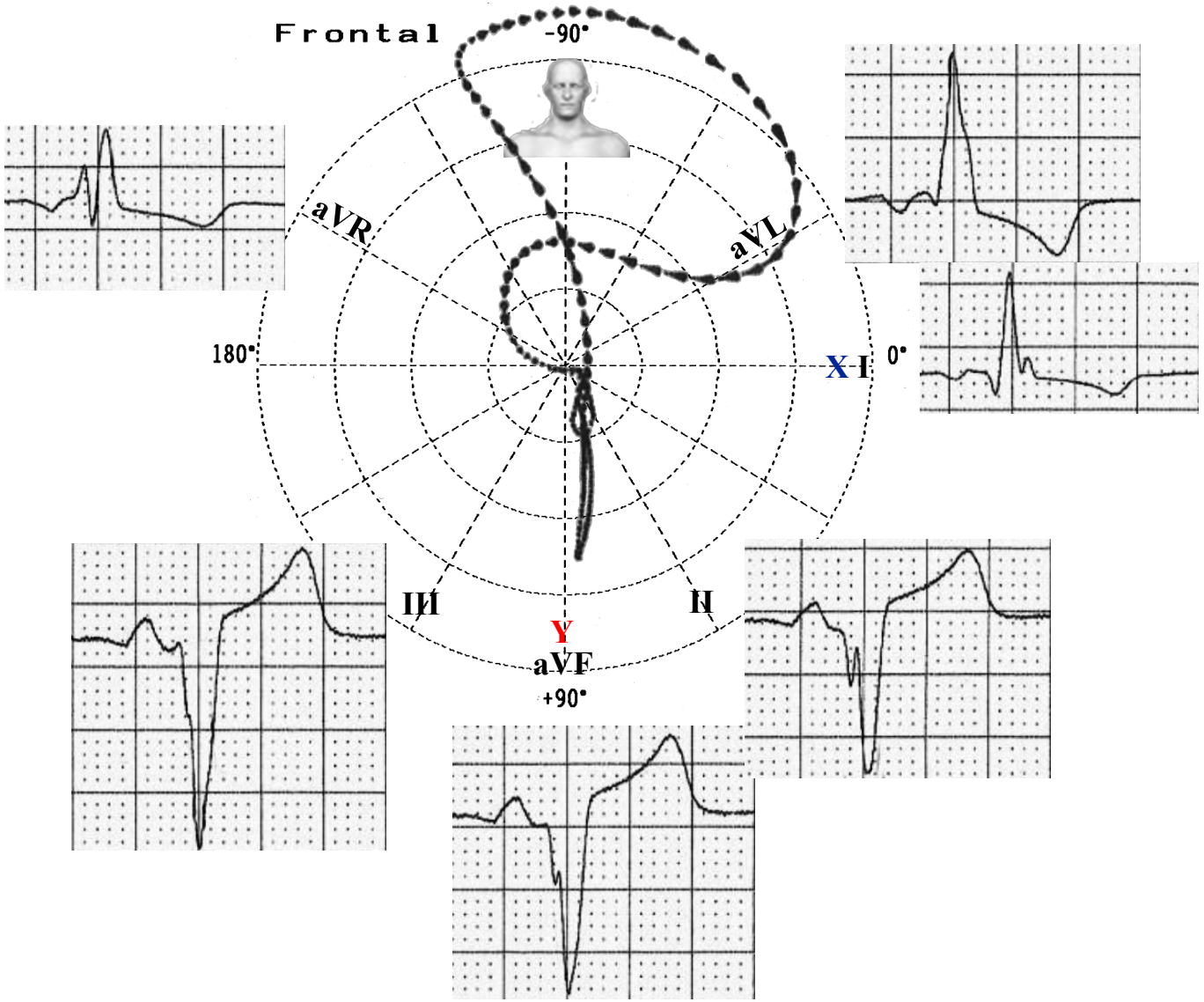
ECG3 - 2016



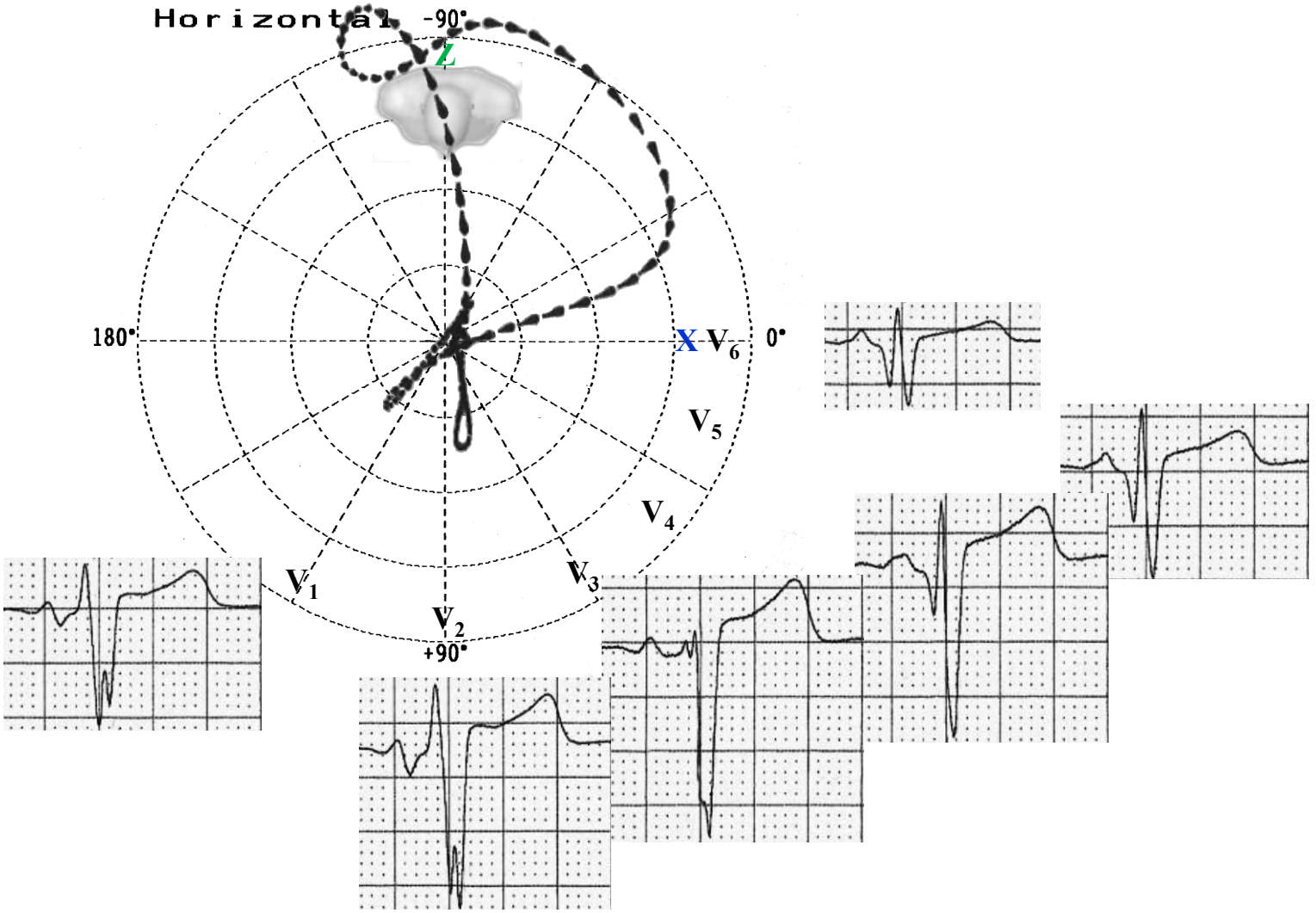
ECG4 – March 3, 2017



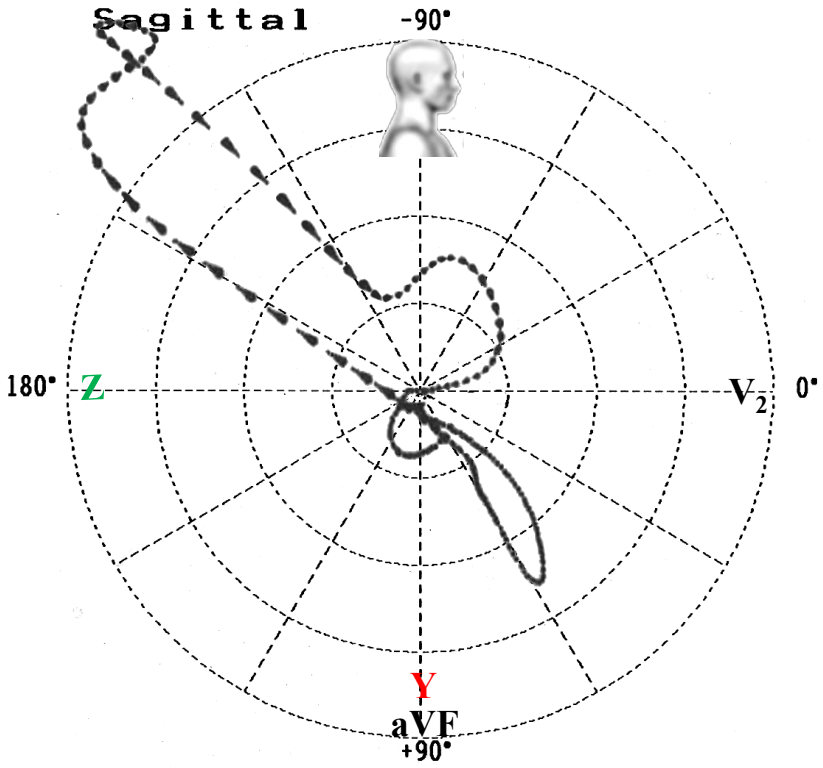
ECG/VCG 2017 correlation in the frontal plane

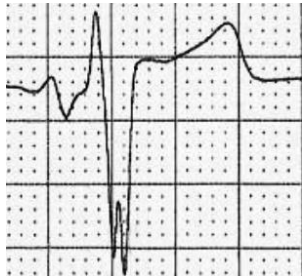


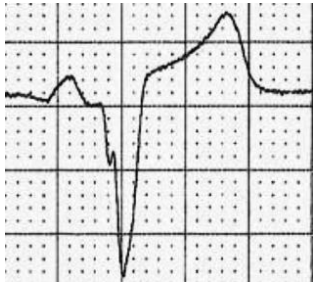
ECG/VCG 2017 correlation in the horizontal plane

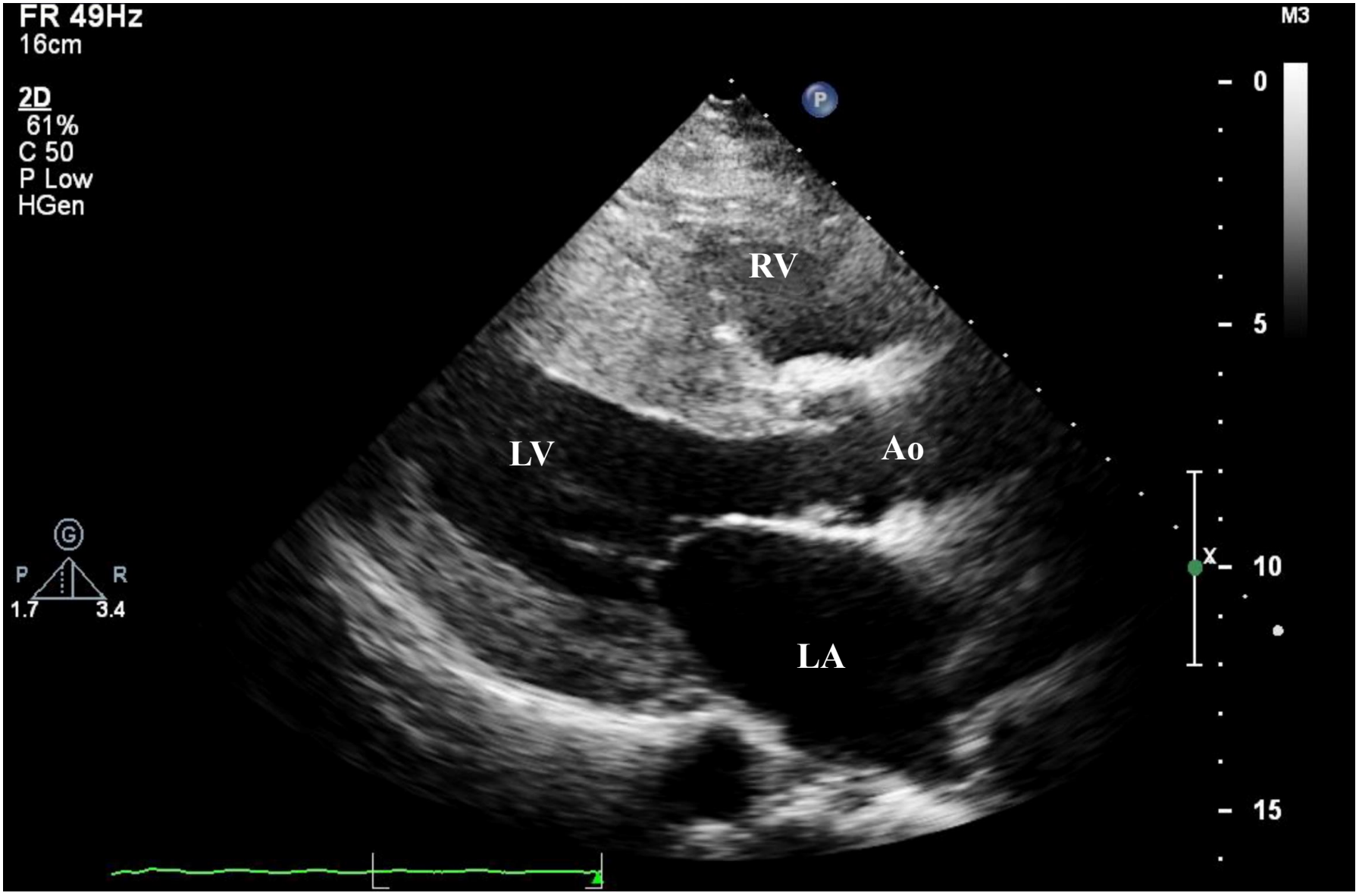


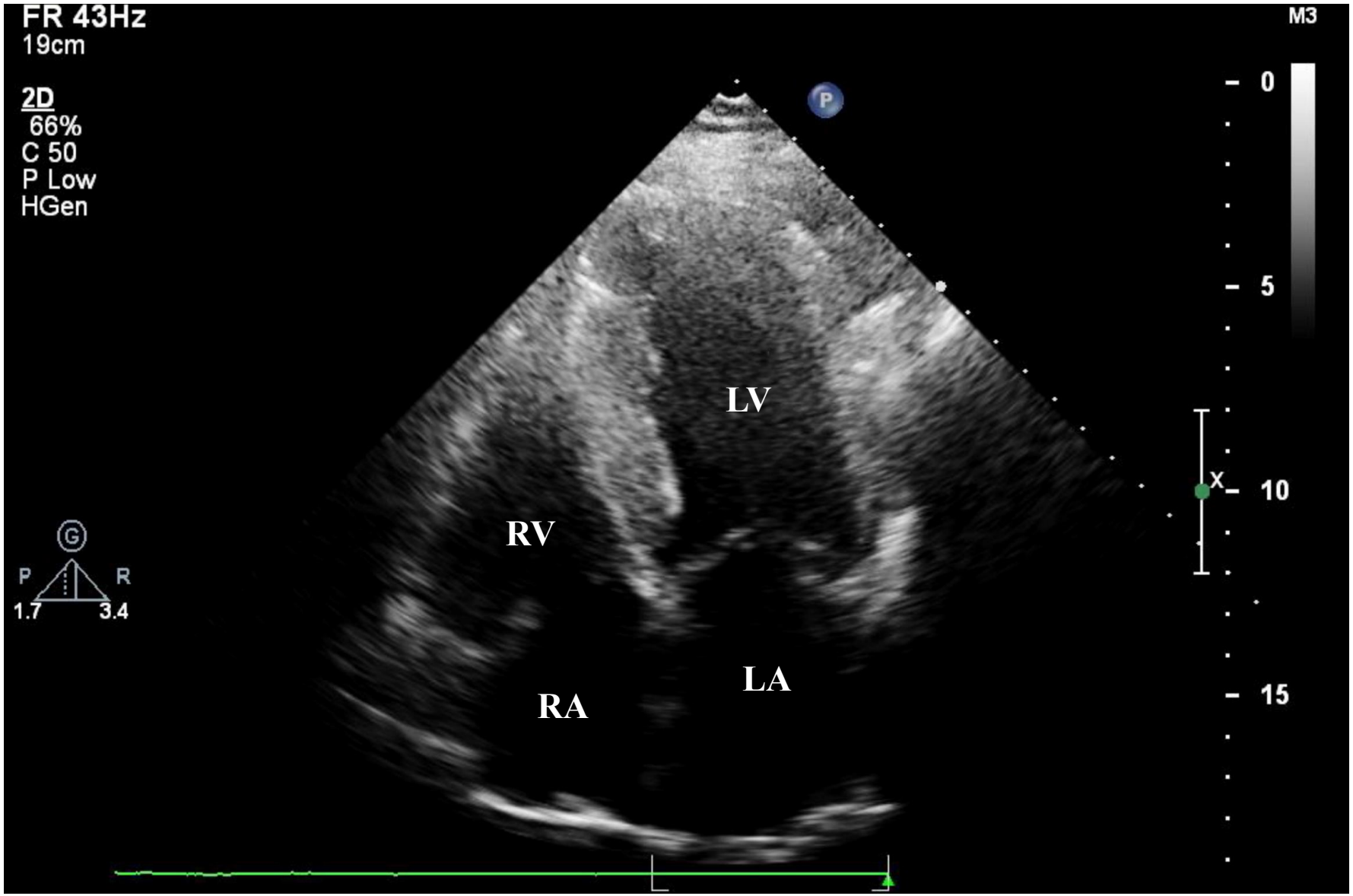
ECG/VCG 2017 correlation in the right sagittal plane








FR 49Hz
16cm
2D
61%
C 50
P Low
HGen
M3
0
5
10
15
RV
LV
Ao
LA
P
R
1.7
3.4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19cm
2D
66%
C 50
P Low
HGen
M3
0
5
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15
LV
RV
LA
RA
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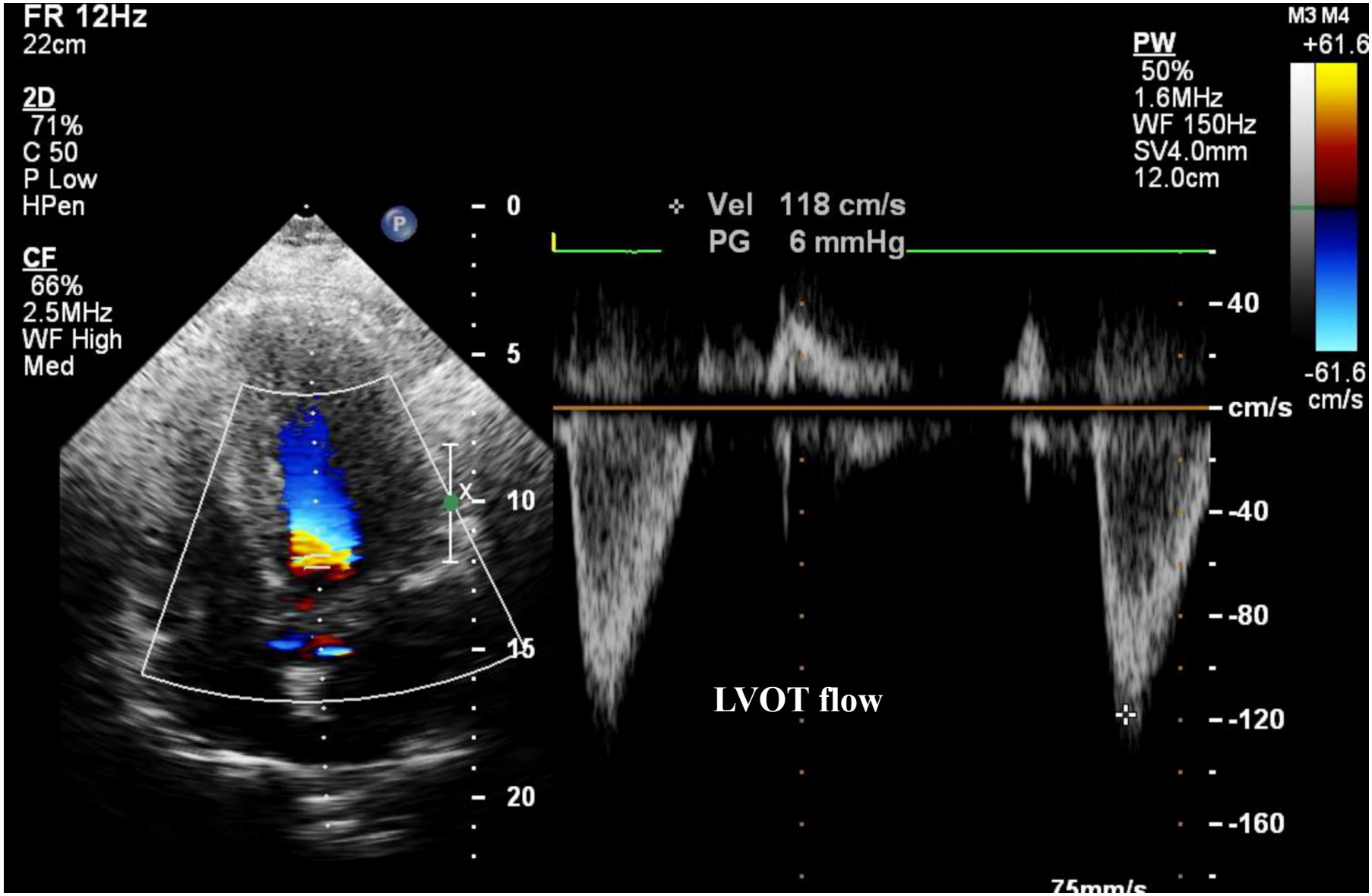
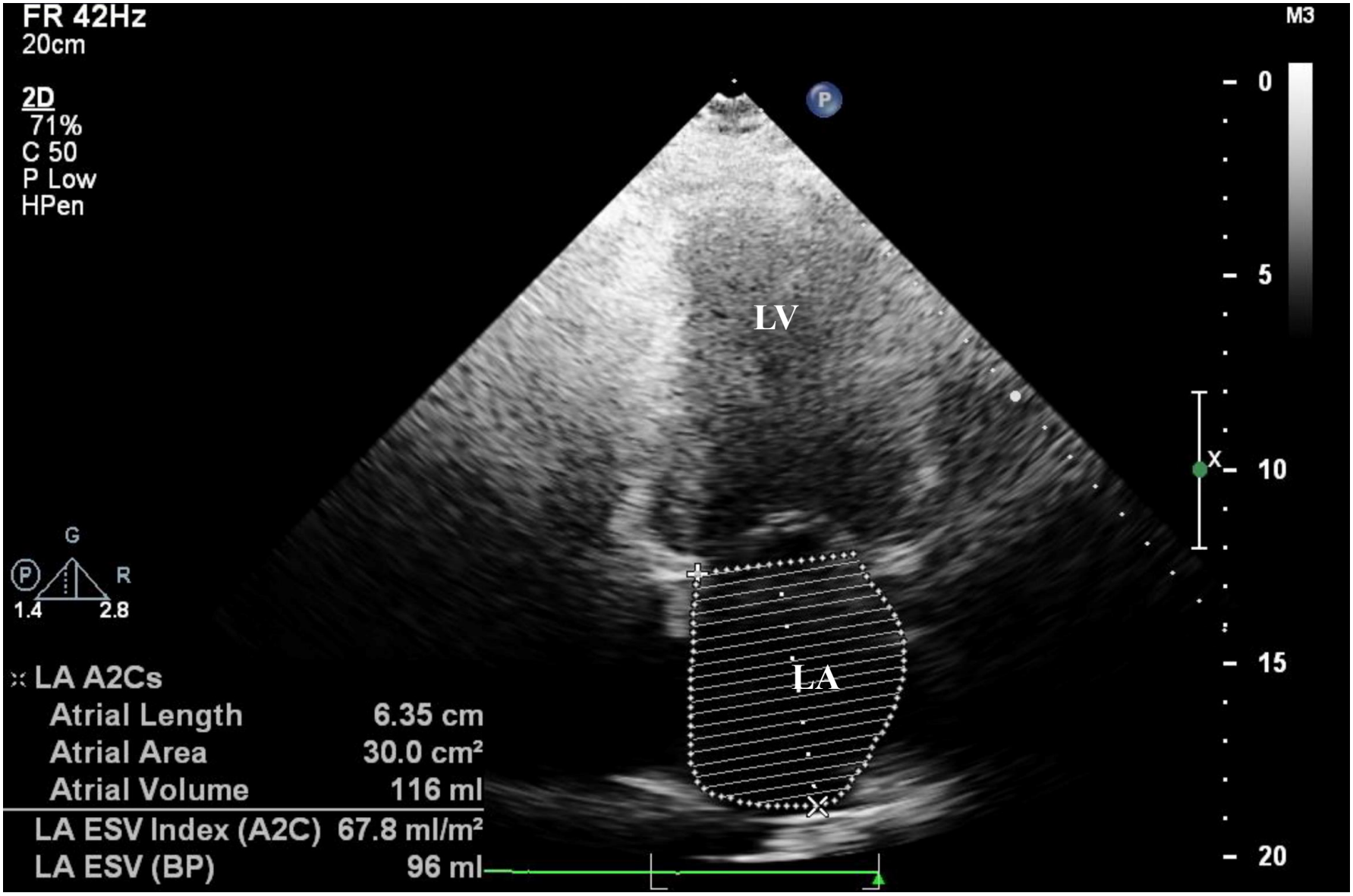
1.7
3.4


FR 12Hz
22cm
2D
71%
C 50
P Low
HPen
CF
66%
2.5MHz
WF High
Med
PW
50%
1.6MHz
WF 150Hz
SV4.0mm
12.0cm
M3 M4
+61.6
-61.6
cm/s
Vel 118 cm/s
PG 6 mmHg
0
5
10
15
20
40
cm/s
-40
-80
-120
-160
LVOT flow


FR 42Hz
20cm
2D
71%
C 50
P Low
HPen
M3
0
5
10
15
20
LV
LA
G
P
R
1.4
2.8
LA A2Cs
Atrial Length 6.35 cm
Atrial Area 30.0 cm²
Atrial Volume 116 ml
LA ESV Index (A2C) 67.8 ml/m²
LA ESV (BP) 96 ml

Colleagues' opinions

Hola Potro: Por lo referido de la historia familiar, el electrocardiograma y su historia clínica la paciente es portadora de una Enfermedad de Fabry con afectación cardíaca. Comúnmente puede cometerse el error de confundirla con la cardiomiocardiopatía hipertrófica.
La enfermedad de Fabry es tratable substituyendo el déficit de la enzima alfa-galactosidasa mediante la administración de alfa-lactosidasa (agente agalsidasa) el cual compensa la deficiencia enzimática.
La enfermedad de Fabry es un trastorno de depósito lisosomal progresivo potencialmente fatal causada por la deficiencia de la enzima α-galactosidasa A. Es una enfermedad hereditaria ligada al cromosoma X que afecta ambos sexos. El diagnóstico y el tratamiento precoces son fundamentales, ya que el daño de los órganos es progresivo y puede ser irreversible y fatal si la tratamos tardíamente.
Un abrazo
Martín **Ibarrola MD** Buenos Aires Argentina

English

Hi Potro: the family history, the electrocardiogram and her clinical history, are strong clues that the patient carrier Fabry's disease with cardiac involvement. Frequently, confusion with hypertrophic cardiomyopathy can be made.
Fabry disease is treatable by replacing the deficiency of the alpha-galactosidase enzyme by the administration of alpha-lactosidase (agalsidase agent) which compensates for enzyme deficiency.
Fabry disease is a potentially fatal progressive lysosomal storage disorder caused by α-galactosidase A deficiency. It is an X-linked hereditary disease that affects both sexes. Early diagnosis and treatment are essential, since organ damage is progressive and can be irreversible and fatal if treated late.
A hug
Martín **Ibarrola MD** Buenos Aires Argentina

43rd International Congress on Electrocardiology
Palma, Balearic Islands, Spain - June, 4-6 2016
Martin Ibarrola and Andrés Ricardo Pérez-Riera

English

Good evening dear teachers! The clinical history of the patient, her symptoms, physical examination, her family history, ECG, MRI, echocardiogram and VCG, I believe that this is a case of Andersen-Fabry disease. It is a multisystemic, metabolic entity, produced by partial or total deficit of the enzyme lysosomal alpha-galactosidase A. This leads to the intracellular accumulation of glucosphingolipids in cardiomyocytes, glomeruli and renal tubules, epithelial cells, valvular fibrocytes, ganglion neurons, autonomic nervous system and endothelium producing:
Progressive renal insufficiency with final dialytic status which is a frequent cause of death.
Heart: Symmetrical or asymmetric, obstructive or non-obstructive hypertrophic cardiomyopathy, myocardial infarction, mitral insufficiency and arrhythmias.
Neurological involvement: Vascular cerebral accident with neurological deficit (which is confused with multiple sclerosis) and auditory alterations.
Pulmonary involvement with obstructive dyspnea.
The diagnosis is based on the determination of the activity of the enzyme in question in the blood, plasma, tissue biopsy, which will be diminished or absent and will be completed with genetic study and detection of mutations.
Differential diagnosis: presents with cardiac amyloidosis (extracellular accumulation) that confers a particular texture to the hypertrophic myocardium.
Sequential ECGs : sinus bradycardia, left atrial enlargement (P-wave duration> 110 ms, and final negative component of P in V1> 0.03 mm / s (Morris criterion), short PR interval, deep Q waves In the inferior and lateral aspect (pseudo-infarction) QRS axis deviated to the left by left anterior fascicular block, prominent R waves in V1 and Q in V5 and V6, I and aVL with positive T waves, which speak of septal hypertrophy and RV overload (R V1 + S de V5 o V6 ≥10.5 mm), and there is also an increased intrinsecoid deflection of the QRS, and fragmented QRS (fQRS) predictor of malignant, fatal arrhythmias> 50 msec.
Treatment consists of enzyme replacement therapy in disease deficit. In the presence of complex arrhythmias, radiofrequency catheter ablation and / or CDI implantation may be indicated

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Dr. Juan Mazzardo in his office. Mendoza Argentina. Mendoza is the land of the good wine.

Spanish: Buenas noches estimados maestros! Por la historia clínica de la paciente, sus síntomas, examen físico, su historia familiar, ECG, RMN, ecocardiograma y VCG creo que se trata de un caso de enfermedad de Andersen-Fabry, entidad multisistémica, metabólica, producida por déficit parcial o total de la enzima lisosomal alfa-galactosidasa A. Lo cual lleva a la acumulación intracelular de glucoesfingolípidos en los cardiomiocitos, glomérulos y túbulos renales, células epiteliales, fibrocitos valvulares, neuronas ganglionares, sistema nervioso autónomom y endotelio produciendo:

A. Insuficiencia renal progresiva dialítica la cual es frecuente causa de muerte.
B. Miocardiopatía hipertrófica simétrica o asimétrica, obstructiva o no, infarto de miocardio, insuficiencia mitral y arritmias.
C. Compromiso neurológico: Accidente cerebral vascular con déficit neurológico (que se confunde con esclerosis múltiple) y alteraciones auditivas.
D. Compromiso pulmonar con disnea obstructiva.

El diagnóstico se fundamenta en la determinación de la actividad de la enzima en cuestión en la sangre, plasma, biopsia de tejidos, la cual estará disminuida o ausente y se completará con estudio genético y detección de mutaciones.
Diagnóstico diferencial: se presenta con amiloidosis cardíaca (acumulación extracelular) que confiere textura particular al miocardio hipertrófico.
En cuanto a los ECGs de esta paciente: bradicardia sinusal, sobrecarga auricular izquierda(duración de onda P > 110 milisegundos, y componente negativo final de P en V1 >0.03 mm/s (criterio de Morris). intervalo PR corto, profundas ondas Q en cara inferior y lateral (pseudo-infarto). Eje del QRS desviado a la izquierda por hemibloqueo anterior izquierdo, ondas R prominentes en V1 y Q en V5 y V6, D1 y aVL con ondas T positivas, que hablan de hipertrofia septal y sobrecarga ventricular derecha (índice de Sokolow-Lyon para hipertrofia de ventrículo derecho positivo: R V1 + S de V5 o V6 ≥10.5 mm). Hay también fragmentación del QRS (fQRS) predictor de arritmias malignas, fatales. También hay una deflexión intrinsecoide aumentada > 50 mseg.
El tratamiento consiste en la terapia de reposición de la enzima en déficit de la enfermedad. En presencia de arritmias complejas, pudiera efectuarse ablación por radiofrecuencia y/o implante CDI.

Dr. Juan Mazzardo MD Hospital Alfredo Perrupato, San Martín, Mendoza Argentina
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Dear colleagues: It´s an interesting diagnostic case. I suggest to test alpha-galactosidase activity for the diagnosis of Fabry disease.

Dr. Sergio Juan Baratta
Jefe de Cardiología no Invasiva
Jefe de Ecocardiografía

Hospital Universitario Austral
Primera institución de la Argentina con acreditación internacional
JOINT COMMISSION INTERNATIONAL

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Cleveland Clinic Foundation. Echocardiography Laboratory. Cleveland, Ohio, USA, 2001.

Hello Andrés. This in not the typical disease progression in hypertrophic cardiomyopathy. Also the family history indicates some infiltrative disease.
I think it is hemochromatosis. We had one case with some similar features, who had a MYH7 gene mutation typical for HCM and also hemochromatosis with a gene mutation (double hetrozygote).
Kind regards
Kjell Nikus MD Ph.D.
Tampere
Finland

Dear Raimundo and Andres,

The most likely diagnosis is Fabry's disease (alpha-galactosidase A deficiency). Concentric LVH, strong family history of stroke, neuropathy, renal disease and positive genetic mutations in 5/6 siblings.

The echo shows in addition to concentric LVH, enhancement of the endocardium with binary appearance.

The ECG shows RBBB + LAFB + inferior and anterolateral fibrosis.

Thank you,
Mario González MD
Penn State Hershey Heart and Vascular Institute
500 University DriveHershey, Hershey, Pennsylvania PA 17033 USA
17033
800-243-1455

mgonzalez@pennstatehealth.psu.edu

The ECG show the Cornell criteria for LVH (R aVL+ S V3) and old inferior scar and RBBB pattern. There is progressive development of anterior wall scar. Coronary disease should be excluded especially with history of diabetes. In addition she has major risk factors for sudden death (Septal size and fibroses) and merits ICD insertion.

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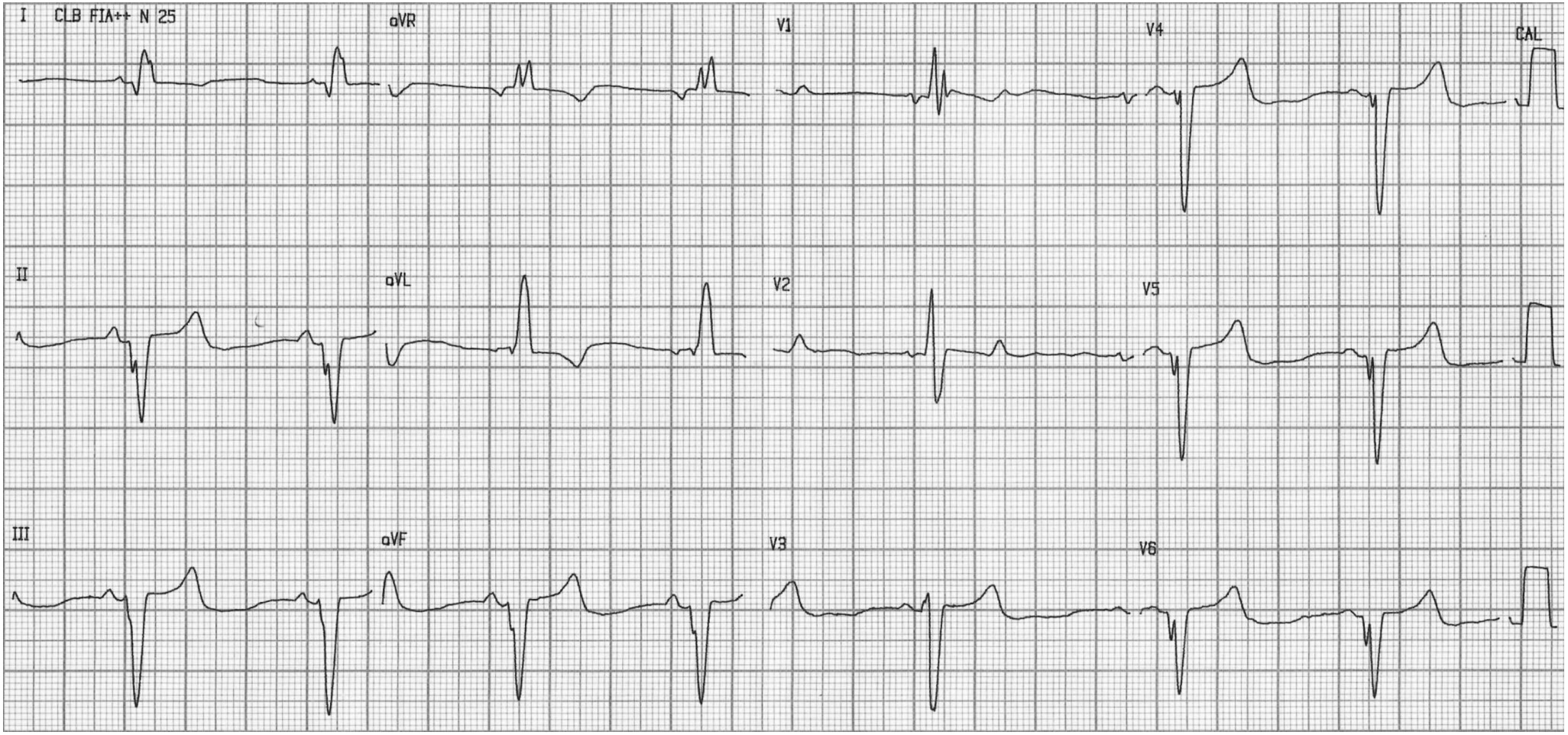
Final comments

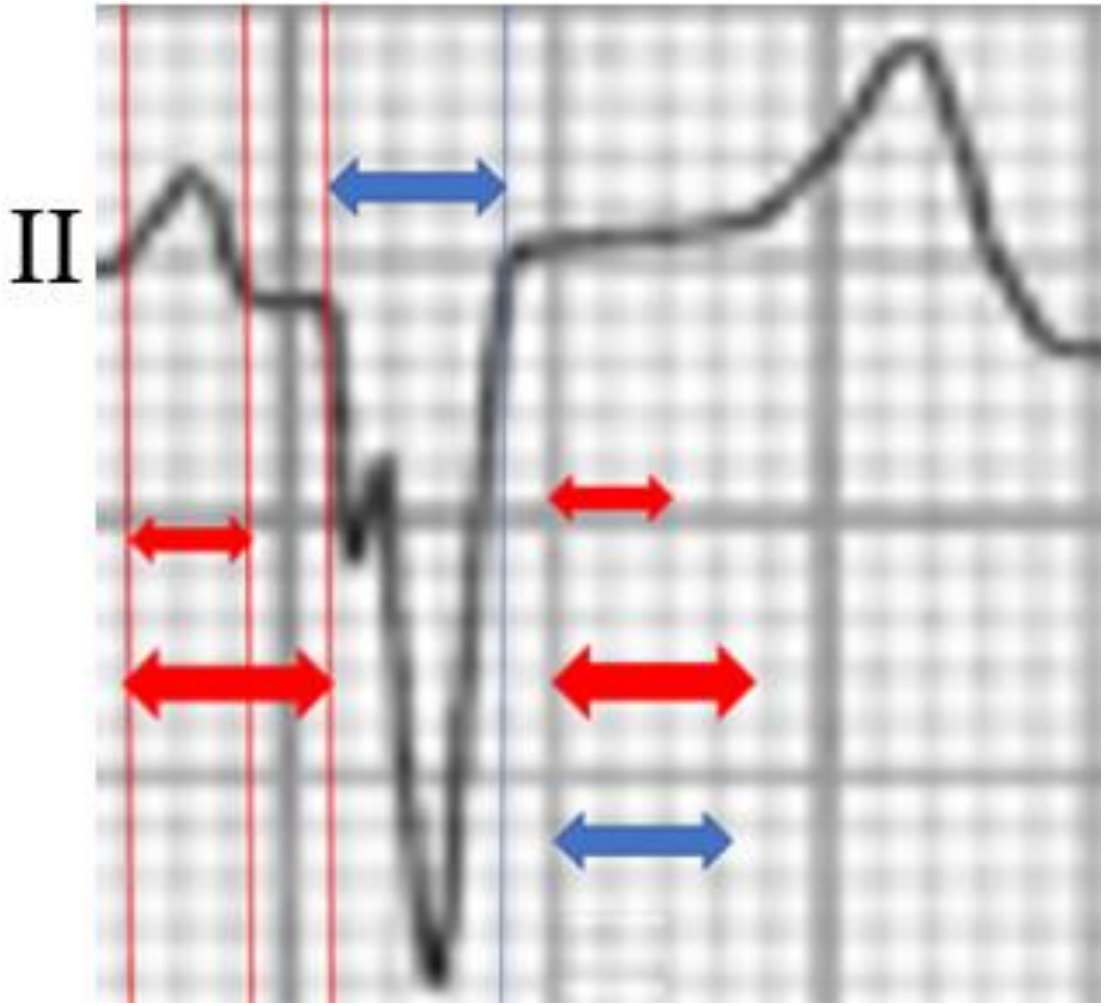
By Andrés Ricardo Pérez-Riera & Raimundo Barbosa-Barros

ECG2 - 2015



ECG diagnosis: sinus bradicardia,(HR 50bpm), P-duration: 80ms, P-axis: +65◦, P-voltage: 1.5mm, P shape: rounded, PR interval 145ms, QRS axis, - 75◦, QRS duration 130ms, wide fragmented QRS(w-fQRS), tetraphasic QRS complex in V1, R<S in V2, QS from V4 to V6 with notch at the begining of S wave and strain pattern of repolarization in I-aVL. **Conclusion:** P-axis to the right of +65° suggesting right iatrial enlargement, LVH w-f-QRS, non-specific intraventricular conduction disturbance/delay(it is defined by the presence of widened QRS complexes without features of left or right bundle branch block.) and electrically inactive area in ínferolateral walls.

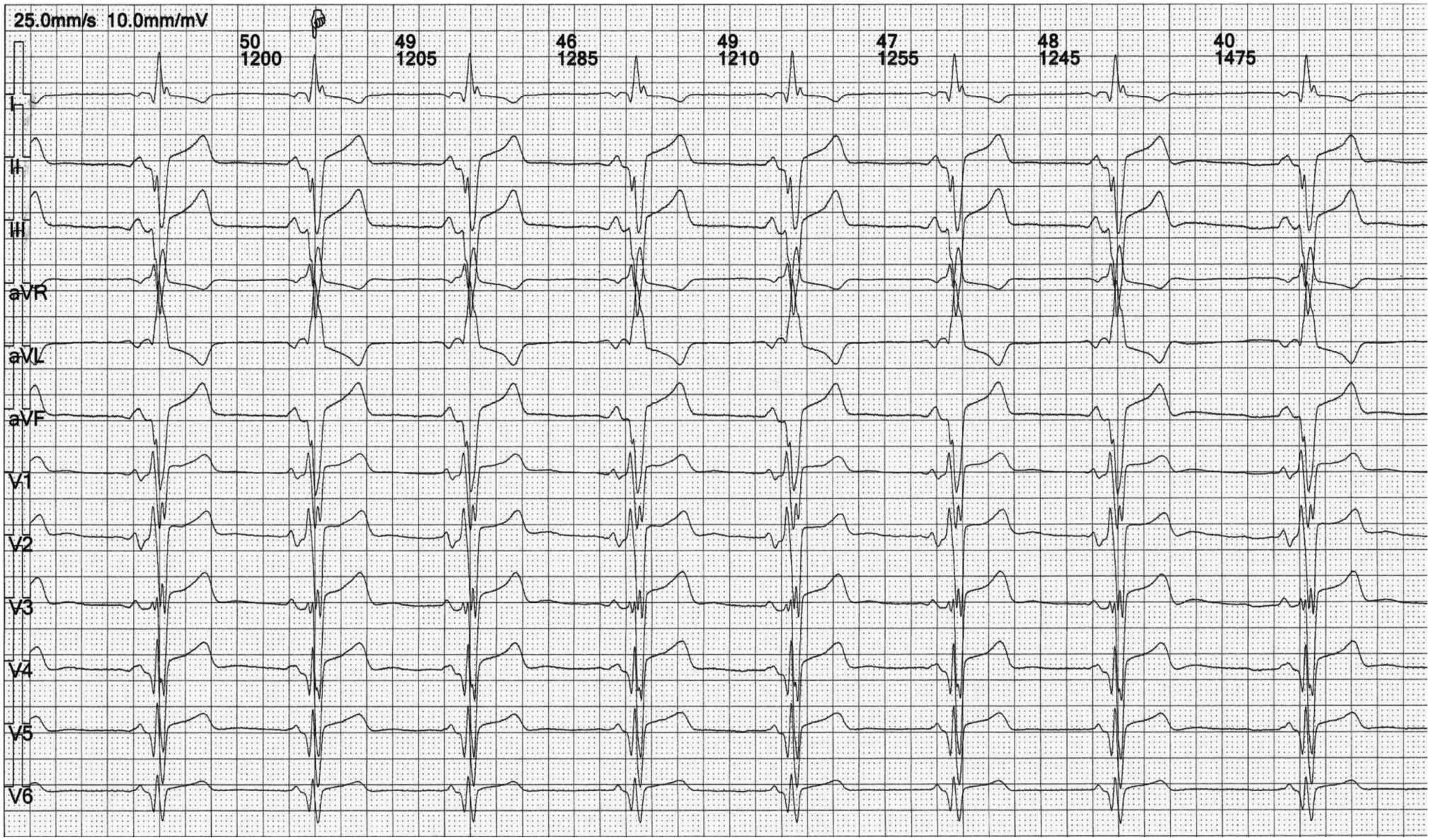
ECG 2 - 2015



PR interval duration minus P wave duration > 40 ms (Namdar 2011) This parametter is considered an important ECG diagnosis clue for FD.

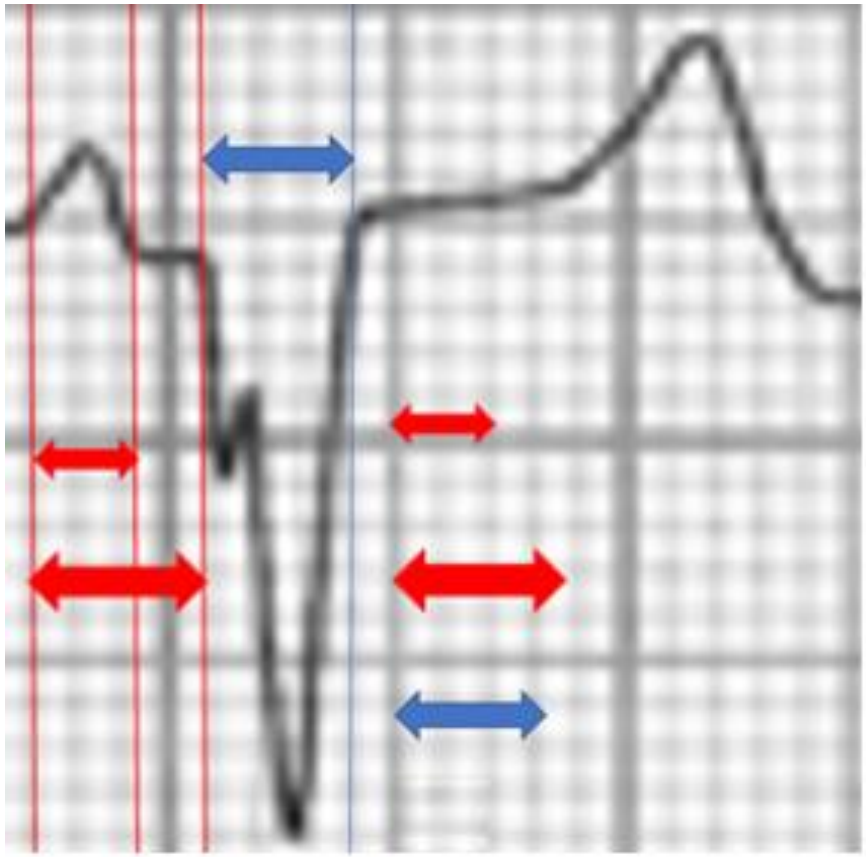
P-duration = 80m
PR interval =145ms
QRS duration = 130ms.

ECG4 – March 3, 2017



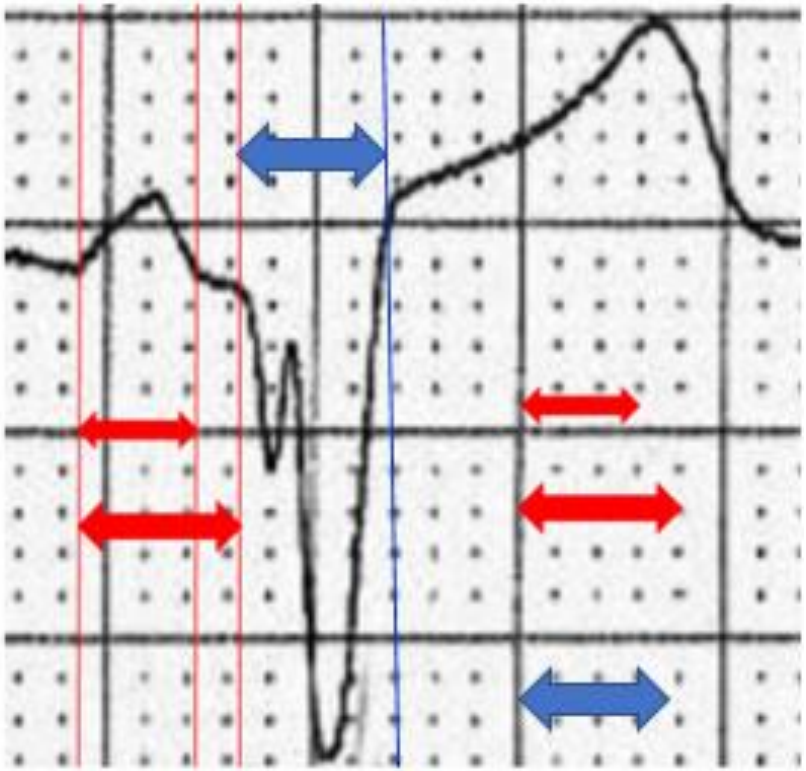
ECG 2 - 2015

II



P-duration = 80m
PR interval =145ms
QRS duration = 130ms

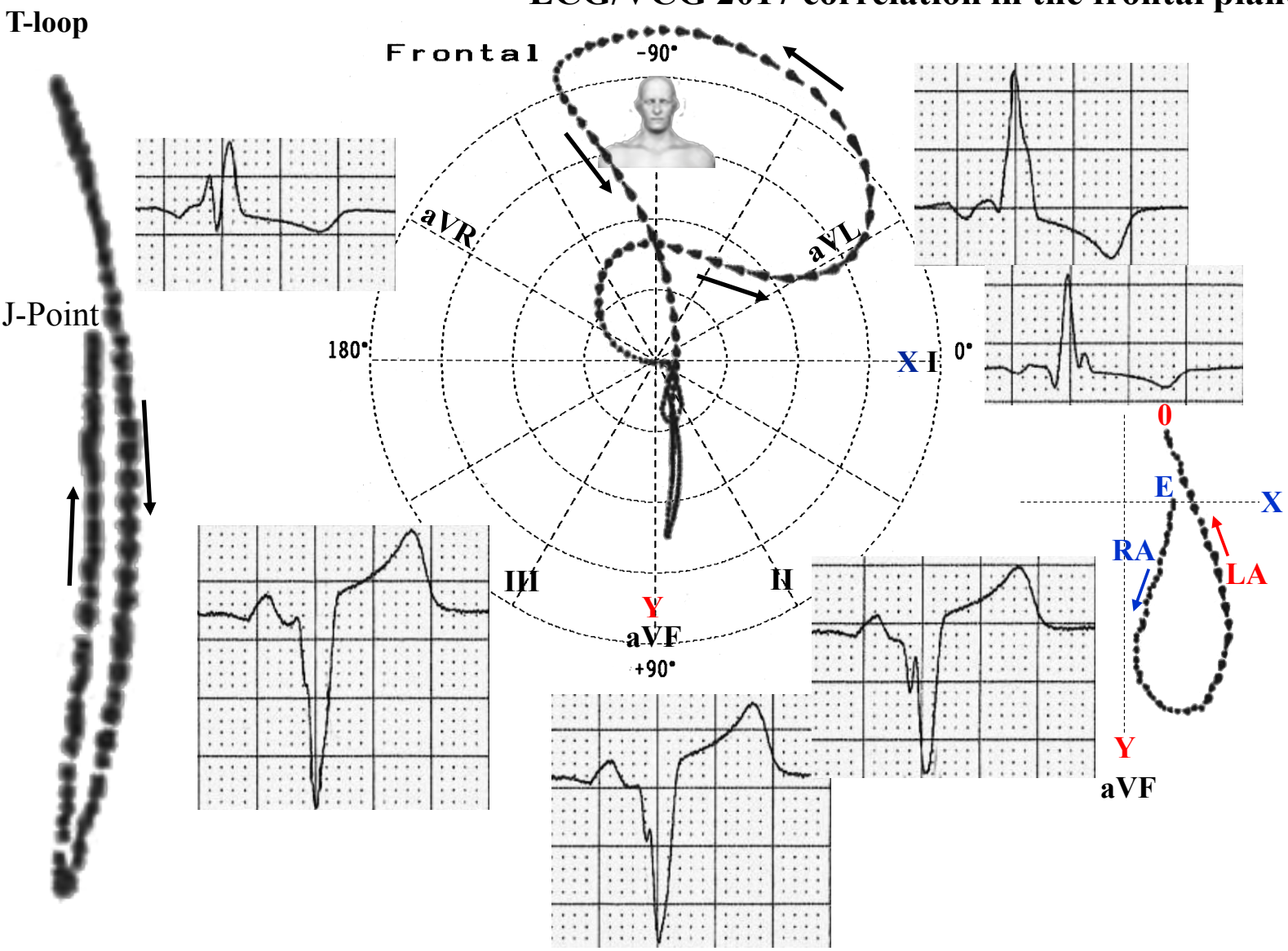
ECG 4 –2017

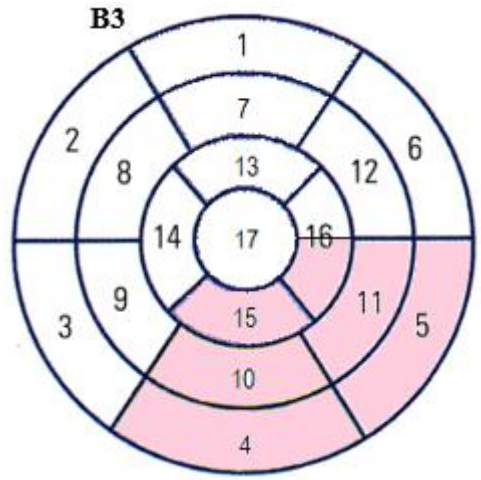


P-duration= 120ms
PR interval 160ms
QRS duration= 150ms

At 2 years of follow-up, ECG worsening manifested by P-wave prolongation (actually with duration criteria of left atrial enlargement), minimal prolongation of PR interval (within normal values) and longer QRS duration. In concordance with the progressive character of the disease. In the first ECG the PR interval duration minus P wave duration > 40 ms (Namdar 2011) This parametter is considered an important ECG clue diagnosis for FD.

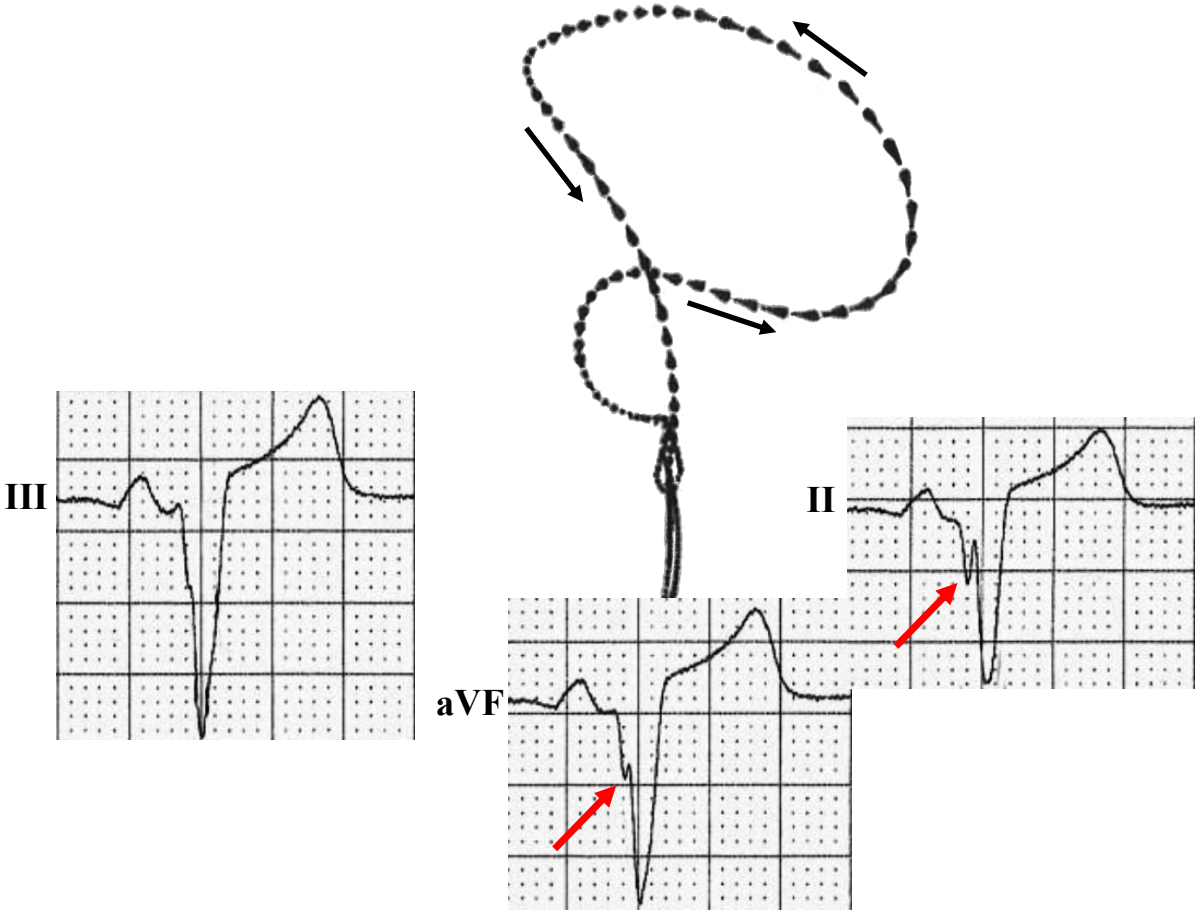
ECG/VCG 2017 correlation in the frontal plane

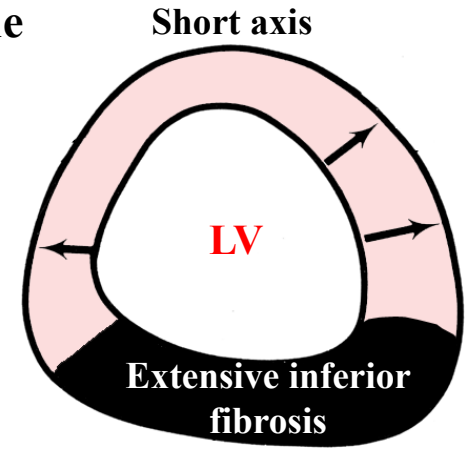


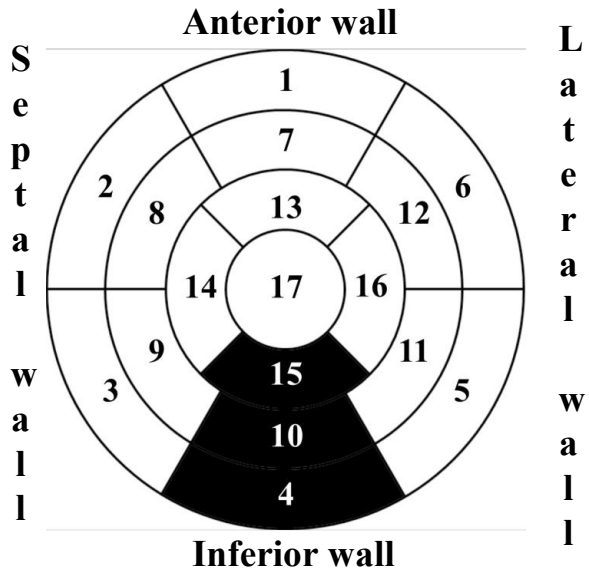


Progressive hypertrophy of the cardiac muscle, with increasing interstitial and fibrotic changes(scar) predominantly in inferior lateral wall(old dorsal nomenclature). This feature is coincident with diffuse fibrosis to late enhancement in **inferolateral** walls in MRI.(segments 15, 10. 4(inferior) and 16, 11 and 5. (lateral) Scar-based reentry, is the arrhythmogenic substrate in non-ischemic cardiomyopathies has been demonstrated to be represented by an increased myocardial collagen content and regional fibrosis (**Shah 2005; Eckart 2000**).

ECG/VCG 2017 correlation in the frontal plane

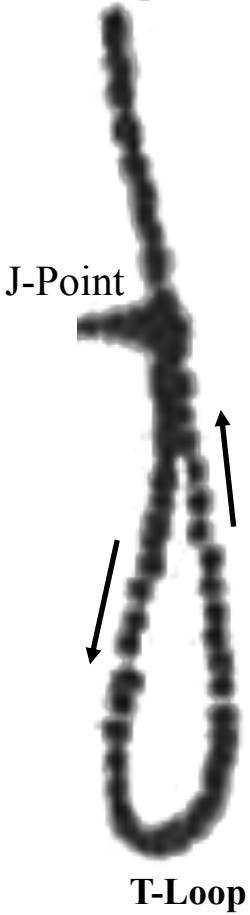


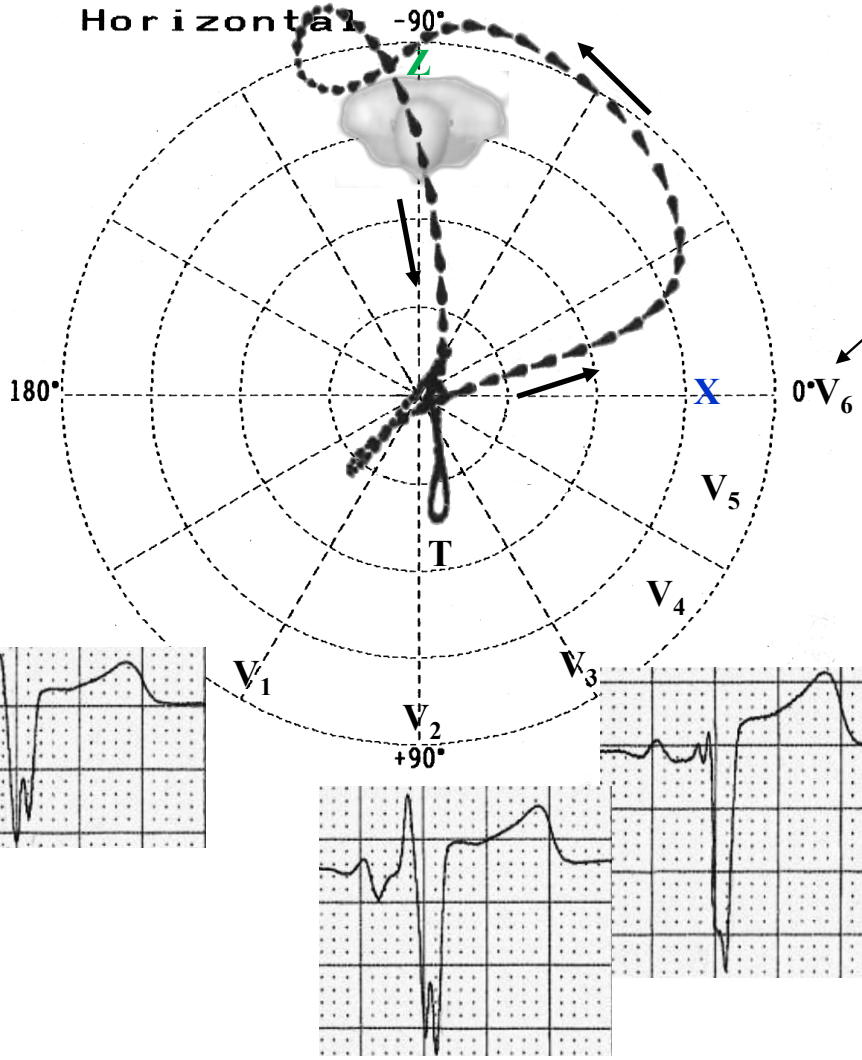


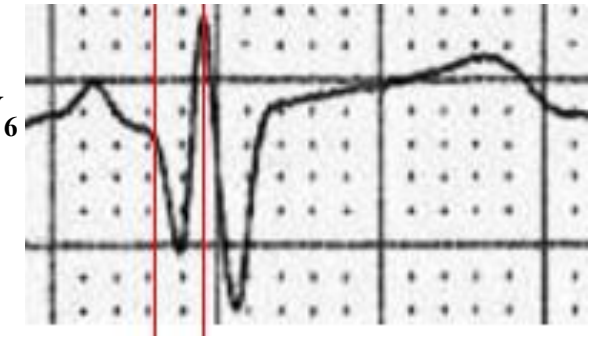


Extensive inferior inactive electrically area (coincident with the diffuse fibrosis to late enhancement in lateral and inferior walls in MRI that involves all the inferior wall, which would explain the absence (or embryonic) of r wave in II, III and aVF. Note that in the initial portion of the QRS loop the comets are very close each other indicating slow conduction coincident with wide fragmented wide QRS complexes (w-fQRS) (red arrows). Please, it is not δ-wave!!!!

ECG/VCG 2017 correlation in the horizontal plane

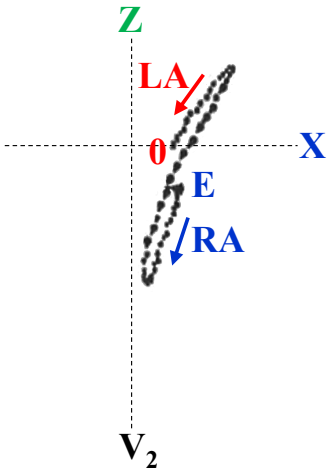






R-Wave Peak Time = 55ms LVI

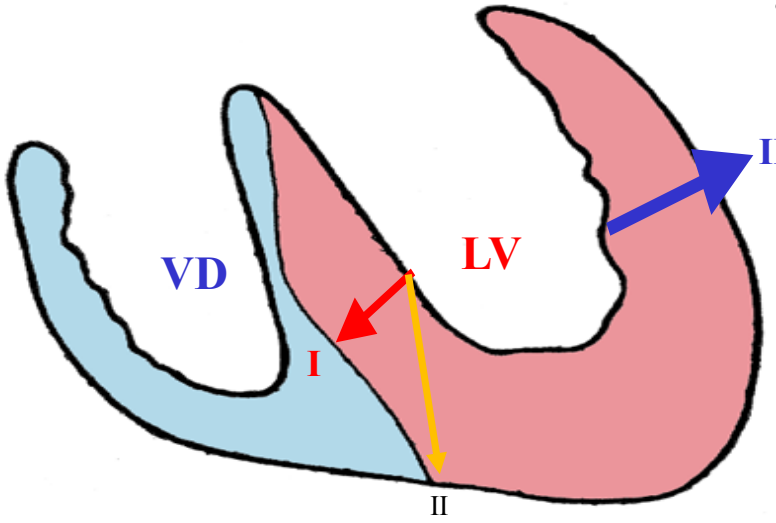
P-loop

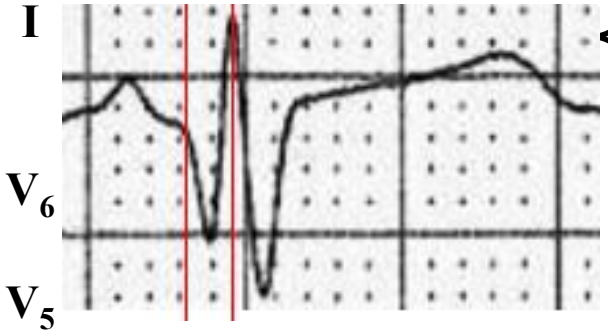


Very broad Spatial angle QRS-T (SA) Normally, the angle formed by the maximum vectors of the QRS and T loop is usually less than <75°. In the present case it is very wide near 180°. Equivalent to ECG “Strain pattern of repolarization”

Ventricular Activation Time (VAT), intrinsicoid deflection, or "R wave peak time" in left leads I, aVL, V5-V6

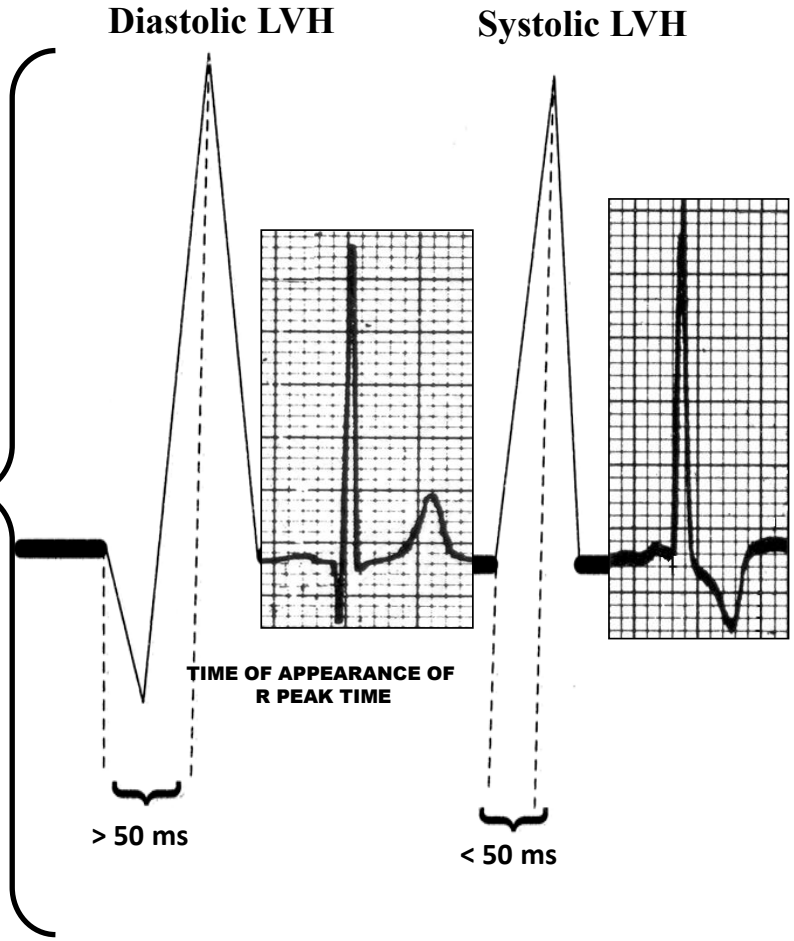
Left Ventricular Activation Time (VAT): it is the time from QRS complex onset to peak of R wave on left leads (time of appearance of R peak). The normal value of VAT is <0.05 sec or 50 ms in V5 or V6. This parameter is prolonged in diastolic, volumetric, or eccentric LVH. VAT is shorter in systolic or concentric LVH than in diastolic LVH. The prolongation of VAT is associated with diastolic dysfunction in patients with newly diagnosed untreated hypertension.



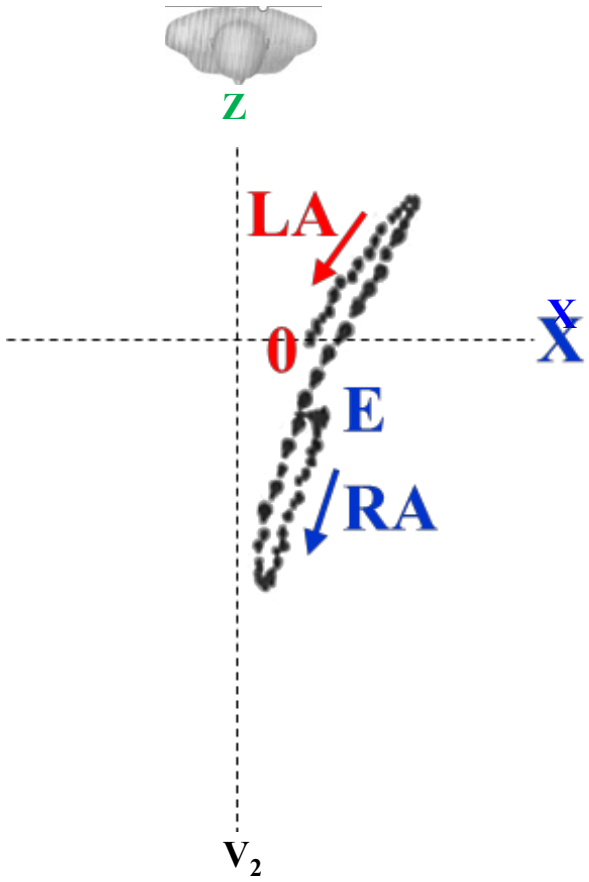


Ventricular Activation Time (VAT) or R-Wave Peak Time = 55ms LVI

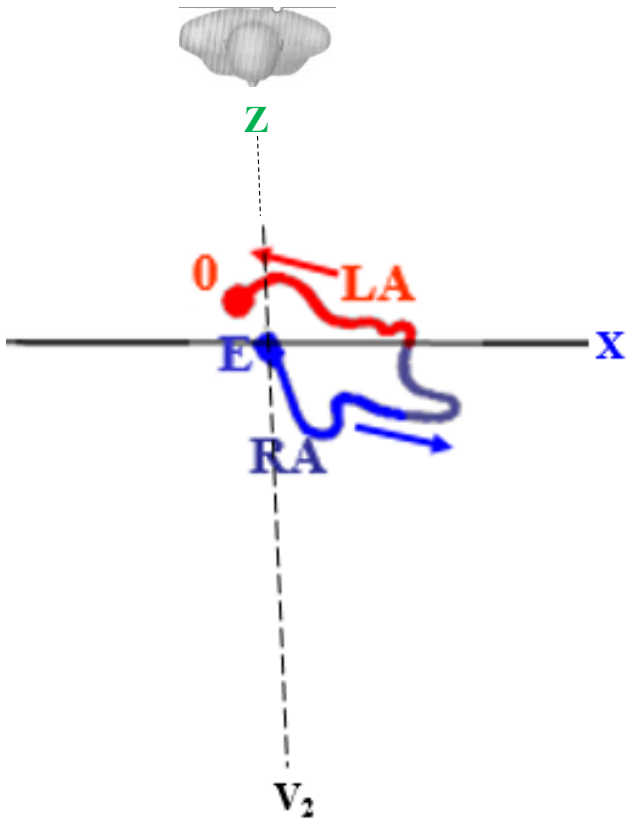
Prolongued > 50 ms



P-loop in the present case Horizontal Plane 2017



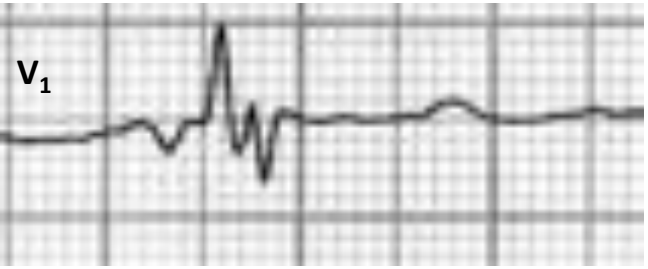
Normal P-loop in the Horizontal Plane



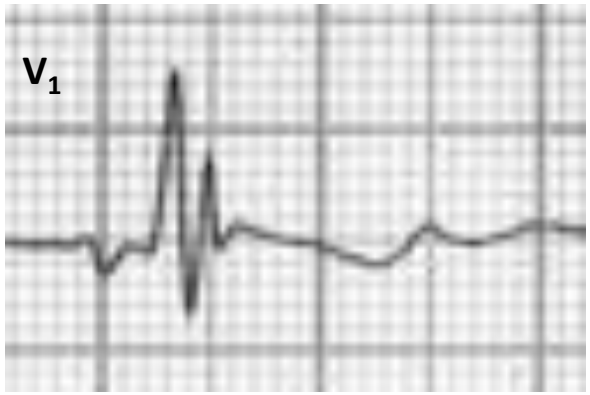
Normally, maximum anterior P-loop forces in adults up to **0,06mV.** Maximum posterior forces: up to **0,04mV**. In the present case we have increase of both anterior and posterior voltages of the P- loop: Biatrial enlargement

Why do the patterns in precordial leads V1 from the years 2014 and 2015 being polyphasic tetraphasic (Rsr's"/RsR's") with wide QRSs (> 120ms) not correspond to a right bundle branch block?

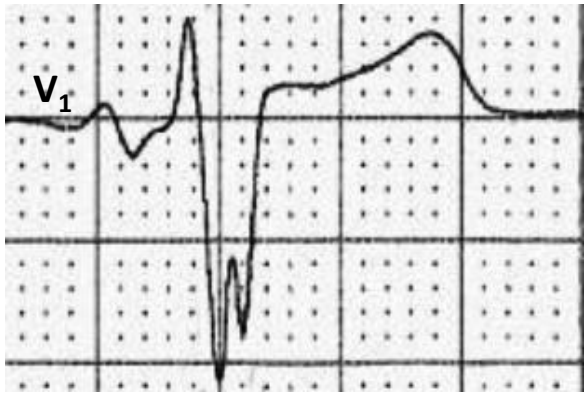
2014



2015

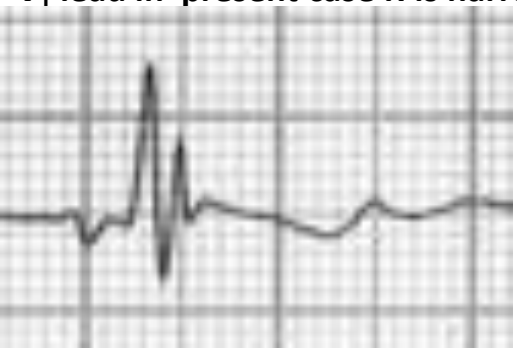


2017

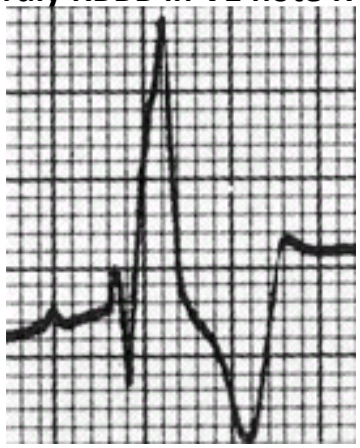


The key to the differential diagnosis with right bundle branch block is that r' or R' is narrow and not wide as in genuine RBBB.

V_1 lead in present case R'is narrow



Truly RBBB in V1 note R'broad



Ludic response in next slide……

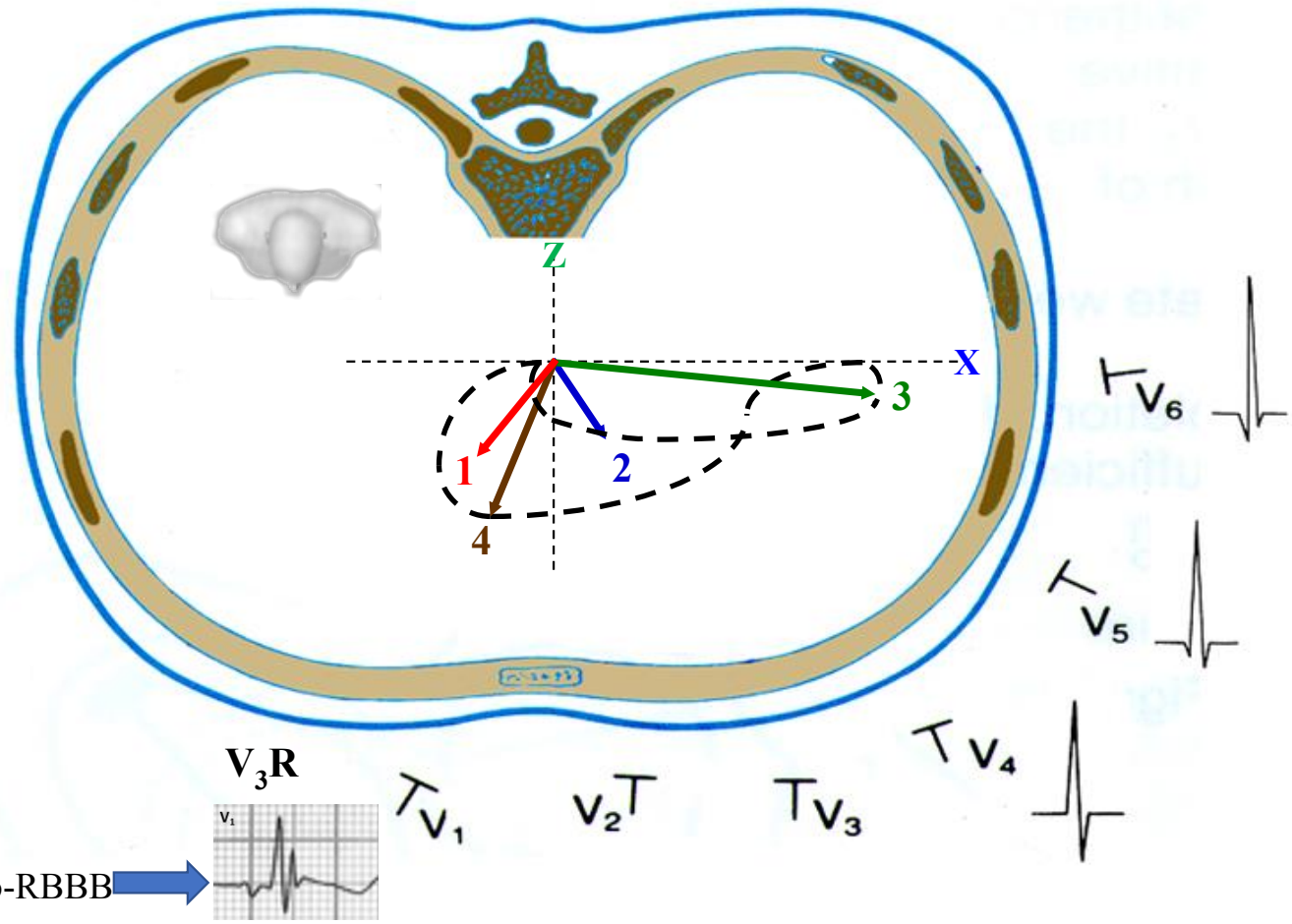
Vector representation of ventricular activation in lateral MI (old strict dorsal MI) in the HP

I. **Vector 1:** septal vector no modified.

II. **Vector 2, second vector or vector of the low portion of the interventricular septum activation**.
Vector 1 and **Vector 2** are not affected.

III. **Vector 3 or vector of the free wall of both ventricles** shows mild anterior dislocation.

IV. **Vector 4 or vector of the basal portions of both ventricles** shows an important anterior dislocation of (inferobasal portion). this explains the triphasic or polyphasic (pseudo RBBB) pattern registered in ≈ 40% of cases of fibrosis or MI in inferior basal wall in V_3R, V_1 and/or V_2. The key to the differential diagnosis with right bundle branch block is that r‘ or R' is narrow and not wide as in genuine RBBB.



Abnormal anterior shift of QRS loop in the HP: at least 50% of the area or QRS-loop facing the orthogonal **X** lead. Triphasic complexes that resemble IRBBB of the rSr”, rSR’ or rsR’ type in V_3R and V_1 appear in 40% of the cases. Basal inferolateral MI (old strict dorsal MI affects only the middle and final portion or the second half of the QRS-loop between 30 and 100 ms)

Presence of LVH + RVH: criteria = biventricular hypertrophy

I. Positive a point-score system for the ECG diagnosis of left ventricular hypertrophy

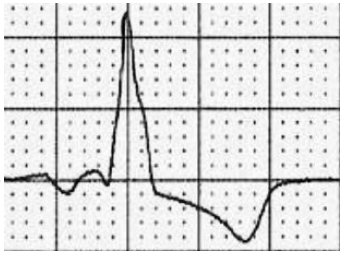
I. Presence of positive point score system for LVE/LVH or Romhilt-Estes Score system (**Romhilt 1968**) The authors attribute values from 1 to 3 points to the different existing criteria, 5 or more points: certain LVH; 4 points: probable LVH

ECG finding	Scoring
Voltage criteria Voltage Criteria (any of): R or S wave in limb leads ≥20 mm S wave in V1 or V2 ≥30 mm R wave in V5 or V6 ≥30 mm	3 points
ST-T vector opposite to QRS without digitalis ST-T vector opposite to QRS without digitalis	3 points 1 point
Left atrial abnormality; terminal negativity of the P wave in V1 >1 mm in depth with a duration of ≥0.042	3 points
Left axis deviation ≥30º	2 points
QRS duration >90 ms	1 point
Delayed ventricular activation time, R peak time or intrinsicoid deflection in V5 or V6 (> 0.05 sec) or ≥50 ms	1 point

Observation in the present case the Romhilt score has 8 points.(In red color the criteria present in this case).

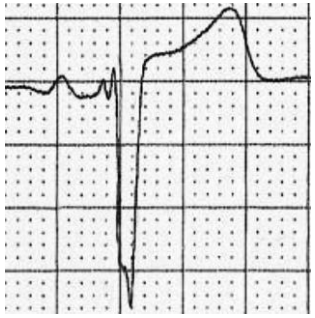
II. Presence of the Cornell criteria for LVH (Casale 1985): Add the R wave in aVL and the S wave in V3. If the sum is >28 mm in males or >20 mm in females, then LVH is present.
CI = R aVL + SV3: >28 mm (>2.8 mV) in men or >20 mm (>2.0 mV) in women suggests LVH.
Gender-specific Cornell voltage (SV3 + RaVL >2.8 mV in men and >2.0 mV in women.
The criterion has high sensitivity and specificity for LVH, and is the best ECG criterion to evaluate LVH.

aVL



R aVL = 11mm

V3



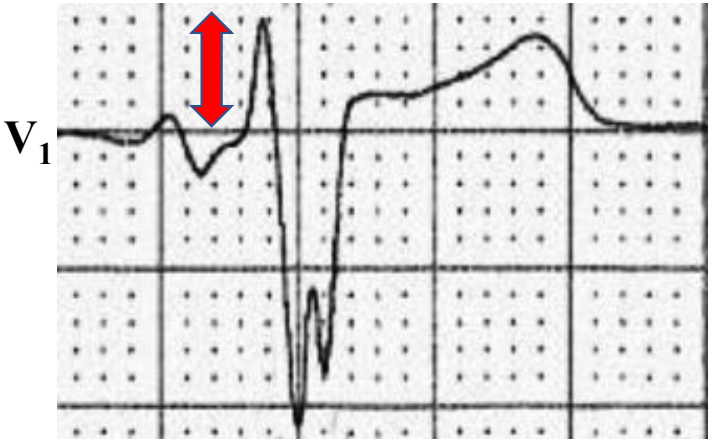
SV3 = 18mm

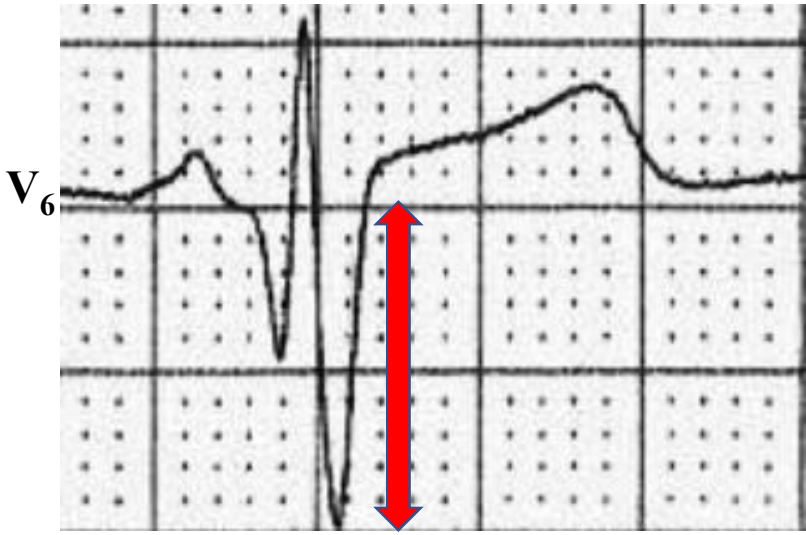
R aVL = 11mm +SV3 = 18mm: 29mm. >20 mm (>2.0 mV) in women suggests LVH.

III. Positive Cornell product criteria for LVH: (Molloy 1992) It is the product of QRS voltage and QRS duration (QRS voltage-duration product); Cornell voltage-duration product (RaVL + SV3 with 6 mm added in women x QRS duration). Values ≥2440 mm/ms are diagnostic of LVH (Positive criteria of LVH CP≥2440 mm x ms).
The Cornell product is a useful ECG marker, reflecting not only left ventricular mass but also LV geometry and diastolic function in Japanese hypertensive patients. (**Shira 2007**)

Presence of Right Ventricular Hypertrophy ECG criteria: R V_1 + S of V_6 ≥10.5 mm

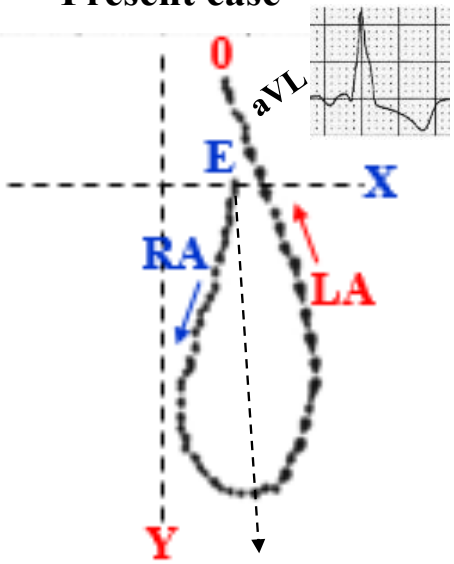
R V_1 = 4 mm +S V_6 = 10mm= 14mm: Positive Sokolow-Lyon index for the RV: Right Ventricular Hypertrophy





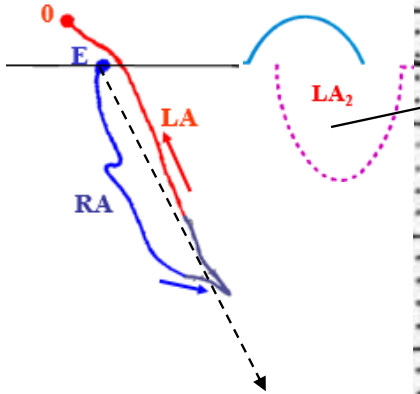
P-loop in the frontal plane and P-wave in the right precordial leads V_1-V_2

P-loop (FP)
Present case

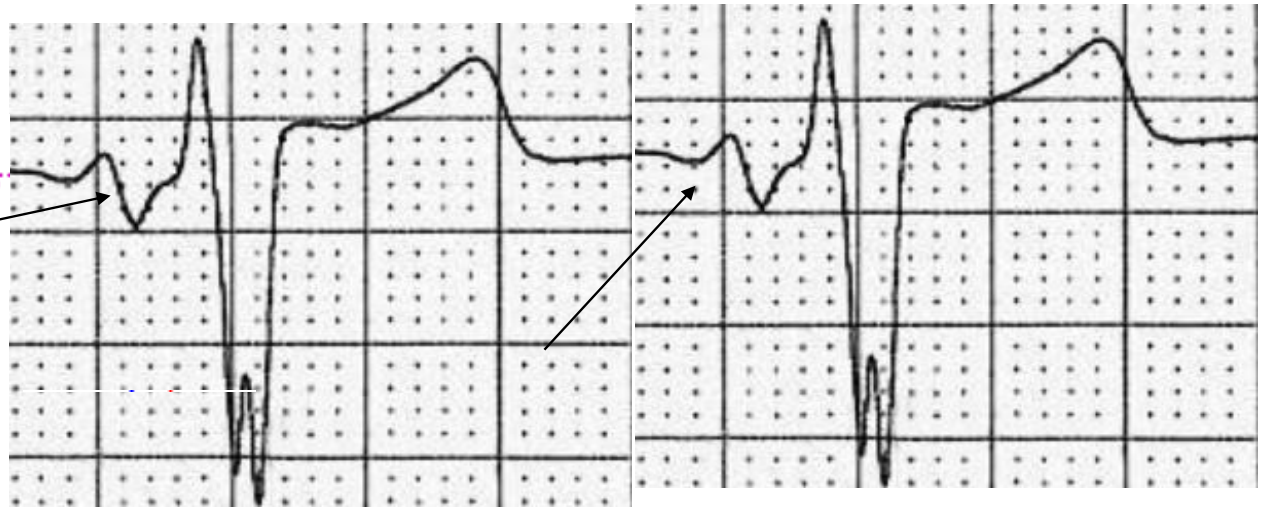


P-axis + 75°

Normal
P-loop (FP)



P-axis + 55°

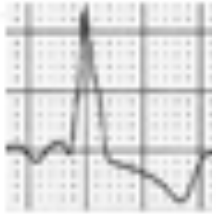


The P-loop in the present case is more vertical than normal (P-axis + 75°), and the maximal P-vector exceed 0.2mV: right atrial enlargement(**RAE**). P-wave negative in aVL.

Plus-minus P-wave with increase in depth and duration of final negative component of the wave in V_1 or V1-V2 deeply negative: positive Morris index (**Morris 1964**): PTFV1. P terminal force in lead V_1 ≥ negative than 0.04 mm/s Greater than 0.03 mm/s: product of the duration of the final negative component (duration expressed in seconds); while depth is expressed in mm. Values above 0.03 mm per second constitute a highly sensitive criterion for diagnosis of **LAE**.
P duration ≥ 120 ms + terminal mode negative of P in V1 > 40 ms, interpeaks of P wave >40 ms

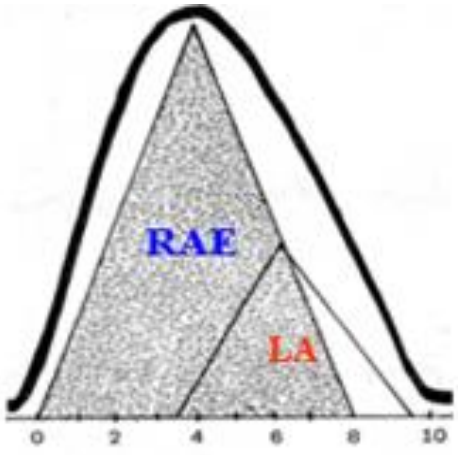
Conclusions: Signs of LAE (P waves of duration >120 ms and bimodal/ plus-minus P-wave with increase in depth and duration of final negative component of the wave in V_1 or V1-V2) associated with right P axis SÂP.: biatrial enlargement

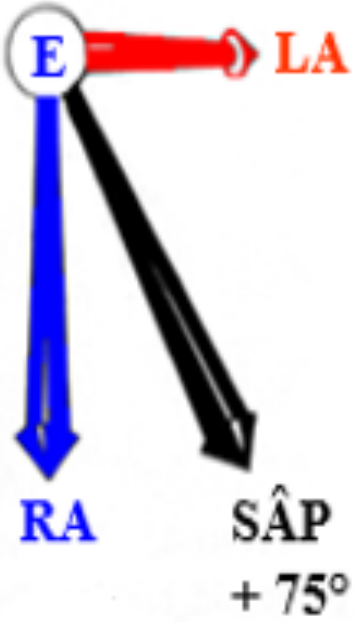
P-loop (FP)
Present case



P-axis + 75°

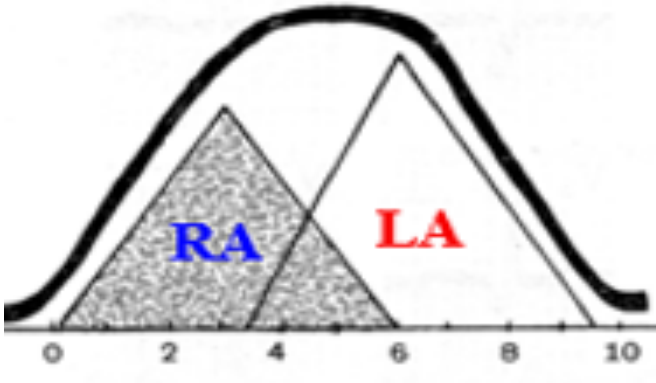
RAE

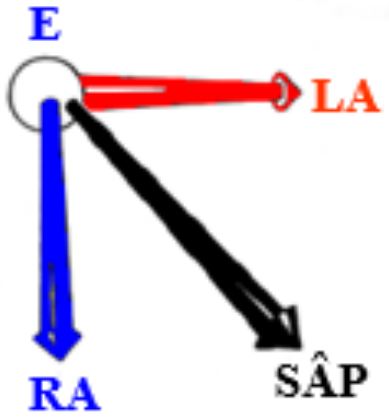




The maximal P-vector > 0.2mV

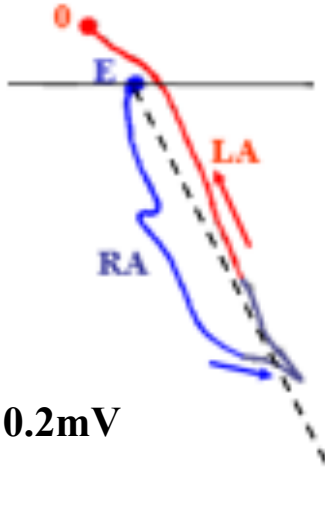
Normal





The maximal P-vector < 0.2mV

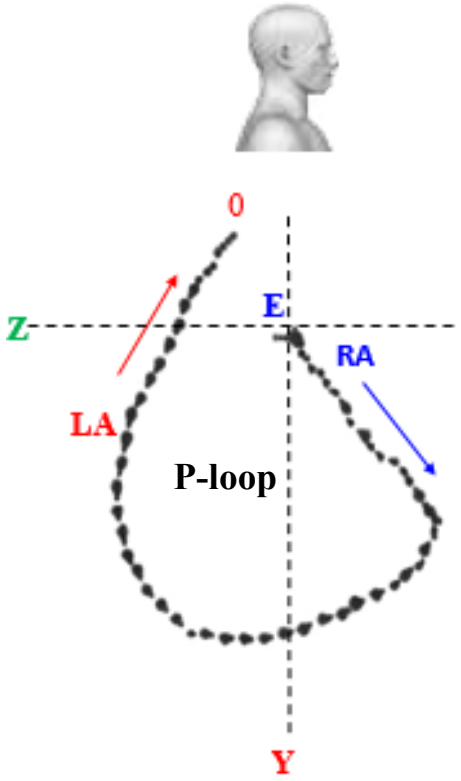
Normal
P-loop (FP)



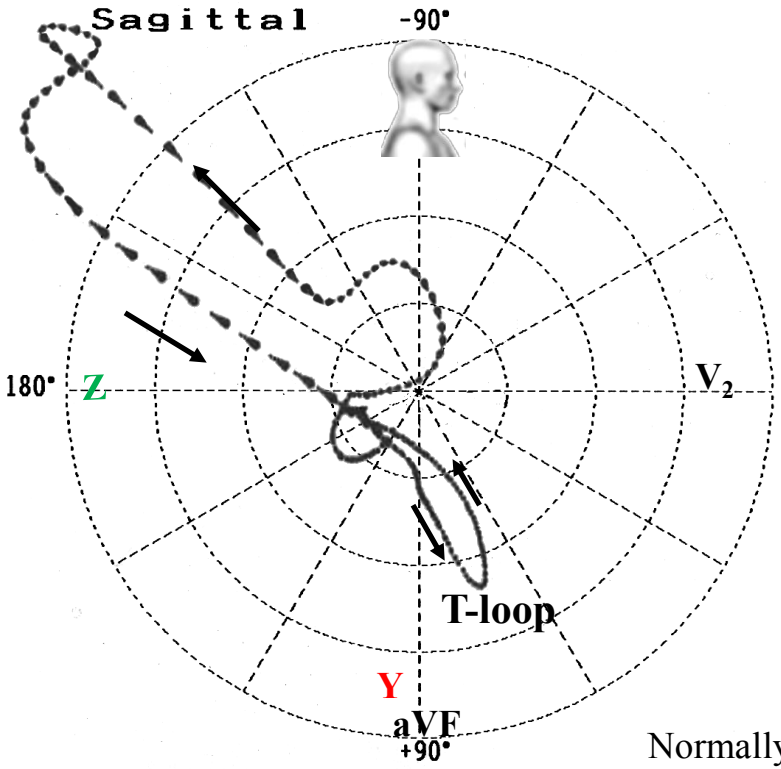
P-axis + 55°

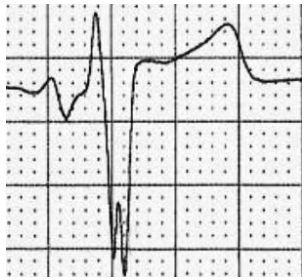
ECG/VCG 2017 correlation in the right sagittal plane

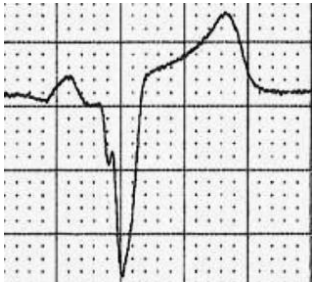
P-loop in the present case



T-loop in the present case

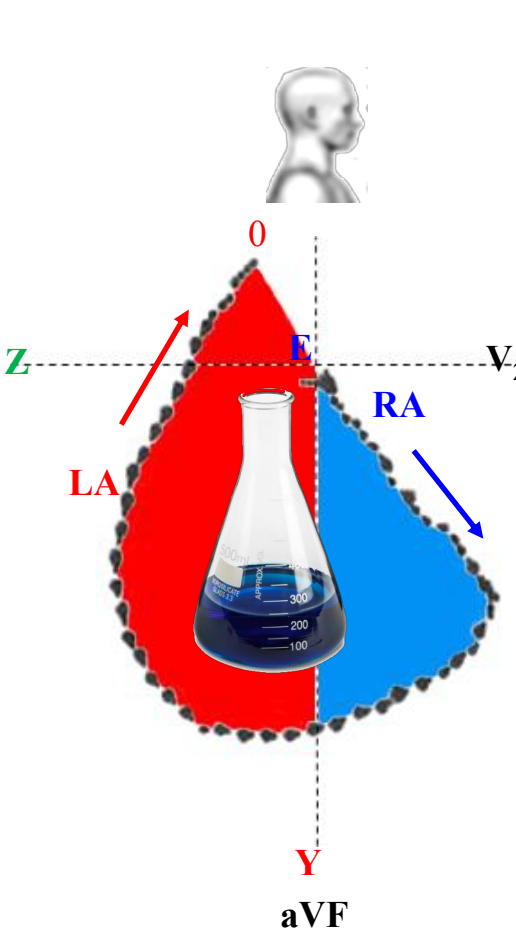


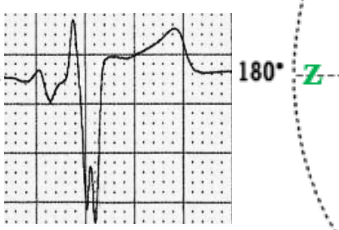


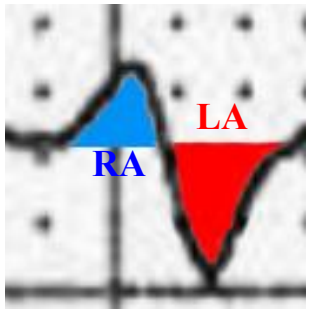


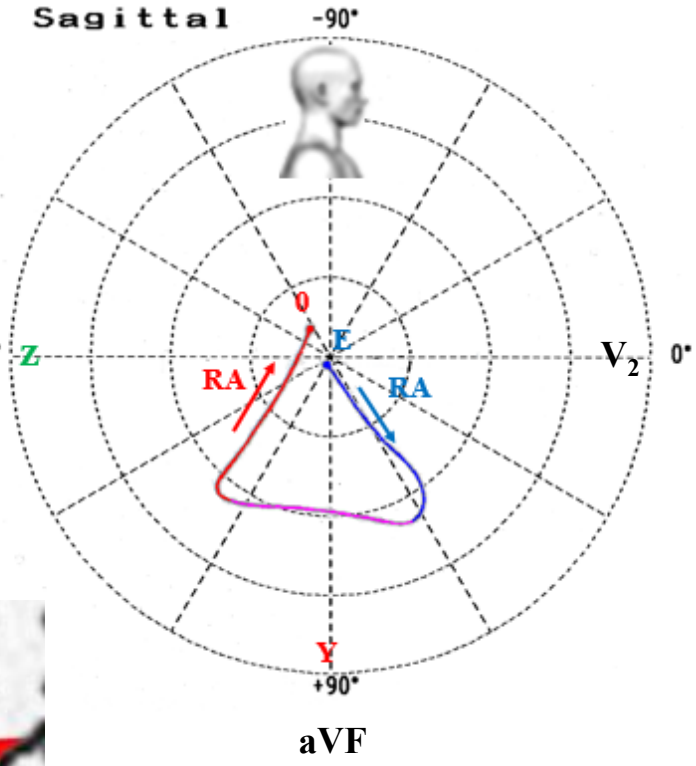
Normally, the angle formed by the maximum vectors of the QRS and T loop is usually less than <75°. In the present case it is very wide near 180°. Equivalent to ECG "Strain pattern of repolarization"

P-loop in the Right Sagittal Plane (the present case)

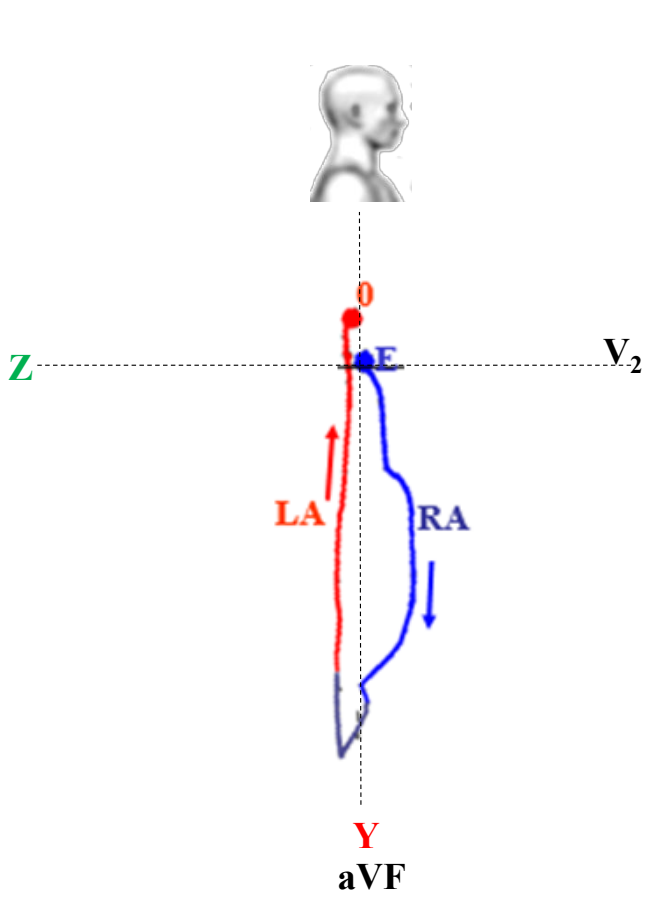








Normal P-loop in the Right Sagittal Plane



Charcteristic “Erlenmeyer-like shape” (in the form of an inverted cone) indicative of **biatrial enlargement**

Characteristics of the T loop regarding morphology, magnitude of maximal vector, rotation, recording velocity of efferent and afferent limbs, location and QRS/T angle

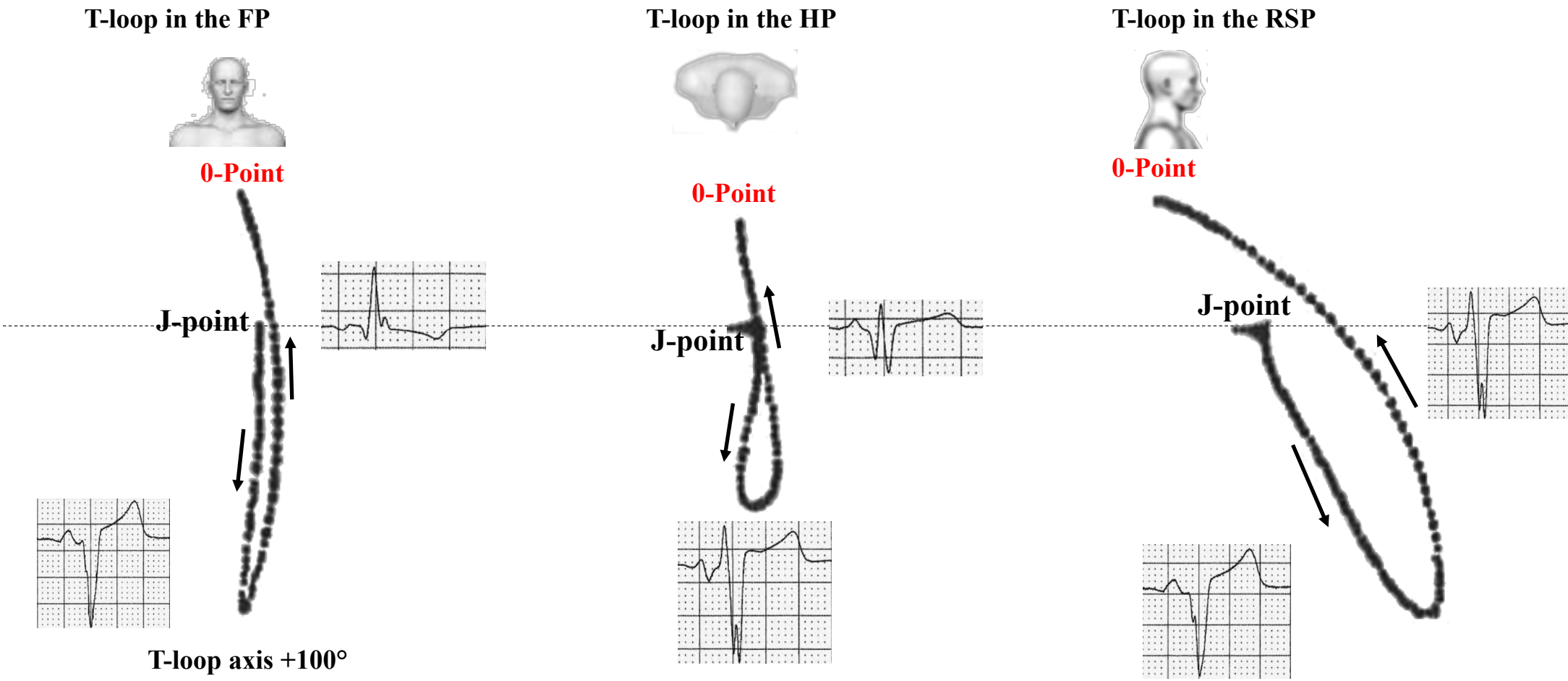
1) **Morphology:** it tends to be elliptic; elongated or elliptical (fusiform) and eventually linear;
2) **Formation:** composed by a centrifugal or efferent limb of slower inscription and a the afferent limb of faster inscription (comets more separated from each other). The T-loop begins at J-point and ends at . 0 point
3) **Magnitude of maximal T vector:** this is obtained from the **0** point up to the farthest point of the T-Loop. The maximal normal magnitudes in the three planes are: FP: ≤≤0.75 mV.; HP: ≤0.75 mV. Sagittal planes (RSP and LSP): ≤0.70 mV.
3) **Rotation:**

   FP: variable: clockwise or counterclockwise.

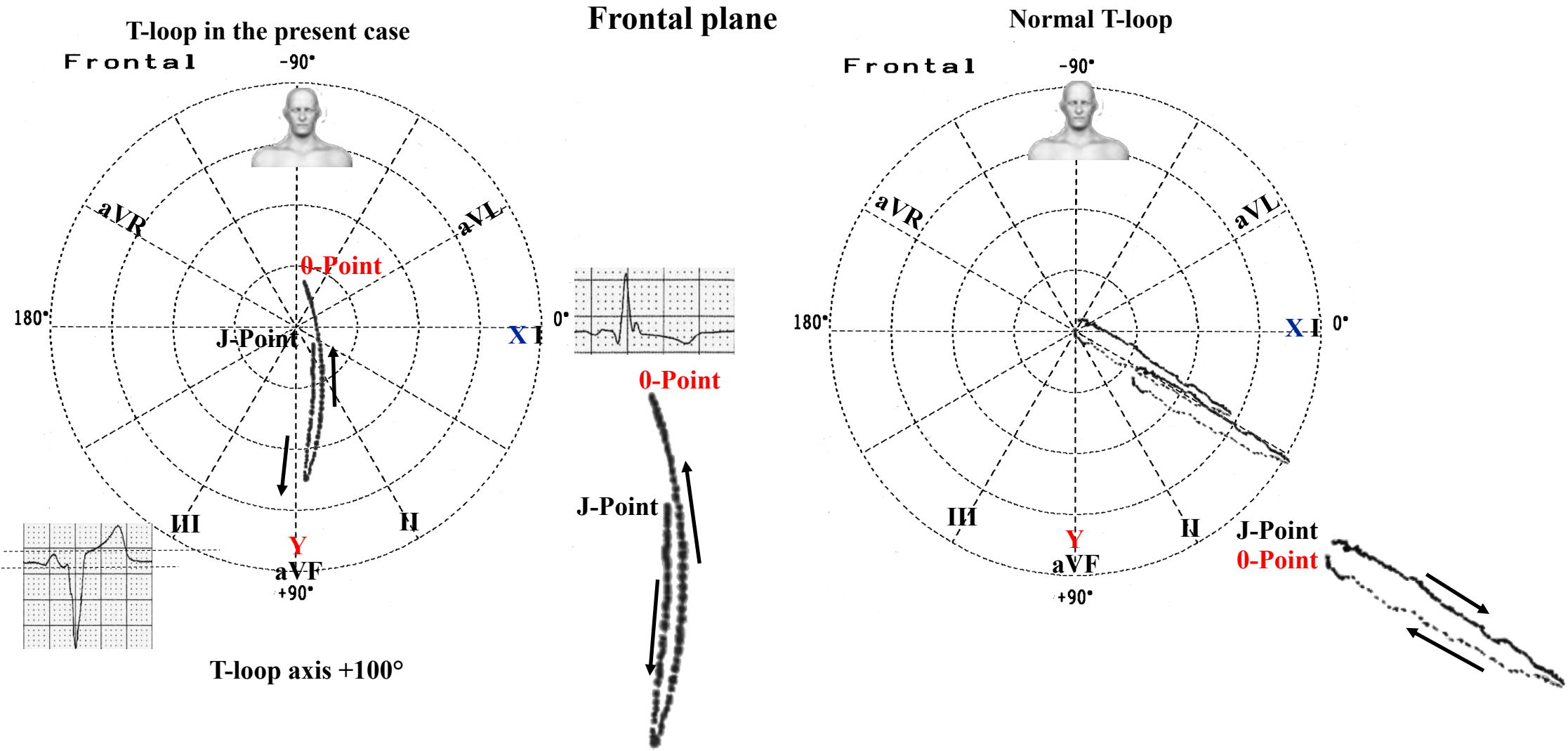
   HP: counterclockwise exclusively. Clockwise rotation in this plane indicates heart disease.

   RSP: clockwise. LSP: counterclockwise.

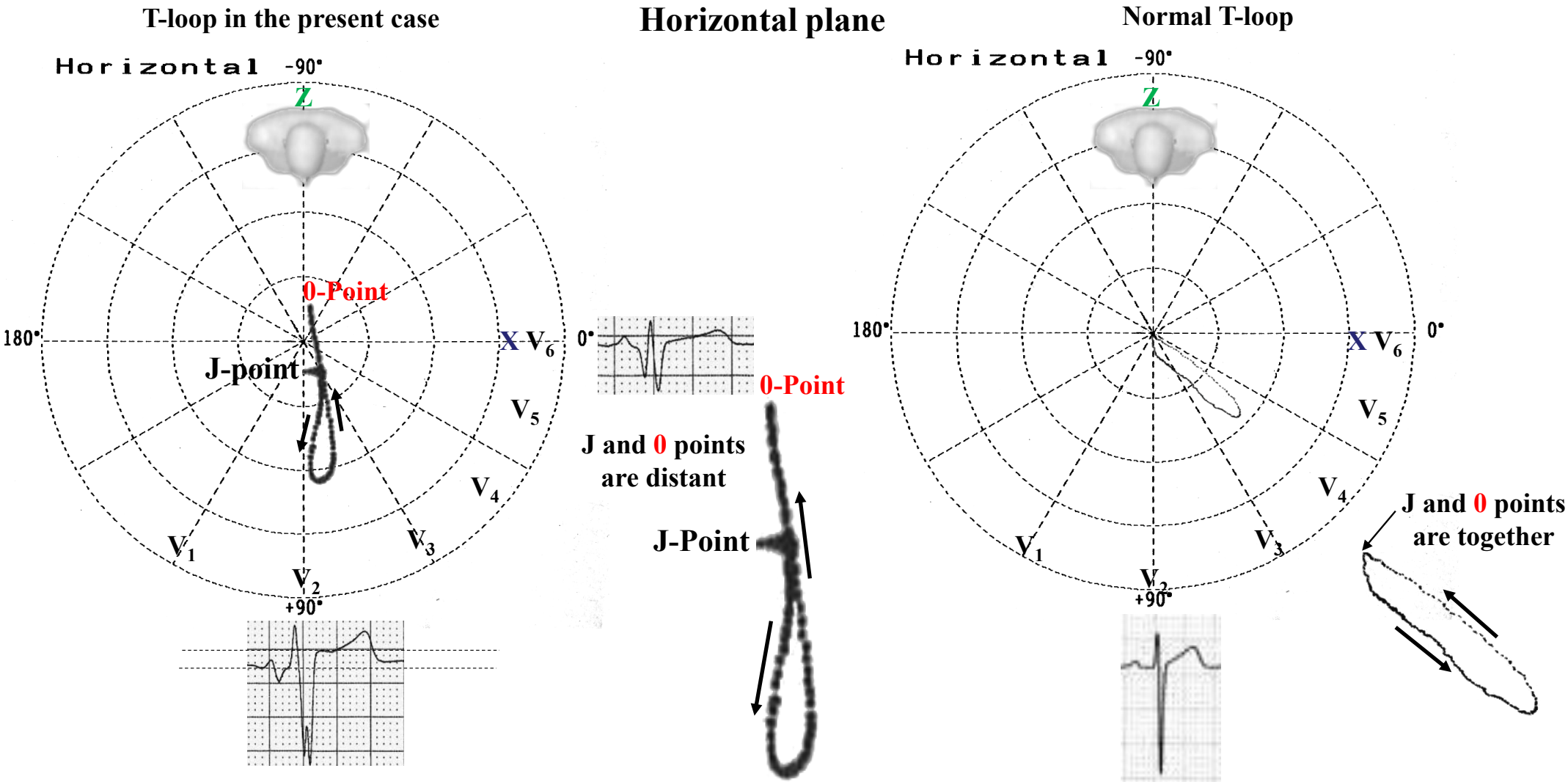
4. **Velocity of recording of its efferent and afferent limbs**: the efferent limb is always recorded more slowly than the afferent one;
5. **Localization:** usually, left and inferior, and to the front in adults. FP: in left inferior quadrant.; HP: in left anterior quadrant.; RSP: in anteroinferior quadrant.
6. **Spatial angle QRS-T (SA):** It is the angle formed by the maximum vectors of the QRS and T-loop. Even variable is usually less than <75°. Usually smaller in FP than in PH. In PF and PS large variations of this angle can be observed. The spatial QRS-T angle (SA) is derived from a VCG, which is a three-dimensional representation of the 12-lead ECG (ECG) created with a computerized matrix operation. The SA is the angle of deviation between two maximum QRS and T vectors. The spatial QRS axis representing all the electrical forces produced by ventricular depolarization(QRS-loop) and the spatial axis T-loop representing all the electrical forces produced by ventricular repolarization (**Voulgari 2009**)



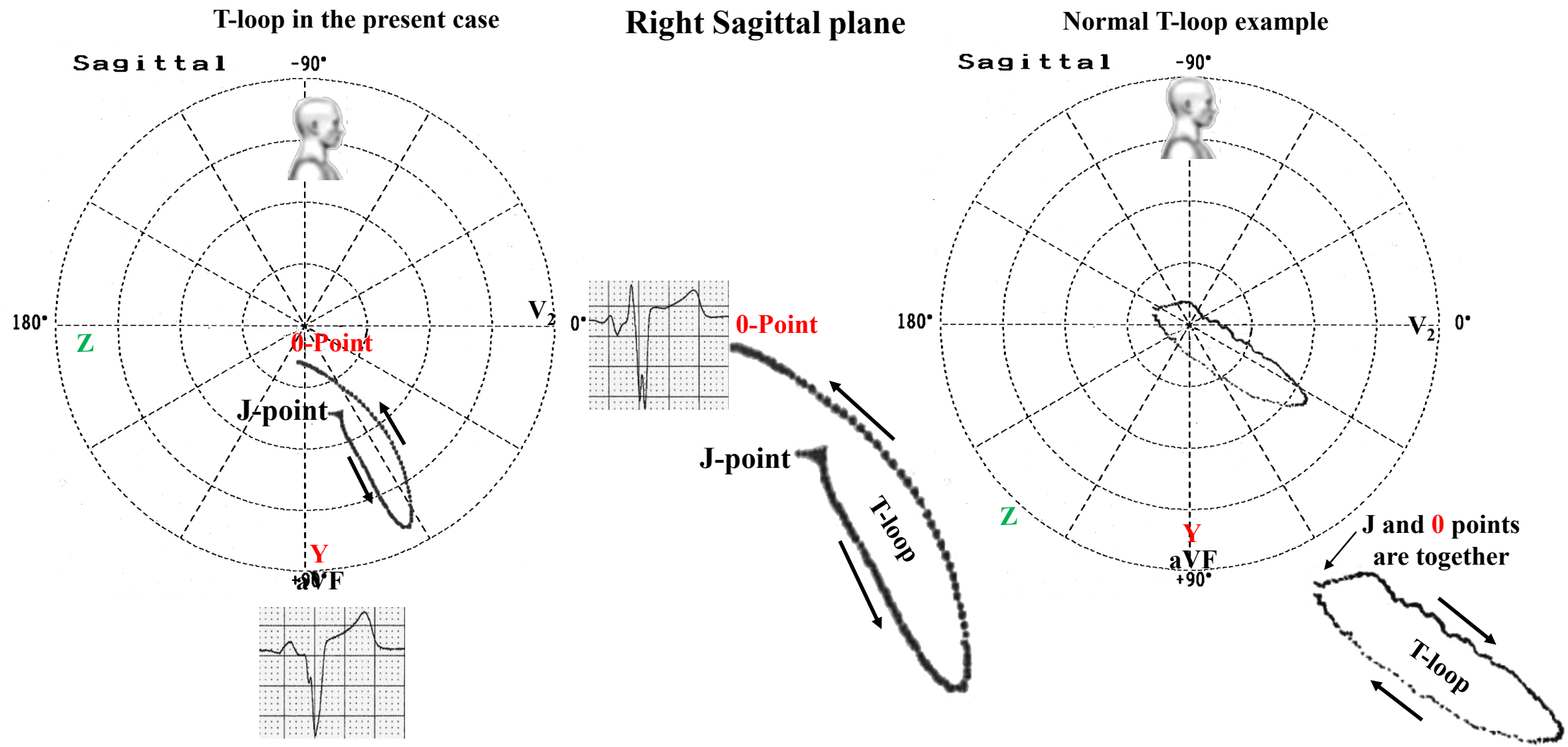
The J and 0 points are very distant in the present case, indicating the presence of elevation or depression of the ST segment in the 3 planes. Acute MI (STEMI), Coronary vasospasm (Printzmetal's angina), left ventricular aneurism, pericarditis, early repolarization pattern, eary repoarization syndrome, Brugada syndrome, idiopathic ventricular fibrillation, congenital SQTS, LBBB, LVH, Ventricular paced rhythm, raised intracranial pressure, acute pulmonary embolism, hyperkalemia, sodium channel blocking drugs, following electrical cardioversion, cardiac tumors, myocarditis, pancreas or gallbladder disease.



Both T-loops have the efferent limb of slower inscription and a the afferent limb of faster inscription, the present case has CCW rotation and normal T-loop CW rotation, the magnitude of maximal T vector is > 0.70mV in the present case and ≤0.70 mV in the normal T-loop, and the J and **0 points** are very distant in the present case, indicating the presence of elevation or depression of the ST segment. Under normal conditions and in the absence of the early repolarization pattern both J and **0** points are together or very close each other such as the normal T.



Both T-loops have the efferent limb of slower inscription and the afferent limb of faster inscription, both have CCW rotation, the magnitude of maximal T vector is > 0.70mV in the present case and ≤0.70 mV in normal T-loop, and the J and 0 points are very distant in the present case, indicating the presence of elevation or depression of the ST segment. Under normal conditions and in the absence of the early repolarization pattern both J and 0 points are together or very close each other.



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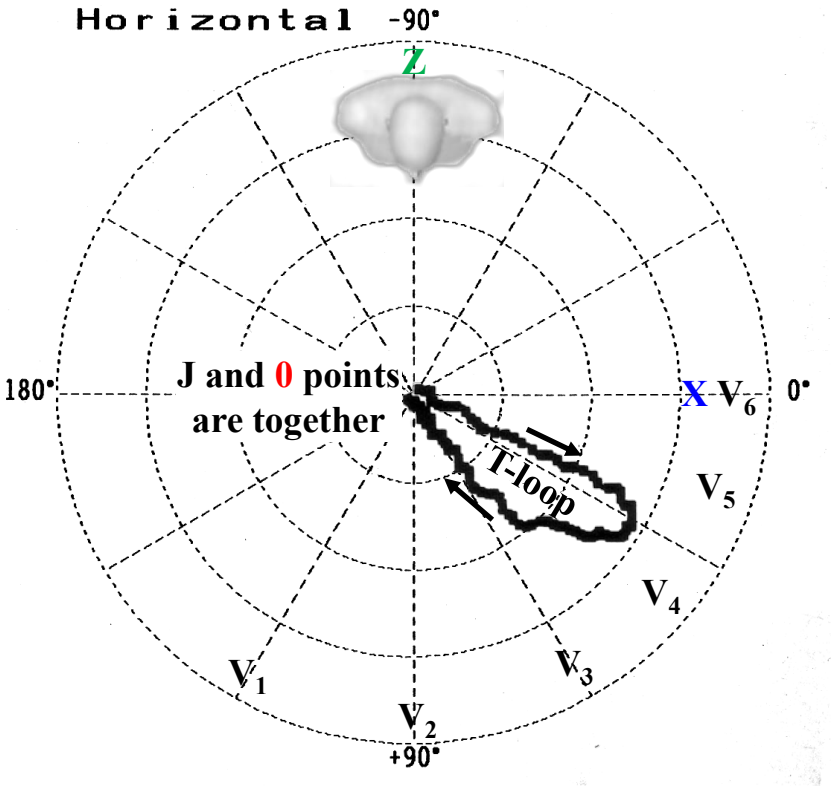
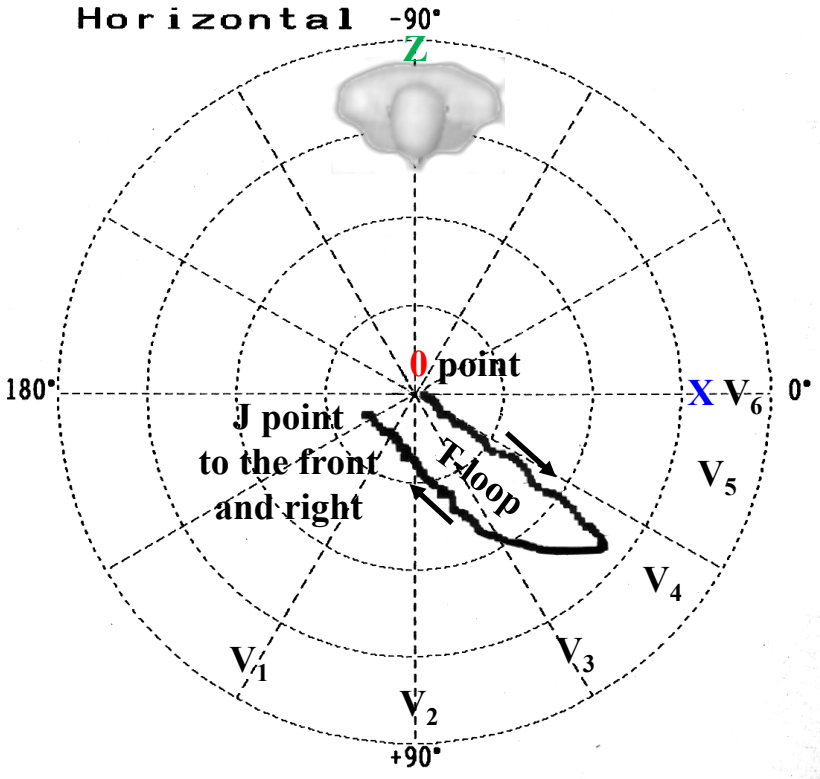
When ST Segment is not elevated or depressed the J-Point and 0-Point are coincident



When ST segment is elevated or depressed, the J and 0 points do not coincident



Normally the distance between both J and 0 points does not exceed 0.1mV, with exception of early repolarization pattern. In pathological situation, J and 0 points are very distant each other, such as ST segment elevation MI, pericarditis, early repolarization pattern/ syndrome, Brugada syndrome, idiopathic ventricular fibrillation, congenital short QT syndrome and others.

ECG diagnosis conclusion

1) **Left atrial enlargement (LAE):** only in the last ECG(2017) P duration > 110ms, (≥ 120 ms) , positive Morris index (**Morris 1964**): P terminal force in lead V_1 (PTFV1.) ≥ negative than 0.04 mm/s Greater than 0.03 mm/s: product of the duration of the final negative component (duration expressed in seconds)
2) **Righ atrial enlargement (RAE):** The P-loop axis with tendency to right in FP (+ 75°) in concomitance of **LAE**.The maximal P-vector of P-loop > 0.2mV and
3) **Biatrial enlargement (BAE):** P-wave duration 120ms + P-axis in the frontal plane to right. Additionally, increase of anterior and posterior voltages of the P-loop in the Horizontal plane and characteristic P-loop with "Erlenmeyer-like shape" (in the form of an inverted cone) in the right sagittal plane of the VCG.
4) **Left ventricular hypertrophy:** Positive Romhilt-Estes point-score system (**Romhilt 1968**) +positive gender-specific Cornell voltage criteria (SV3 + RaVL >2.8 mV in men and >2.0 mV in women.)+ positive Cornell product criteria for LVH: (**Molloy 1992**) . It is the product of QRS voltage and QRS duration (QRS voltage-duration product); Cornell voltage-duration product (RaVL + SV3 with 6 mm added in women x QRS duration). Values ≥2440 mm/ms are diagnostic of LVH (Positive criteria of LVH CP≥2440 mm x ms). In the present case, the Sokolow-Lyon index is negative for LVH, which can be explained by the extensive fibrosis that decreases the QRS voltage/amplitude.
5) **Rigth ventricular hypertrophy:** R V_1 + S of V_6 ≥10.5 mm
6) **Biventricular hypertrophy**
7) **Nonspecific or Unspecified Intraventricular Conduction Disturbance (NSIVCD):** When QRS duration is ≥120 ms in adults following a normally conducted P wave or with atrial fibrillation but the morphology is not that of LBBB, RBBB, or WPW then the diagnosis of NSIVCD is made. If Q waves are present this can be called peri-infarction block. In the present case we have Q waves, but secondary to fibrotic scar.
8) **Wide fragmented QRS(W-f QRS:** W-fQRS included various RSR' patterns (QRS duration ≥120 ms), such as ≥1 R prime or notching of the R wave or S wave present on at least two contiguous leads of those representing anterior (V_1-V_4), lateral I, aVL, V_5-V_6, or inferior (II, III, aVF) myocardial walls. indicative of myocardial scar is a substrate for reentrant ventricular arrhythmias and is associated with poor prognosis. W-fQRS on a standard 12-lead ECG is a moderately sensitive and highly specific sign for myocardial scar in patients with known or suspected coronary artery disease. W-fQRS is also an independent predictor of mortality.**(Das 2008**)

Overview of Fabry Disease

Other names for this condition: Anderson-Fabry Disease, α-galactosidase A deficiency, angiokeratoma corporis diffusum, angiokeratoma diffuse, ceramide trihexosidase deficiency, GLA deficiency and hereditary dystopic lipidosis, X-linked lysosomal storage disorder

Fabry disease (FD) is an X-linked lysosomal disorder that leads to excessive deposition of neutral glycosphingolipids in the vascular endothelium of several organs and in epithelial and smooth muscle cells. Progressive endothelial accumulation of glycosphingolipids accounts for the associated clinical abnormalities of skin, eye, kidney, heart, brain, and peripheral nervous system.

When young patients present with signs and symptoms of a stroke, along with a history of skin lesions, renal insufficiency or failure, and heart attacks, FD is a consideration.

Incidence: estimated incidences ranging from as high as 1 in 40 000 live male births to 1 in 117 000 live male births (**Meike 1999; Desnick 2001**). This disorder also occurs in females, although the prevalence is unknown. Milder, late-onset forms of the disorder are probably more common than the classic, severe form. FD is uncommon, although research suggests that FD mutations may be more frequent than previously thought in cryptogenic stroke patients. However, the patients studied invariably had other signs of FD, including proteinuria and acroparesthesias.(**Altarescu 2005**)

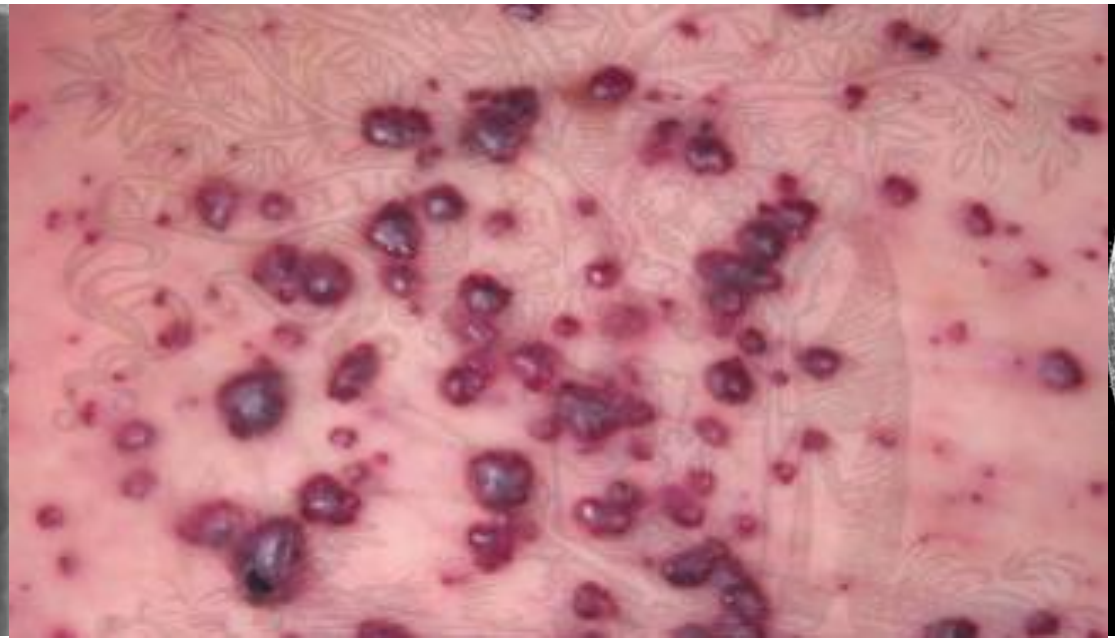
The diagnosis of FD has considerable implications regarding treatment, management, and counseling. Specifically, physicians may be alert to the involvement of other organs besides those of the central nervous system (CNS), thus making early intervention possible. With early identification, counseling and prenatal diagnosis may be offered to family members.(**Eng 2005; Inoue 2013**)

History

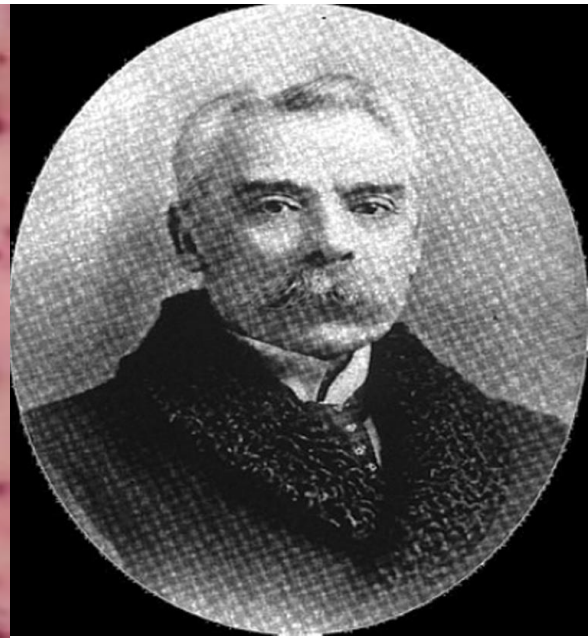
The first descriptions of FD were made in 1898 by two dermatologists working independently of each other, William Anderson in England. (**Anderson 1898**) and Johannes *Hubert* Fabry (**Fabry 1898**) described patients with "**angiokeratoma corporis diffusum**", the red–purple maculopapular skin lesions that are now recognized Germany characteristic feature of the disorder (**Hulkova1995; Cantor 1998; Becker 1975**.).Both also mentioned the presence of proteinuria. William Anderson, who trained at St Thomas' Hospital in London, first saw his patient in 1897, and described the dermatological symptoms without commenting on the possible cause. Johannes Fabry, who studied dermatology at the University of Bonn, also saw his first patient in 1897. The patient was 13 years of age at the time, and 4 years previously had developed cutaneous eruptions in the hollow of his left knee, which spread to the left thigh and trunk. It was suggested that the disease might represent a form of nevus or developmental defect. In 1898 Fabry described a 13-year-old patient affected by nodular purpura and subsequent albuminuria and he classified this clinical case as angiokeratoma corporis diffusum. In the same year Anderson presented the clinical case of a patient aged 39 with angiokeratomas, proteinuria, fingers deformity, varicose veins and lymphedema and he suggested this was a case of systemic disorder. In the first

ten years of the 20th century other similar cases were described: in the 1912, Madden illustrated the clinical case of a young Egyptian patient with diffuse angiokeratoma; later, in 1915, Fabry reproposed this condition as "Angiokeratoma corporis naeviforme. Four decades later Maximiliaan Ruiter concluded that angiokeratoma corporis diffusum is the cutaneous manifestation of an inherited systemic internal disease. In 1947 Pompen began to suspect that the Anderson - Fabry disease was “familial”, after the clinical case of two brothers died of the same disease. In 1947 autopsy findings of two cases who died from uraemia revealed sclerosis of glomeruli. At this time the presence of a thesaurismosis was also considered. The first renal needle biopsy in 1958 showed vacuolation and distension of the cells of the glomerular tufts and distal tubules suggestive of a storage disorder. The ability to concentrate the urine was also impaired in these patients. Sweely und Klionsky in 1963 demonstrated that the major storage component is a trihexoside.(**Gaggl 2016**) As of 1967 Roscoe Brady described the deficiency of the enzyme ceramidetrihexosidase/-galactosidase A characteristic in patients with FS. Right in 1964 the clinical features of the main two phenotypes of the disease, the classical form and the atypical variants, were already described.

Johannes *Hubert* Fabry
1. Jun 1860 in Jülich; † Jun 29 1930 in Dortmund)



Angiokeratoma corporis diffusum - the red–purple maculopapular skin lesions



William Anderson
(18 December 1842 – 27 October 1900)
English surgeon and dermatologist

Prevalence

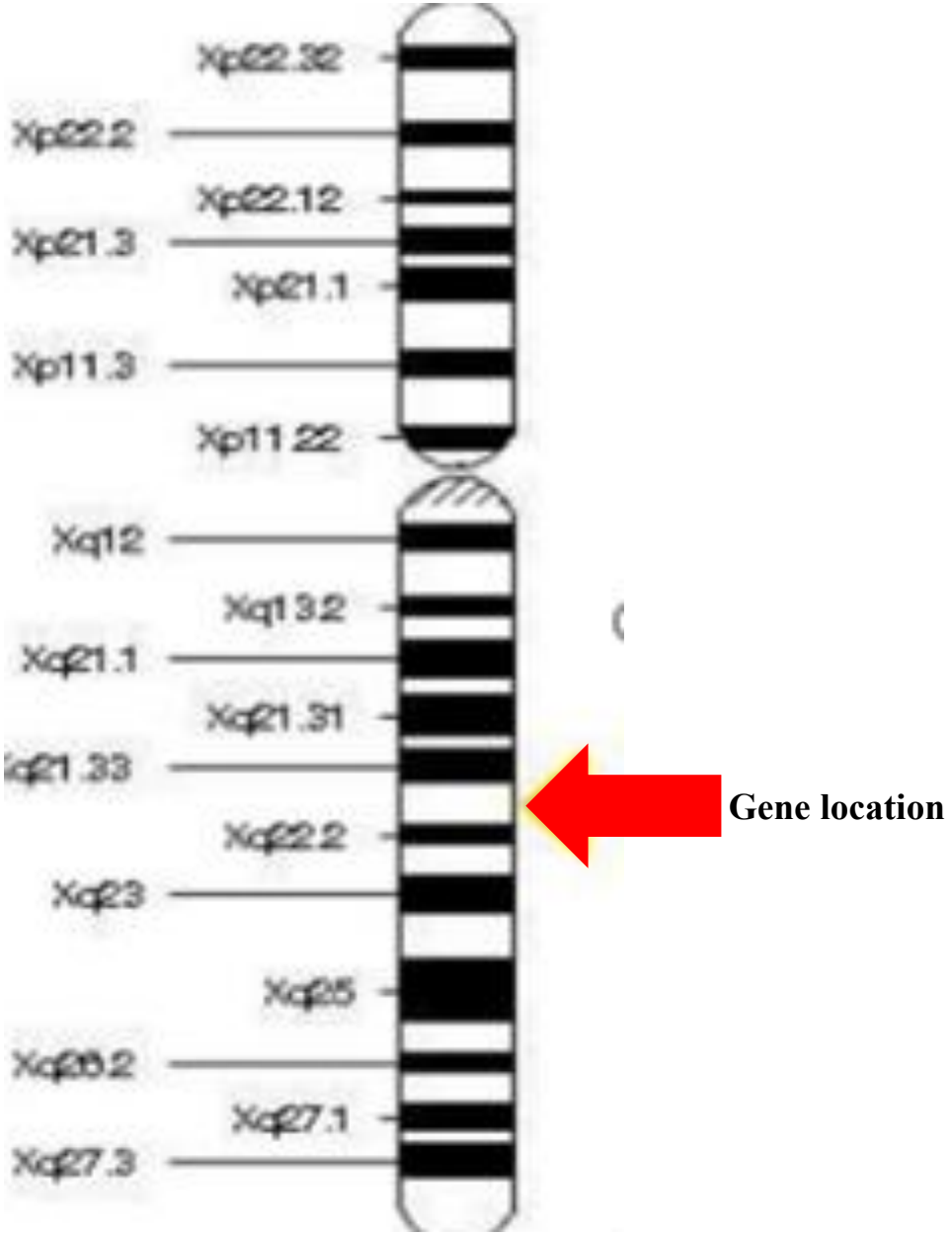
The prevalence of FD has been previously estimated to be 1 per 40,000 people. Most of the patients are white, but it is also found in African Americans and in persons of Hispanic or Asian descent.

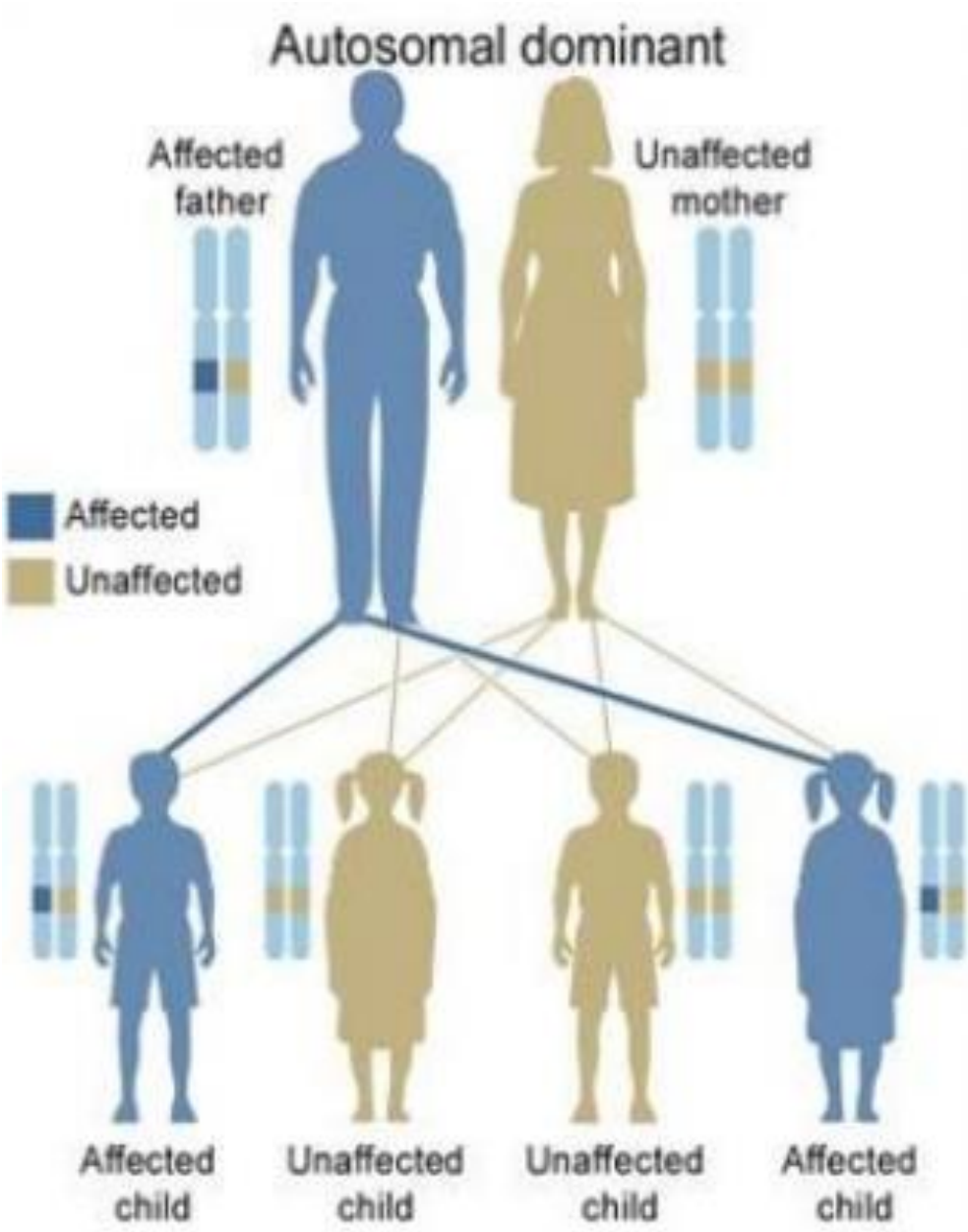
A prospective, multicenter study of cryptogenic strokes from Germany suggested that the prevalence of Fabry disease could be as high as 1.2%.(**Rolfs 2005**) This would mean that the prevalence rate is higher than that for mutations of factor V Leiden.

Genetic changes

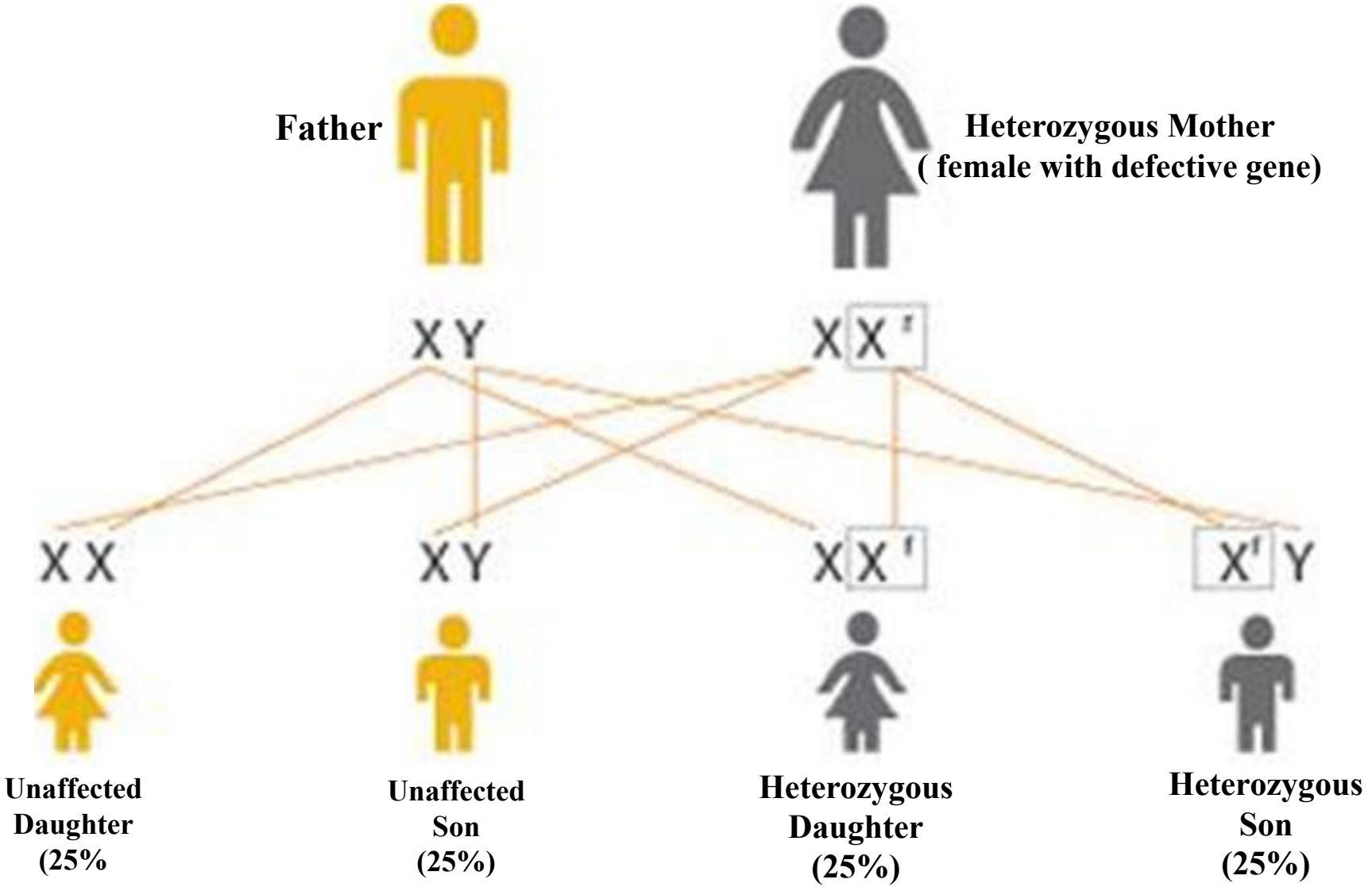
FD is caused by mutations in the *GLA* gene. This gene provides instructions for making an enzyme called α-galactosidase A. This enzyme is active in lysosomes, which are structures that serve as recycling centers within cells. α-galactosidase A normally breaks down a fatty substance called globotriaosylceramide. Mutations in the *GLA* gene alter the structure and function of the enzyme, preventing it from breaking down this substance effectively. As a result, globotriaosylceramide builds up in cells throughout the body, particularly cells lining blood vessels in the skin and cells in the kidneys, heart, and nervous system. The progressive accumulation of this substance damages cells, leading to the varied signs and symptoms of FD result in an absence of α-galactosidase A activity lead to the classic, severe form of FD. Mutations that decrease but do not eliminate the enzyme's activity usually cause the milder, late-onset forms of FD that affect only the heart or kidneys.

Inheritance pattern: This condition is inherited in an X-linked pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome(Xq21.3-q22), one of the two sex chromosomes in each cell. In males (who have only one X chromosome), one altered copy of the *GLA* gene in each cell is sufficient to cause the condition. Thhe DNA mutations which cause the diseae are X-linked dominant with incomplete penetrance in heterozygous females. Because females have two copies of the X chromosome, one altered copy of the gene in each cell usually leads to less severe symptoms in females than in males, or rarely may cause no symptoms at all. The condition affects hemozygous males(i.e. all males), as well as homozygous, and in many cases heterozygous females. Genomic coordinates(GRCh37): X:100,652,778-100,663,000Unlike other X-linked disorders, FD causes significant medical problems in many females who have one altered copy of the *GLA* gene. These women may experience many of the classic features of the disorder, including nervous system abnormalities, kidney problems, chronic pain, and fatigue. They also have an increased risk of developing high blood pressure, heart disease, stroke, and kidney failure. The signs and symptoms of FD usually begin later in life and are milder in females than in their affected male relatives. A small percentage of females who carry a mutation in one copy of the *GLA* gene never develop signs and symptoms of FD.


Xp22.32
Xp22.2
Xp22.12
Xp21.3
Xp21.1
Xp11.3
Xp11.22
Xq12
Xq13.2
Xq21.1
Xq21.31
Xq21.33
Xq22.2
Xq23
Xq25
Xq26.2
Xq27.1
Xq27.3
Gene location


Autosomal dominant
Affected father
Unaffected mother
Affected
Unaffected
Affected child
Unaffected child
Unaffected child
Affected child

Segregation of X-linked Trait (Heterozygous Mother)



Morbidity and Mortality in Fabry Disease

Because FD affects several organ systems, morbidity and mortality are related to the combined effects of renal failure, heart failure, and stroke .The rate of stroke is reportedly 10-24%. However, this rate may be an overestimation, because the data are from tertiary referral centers. About 70% of cerebral infarcts are in the vertebrobasilar circulation; most of the remainder involves the perforating arteries in the anterior circulation.

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Intracranial hemorrhage is rare. Recurrence of cerebrovascular events is common, and lesion load (measured radiologically) increases with advancing age.

Sex and Age Predilections

FD follows X-linked genetics, manifesting predominantly in men. However, female heterozygotes also present with clinical and laboratory features of FD. Different investigators have reported that the mean age of hemizygotic men at the onset of symptomatic stroke is 29-38 years. The mean age of female heterozygotes at the onset of symptomatic strokes is 40-43 years. Other symptoms and signs of FD may be present in male children as young as age 9 years and in females by age 13 years.

Etiology and Pathophysiology

Deficiency of α-galactosidase A activity leads to lysosomal accumulation of glycosphingolipids, predominantly the cerebroside trihexosides. Diffuse, abnormal accumulation of glycosphingolipids occurs in all tissues, producing swelling and proliferation of endothelial cells. Abnormal reactivity of endothelial cells, with changes in blood flow in the brain and in peripheral vessels, has been documented on magnetic resonance imaging (MRI), positron emission tomography (PET) scanning, transcranial Doppler imaging (TCD), and plethysmography.(**Wilcox 2004.**) Disturbances in intraluminal pressure and angioarchitecture are thought to lead to dilatation, angiectasia, and dolichoectasia. The vertebrobasilar arteries appear particularly susceptible to dilatational arteriopathy. Small penetrating arteries frequently become narrowed and occluded. Cerebral infarcts result from direct vascular occlusion or stretching and from the distension of branches of the dolichoectatic parent vessels. Decreased levels of thrombomodulin and increased plasminogen activator inhibitor have been found in FD patients, thus suggesting that a prothrombotic state may be one cause of stroke in these patients. The precise cause of increased incidence of stroke has not been established.

Findings that could contribute to this increased risk include abnormal nitric oxide and non-nitric oxide dependent endothelial dilation and abnormal endothelial nitric oxide synthase (eNOS) activity leading to aberrant vascular functioning. Paradoxical hyperperfusion is seen in strokelike lesions whose significance is not known.(**Hilz 2004**)

Nonischemic, compressive complications of dolichoectatic intracranial arteries include hydrocephalus, optic atrophy, trigeminal neuralgia, and cranial nerve palsies.

Diagnostic considerations

Patients with FD seek care from a variety of specialists, usually because of the involvement of a number of organ systems.

The diagnosis and treatment of FD can be challenging. The signs and symptoms of FD may be nonspecific, and if manifestations in different organs are considered in isolation, the unifying diagnosis may be missed. .(**Eng 2007; Metha 2004**)

The National Society of Genetic Counselors recommends testing for any patient with a family history of FD or corneal verticillata ("whorls") on slit lamp exam. In the absence of these factors, it is recommended to test patients who have any of the following two features: (**Laney 2013**).

I. Dermatologic features: Decreased sweating (anhidrosis, hypohidrosis, or hyperhidrosis), reddish-purple skin rash in the bathing trunk area (angiokeratomas), Raynaud's disease-like symptoms, reduction of body hair density, xerophthalmia(lacrimal glands),
II. Pain: Extremities or GI tract(Acroparesthesia)
III. Ocular manifestation: Keratopathy, cataracts, papilloedema, macular edema, optical atrophy. "Tortuositas vasorum" (venous vascular aneurismal dilatation, typically on the inferior bulbar conjunctivae
IV. Personal and/or family history of kidney failure: proteinuria
V. Personal or family history of "burning" or "hot" pain in the hands and feet, particularly during fevers (acroparesthesias), fatigue, neuropathy, tinnitus, vertigo, nausea, chemical imbalaces, diarrheia and stroke of unknown etiology in young adulthood
VI. Personal or family history of exercise, heat, or cold intolerance
VII. Patients with sporadic or non-autosomal dominant (no male-to-male) transmission of unexplained cardiac hypertrophy
VIII. If the family history suggests a diagnosis of FD, genetic testing and counseling should be offered to all family members, regardless of their sex.
IX. The presence of FD symptoms in boys and girls of any age is a strong indication for treatment initiation.

Recommended assessment in children and adolescents patients with Fabry disease (Hopkin 2016)

	Assessment(s)	Schedule of monitoring
General	Complete physical examination including evaluation of quality of life, school performance, level of depression anxiety Genotyping Genetic counseling	At diagnosis and yearly At diagnosis At diagnosis and as needed during maturity
Kidney	Measured GFR(preferred) eGFR to be calculated using age-appropriate formulae (abbreviated Schwartz formula for patients aged, < 18 years Urine test to detect albuminuria/creatinine ratio Kidney biopsy	At diagnosis an regular intervals (at least annually) If clinically indicated; can be a useful tool to guide management
Heart	Blood pressure and cardiac rhythm Echocardiogram Electrocardiogram Cardiac MRI Holter	Every clinic visit Diagnosis and every 2 years Starting at age 10 years, and as clinically indicated. No routine studies are recommended(maybe useful in detection of latent fibrosis). Carried out if an abnormal rhythm is suspected or palpitations are reported: if arrhythmias detected then more frequent. Detailed rhythm surveillance should be instituted.
Central nervous system	MRI	No routine studies are recommended. Perform promptly if a pediatric patient experiences any neurological change that could potentially relate to stroke or transient ischemic attack.

	Assessment(s)	Schedule of monitoring
Neuropathic pain	Pain evaluation and history Pain measurement scale such as the Neuropathic Pain Symptom inventory or Pediatric Brief Pain Inventory Fabry-specific Pediatric Health And Pain Questionnaire	
Gastrointestinal tract	Medical history focusing on Bowel habits. Nausea. vomiting, weight gain, and diet Radiographic or endoscopic evaluation may be helpful to exclude non Fabry-related causes of sever abdominal pain	At diagnosis an at least annually

Cardiac manifestations

Cardiac involvement is common in FD, both in hemizygous men and heterozygous women, and is one of the three major causes of morbidity and mortality. Cardiac hypertrophy associated with depressed contractility and diastolic filling impairment is common. In addition, coronary insufficiency, atrioventricular conduction disturbances, arrhythmias and valvular involvement may be present. In patients with the atypical 'cardiac variant', the disease manifestations may be limited to the heart. Enzyme replacement therapy is now the treatment of choice for patients with FD, and preliminary results indicate promising effects not only on the renal and neurological manifestations of the disease but also on the cardiac manifestations. Cardiac involvement, together with end-stage renal disease and cerebrovascular events are frequent. Lysosomal storage occurs within almost all cardiac tissues and leads to clinically important symptoms, including dyspnea, chest pain, palpitations and syncope. These symptoms relate mainly to the development of progressive cardiac hypertrophy, conduction abnormalities and arrhythmias

Pathogenesis of the cardiac involvement

Storage of globotriaosylceramide (Gb3) is found in various cells of the heart, including cardiomyocytes, conduction system cells, valvular fibroblasts, endothelial cells within all types of vessels, and vascular smooth muscle cells(**Hulkova 1999**). In women, a mosaic pattern caused by random X-chromosome inactivation is observed (**Uchino**). Gb3 storage by itself, however, is unable to explain the observed level of cardiac hypertrophy, conduction abnormalities and other cardiac manifestations. Autopsy of an individual with FD who had an extremely hypertrophied heart revealed a relatively limited contribution (1–2%) of the stored material to the enormous increase in cardiac mass (**Elleder 1990**). It appears that storage induces progressive lysosomal and cellular malfunctioning that, in turn, activates common signaling pathways leading to hypertrophy, apoptosis, necrosis and fibrosis. Energy depletion was proposed as the common denominator in multiple metabolic and even sarcomeric hypertrophic cardiomyopathies (**Ashrafian 2003**) Energy depletion may also occur in FD, as suggested by the impairment in energy handling seen in skin fibroblasts (**Lücke 2004**) This might be further supported by the observation of a decreased ratio of ATP to inorganic orthophosphate, as has been shown by magnetic resonance imaging (MRI) studies in patients with sarcomeric hypertrophic cardiomyopathies (**Jung 1998**). In summary, the natural history of FD is characterized by progressive hypertrophy of the cardiac muscle, with increasing interstitial and fibrotic changes. This is consistent with observations of relatively mild diastolic dysfunction in early stages of the disease and with the late appearance of signs and symptoms that might be observed in patients with restrictive cardiomyopathy (**Linhart 2000**). The disease process is potentiated by absolute or relative ischemia, occurring even in the absence of significant epicardial CAD. This might be mainly due to the increased oxygen demand of the hypertrophied muscle, decreased capillary density, increased diastolic filling pressures that impair blood flow throughout the subendocardial layers in diastole, and to the infiltration of small arterioles and capillaries within endothelial cells and the smooth muscle layer (**Hulkova 1999; Cecchi 2003**). A similar pattern of progressive involvement is observed in the conduction system of the heart.

Early stages of the disease are associated with accelerated conduction, and late stages are characterized by progressive bradycardia and atrioventricular conduction defects, frequently necessitating pacemaker implantation (**Ikari 1992**).

Cardiac hypertrophy

LVH is the predominant finding, detected both by ECG and imaging techniques (echocardiography, MRI) In ECG LVH voltage criteria (Sokolow-Lyon) and strain pattern of repolarization in left leads) (**Linhart 2000; Kampmann 2002; Senechal 2003**.) Histologically, hypertrophy is characterized by the absence of myofibrillar disarray, lysosomal inclusions within myofibrils and vascular structures, and a variable degree of fibrosis depending on the stage of the disease (**Elleder 1990; Cantor 1998**). Although the absolute amount of Gb3 within cardiomyocytes is low, the heart contains the highest quantity of glycosphin-golipid compared with other organs (kidney, liver, skin) (**Elleder 1990; von Scheidt 1991**). The hypertrophy is progressive and occurs earlier in men than in women. Early stages are characterized by concentric remodeling, progressing later to overt hypertrophy. In a large majority of patients, the hypertrophy is symmetrical; however, asymmetric septal hypertrophy, indistinguishable from that considered typical for sarcomeric hypetrophic cardiomyopathies, may be present in about 5% of all cases (**Linhart 2001**). Asymmetric hypertrophy may be associated with marked LV outflow obstruction. In these patients, treatment by alcohol ablation may bring substantial relief and stabilization, in spite of the progressive nature of the hypertrophy (**Magage 2005**). Although early autopsy reports indicated important disease-related organ involvement in females heterozygous for FD, for a long time women were considered as carriers (**Burda 1967**). Due to random X-chromosome inactivation and the inability of cells expressing the wild-type allele to cross-correct the metabolic defect, affected women may express symptoms that are similar to those of hemizygous males (**Dobrovolny 2005; Morrone 2003**). In women symptoms are often milder, the onset delayed and disease progression slower than in men (**Kampmann 2002**). These observations have been confirmed by analysis of data from FOS – the Fabry Outcome Survey – in untreated patients, which shows the delayed onset of hypertrophy in females.

Ischemia and coronary events

Traditional descriptions of FD report a high frequency of ischemic events and myocardial infarctions (MIs). Data from the FOS database, however, suggest a low incidence of proven MIs. By October 2005, the FOS database included 752 patients (393 heterozygous women and 359 hemizygous men). Only 13 MIs were reported, representing a prevalence of <2%. On the other hand, angina and chest pain are frequent, being reported in FOS by almost 23% of females and 22% of males. This, together with frequently suggestive ECG patterns, including ST segment depressions and T-wave inversions, might be the cause of miss-diagnosis of either acute or subacute MI (**Becker 1975**). In addition, anginal pain and ECG changes are more frequent in patients with LVH, in whom minor. increases in markers of cardiac necrosis are possible. Epicardial coronary arteries, however, are only rarely occluded. As shown by Kalliokoski and Elliott, patients with FD have a significantly reduced coronary flow reserve **(Kalliokoski 2005; Elliott. 2006).** This might be due to endothelial infiltration and dysfunction, potentiated by the increased oxygen demand of

the hypertrophied ventricle and further aggravated by elevated diastolic filling pressures. In some cases, vasospasms may contribute to the anginal symptoms (**Ogawa 1996**.) Most patients with FD who are investigated for chest pain have patent large coronary arteries. A history of revascularization due to the presence of stenotic lesions was reported in the FOS database in only five cases, representing a prevalence of <1%. However, as underlined by the case report by Schiffmann and co-workers, the risk of death due to CAD should not be underestimated (**Schiffmann 2006**). In addition to the infiltrative changes within the endothelial and muscular layers of arteries, patients with FD often accumulate a large number of risk factors for atherosclerosis, including high levels of blood lipids, hypertension and renal insufficiency. Another aggravating factor might be the pro thrombotic state associated with the endothelial dysfunction (**DeGraba 2000; Hulkova**).

Electrophysiological abnormalities and arrhythmias

In most patients with FD, resting ECG patterns are perturbed. Besides high voltage and repolarization changes, a short PR interval is frequently found (**Kampmann 2002**.). The shortening is due to accelerated atrioventricular (AV) conduction (**Pochis 1994**). However, as in other lysosomal and glycogen storage diseases, pre-excitation with accessory pathways may also be present in patients with FD (**Murata 1999; Arad 2005**). With disease progression, conduction system dysfunction occurs, leading to bundle branch and AV blocks of varying degrees, requiring pacemaker implantation. In some patients, a pacemaker is needed due to symptomatic bradycardia, as progressive sinus node dysfunction is relatively frequent. Palpitations and arrhythmias are common complaints in patients with FD. The most frequently encountered rhythm abnormalities include supraventricular tachycardias, atrial fibrillation and flutter. NSVT, however, were detected by 24-hour Holter monitoring, and cases of fatal malignant arrhythmias resistant to an implantable cardioverter defibrillator(ICD) have been reported (**Shah 2005; Eckart 2000**). Ventricular arrhythmias were found mostly in very advanced stages of the disease. Studies showing the high incidence of NSVT on Holter monitoring support the regular use of this method to identify high-risk individuals who may benefit from ICD implantation.

Valvar involvement

Valvular disease in patients with FD is due, in part, to infiltrative changes within valvar fibroblasts. Although pulmonary valvar involvement has been reported, valvular changes are found almost exclusively in the left heart valves, probably due to the higher hemodynamic stresses in the left side of the heart (**Matsui 1977; Linhart 2001**). This results in valvar thickening and deformation.

In original reports, the prevalence of mitral valve prolapse was overestimated, probably due to the different diagnostic criteria used (**Desnick 1976**). Subsequent reports confirmed the existence of mitral valve prolapse, but with a lower prevalence (**Linhart 2000; Kampmann 2002**). Valvar regurgitant lesions are usually mild to moderate and only rarely require surgical correction (3 cases out of 752 patients in FOS). At the level of the aortic valve, root dilation may contribute to valvar dysfunction and has been reported repeatedly, particularly in advanced stages of the disease (**Goldman. 1986**).

Clinical symptoms **Patient History**

The predominant symptoms of cardiovascular involvement include dyspnea and chest pain. In most patients, both symptoms are related to LVH. The dyspnea is mainly caused by diastolic dysfunction, although valvular regurgitation and/or systolic LV dysfunction may be the cause in some cases. Anginal pain usually occurs even in the absence of stenotic coronary lesions, due to an increase in oxygen consumption and a decrease in coronary flow reserve. Coronary angiography should, however, be performed in patients with relevant anginal symptoms, as coronary stenosis may be encountered.

The third most frequent complaint includes palpitations and proven arrhythmias. The high frequency of life-threatening ventricular tachycardia, and the potential benefits of implantable cardioverter defibrillators should encourage the investigation of symptomatic patients by 24-hour Holter monitoring.

Finally, syncope may occur in patients with FD. Cardiac causes of syncope include high degrees of AV blockade or, more rarely, severe dynamic obstruction of the LV outflow tract.

Analysis of FOS data has confirmed the high prevalence of cardiovascular symptoms among women. However, the age of onset was delayed compared with that in hemizygous men.

Hypertension occurs with increased frequency in patients with FD because of progressive renal impairment. Other traditional risk factors for stroke, such as diabetes, hypercholesterolemia, and smoking, may or may not be present in these patients. Because FD has an X-linked genetic inheritance pattern, the patient's family history may be positive for the condition.

Physical Examination

The diffuse involvement of different organ systems in FD leads to a number of abnormalities that can be discovered on physical examination.

Abundant punctate, nonblanching, dark red to blue-black clusters of ectatic blood vessels may be found just below the skin. The clusters develop in different parts of the body, although they are most commonly found in a bathing-trunk distribution. The clusters are known as angiokeratomas, although they are also referred to as angiokeratoma corporis diffusum universale. Lenticular opacities and vascular lesions of the conjunctiva and retina may be present. Cardiomegaly and rhythm abnormalities may be evident on chest palpation and auscultation.

Vague complaints of pain in hands and feet may be a presenting feature. These symptoms are called acroparesthesias, as they reflect the peripheral neuropathy that is a frequent manifestation of the disease. This pain may be both episodic and chronic. Acute episodes may be triggered by exposure to extremes of temperature, stress, emotion, and/or fatigue.

Late onset Cardiac variant

Early studies suggested that cardiac hypertrophy might be the sole or predominant manifestation of FD in a small number of male hemizygotes. Histopathological studies revealed Gb3 storage located almost exclusively in the heart (**Auray-Blais 2017**). These cases, described as cardiac variants, were distinguished by relatively high residual α-galactosidase A activity. In addition, some mutations have been shown to be associated almost exclusively with this type of involvement. Several studies have attempted to identify FD among patients with cardiac hypertrophy. An study by Nakao et al. identified seven unrelated patients with FD (3%) among 230 men with unexplained LVH (**Nakao 1995**). A particularly important observation was made by Sachdev et al, indicating that special attention should be paid to patients in whom unexplained LVH is diagnosed after 40 years of age. At this age, most male patients with FD have at least LVH, which is not necessarily present in younger patients (**Sachdev 2002**). The negative findings of Ommen et al (**Ommen 2003**) is an understandable result of population selection. As stated above, only about 5% of patients with FD have asymmetric septal hypertrophy, and even fewer have LV tract obstruction. Therefore, the probability that patients with FD would be identified when investigating individuals referred for septal myomectomy was *a priori* extremely low. The fact that diagnosing FD among individuals with LVH may be subject to chance is documented by the strikingly high prevalence of FD among women with unexplained LVH observed by Chimenti et al. These authors observed that cardiac dysfunction of FD reflects increased myocardial nitric oxide production with oxidative damage of cardiomyocyte myofilaments and DNA, causing cell dysfunction and death (**Chimenti 2015**) which contrasts with the negative result within the series explored by Arad and colleagues (**Arad 2005**).

Electrocardiographic main features (Namdar 2016)

1. PR interval minus P wave duration > 40 ms (**Namdar 2011**). Most importantly, shortening of the P-wave duration was found to be the main contributor to the shorter PQ interval and, while both P-wave and PR-interval duration differ significantly from healthy subjects, P-wave duration yielded a higher diagnostic performance (92% sensitivity and 80% specificity) (**Namdar 2011**).
2. Corrected PR interval <144 ms (**Namdar 2012**). In early stage patients had indeed shorter PR intervals as compared to age and heart rate-matched healthy controls, but PR intervals were mostly still within the "normal" range (i.e., 120–200 ms) and with similar mean values as in the former analysis (139 ± 29 vs. 131 ± 18 ms). Changes of the PR interval have been reported in case studies and observational data from registries and may be the result of different phenomena (**Weidemann 2005**). However, whether abnormalities in the PR-interval duration were of diagnostic value in patients with FD or if they correlated with specific clinical or echocardiographic findings remained unclear. As a matter of fact, a first study "demystified" ECG in FD and reported the relatively low prevalence (14%) of AV conduction abnormalities in a large cohort (N = 207) of patients newly diagnosed with FD, demonstrating that the short PR interval cannot be considered a robust and sensitive sign for the diagnosis of this disease. Clinical cardiac electrophysiologic case studies have specifically excluded accessory pathways as an underlying cause for the observed ECG changes in FD (**Kalliokoski 2005**). Of note, no significant differences in AV conduction comparing patients with and without LVH were found, suggesting that neither PR-interval shortening nor AV block showed any correlation with the severity of the cardiac involvement. These findings indicated that the duration of the PR interval has a low diagnostic yield for early recognition and assessment of disease in patients with a FD-related cardiomyopathy, leading further to a first systematic analysis of early ECG changes in patients without signs of LVH and diastolic dysfunction (**von Scheidt 1991**). Here, accelerated depolarization intervals (shortening of P-wave duration and QRS width),
3. The reported shorter QRS width further suggested that an enhanced conduction velocity might equally occur within the ventricles.
4. Increased repolarization duration (QT and QTc)
5. Pronounced repolarization dispersion (QTc dispersion
6. Prolonged Tpeak–Tend dispersion) could be shown in FD.
7. Cardiac disease is the chief cause of early death in these women. Many have palpitations, and 20% have arrhythmias. The most prevalent arrhythmias are supraventricular tachycardias, atrial fibrillation, and atrial flutter. Although VT has occasionally been reported in men with FD , VT has not been thought to be a typical finding in women. Indeed, Silva-Gburek et al found just one report of a heterozygous woman with NSVT that was detected during 24-hour Holter monitoring (**Silva-Gburek 2016**).

Furthermore, a recent study showed a normalization of the QTc interval, PR interval and, most interestingly, P-wave duration under enzyme replacement therapy along with a reduced disease burden, suggesting that the observed electrocardiographic changes might, at least to some degree, have a link to the Gb3 storage (**Elliott 2006**). While it has been shown for *glycogen* storage diseases that similar phenomena are *directly* caused by glycogen storage acting as independent conducting elements within the myocardial tissue in and around the atrioventricular node, none of the investigations could confirm the same for patients with FD so far (**Ogawa 1996**). It is further noteworthy that an accumulation in and around the AV node does not explain changes in P-wave duration giving rise to the question whether previous reports on PR-interval shortening alone in other storage diseases should be revisited with respect to this observation. These generated the hypothesis that ECG parameters may be of considerable help for an earlier recognition of patients, eventually earlier initiation of enzyme replacement therapy before otherwise irreversible organ manifestations occur and, last but not least, be useful as follow-up parameters during the treatment. However, as various ECG parameters change with macroscopic myocardial changes (QRS width and repolarization indices with LVH, P-wave alterations with LAE), an assessment of their value in the differential diagnosis of hypertrophic cardiopathies has been performed (**Schiffmann 2006**). As expected, mean left atrial size in FD patients with LVH was almost double when compared with early stage patients. Accordingly, these enlarged left atrial dimensions might have outbalanced presumable shorter PR interval and P-wave durations in FD patients and thus impaired their diagnostic value. To overcome this shortcoming, the authors chose PR interval minus P-wave duration in lead II as a more robust measurement for AV conduction. It turned out to have an even higher diagnostic performance for the recognition of Fabry disease as compared to the commonly used PQ interval. Furthermore, a two-step approach combining QTc duration with the above-discussed measure showed a high diagnostic performance for the differentiation of FD from amyloidosis, and a novel index based on these parameters proved very useful for the differentiation of the two entities FD and amyloidosis from hypertensive heart disease, familiar HCM, and LVH owing to significant aortic stenosis.

Value of the Electrocardiogram in Disease Staging Naturally, the thorough investigation of baseline ECG parameters and their diagnostic value in the recognition of early-stage and differentiation of late-stage FD patients begs the question whether these and possibly other parameters might have any value in disease *staging*.ECG changes in a large group of patients with FD in different disease stages have been investigated. Here, the main findings were ST- and T-alterations (ST-declines or elevation; T-wave inversion) giving a clue toward . Different mechanisms are considered to be involved in the pathogenesis of VTs particularly in the presence of fibrosis. While in ischemic cardiomyopathies, the main mechanism is assumed to be scar-based reentry, the arrhythmogenic substrate in non-ischemic cardiomyopathies has been demonstrated to be represented by an increased myocardial collagen content and regional fibrosis (**Shah 2005; Eckart 2000**).

Moreover, EPSs have revealed that patients with S-VT show a greater degree of myocardial fibrosis than patients without arrhythmias and that the basal ECG and intracardiac electrogram abnormalities corresponded very well to the site of origin of the these events (**Eckart 2000**). Accordingly, a number of such ECG abnormalities, invariably coming along with micro- and macroscopic myocardial changes, have been linked to potentially life-threatening reentrant ventricular arrhythmias (**Matsui 1977;Linhart 2001**) and shown to be prevalent not only in patients with overt LVH but also in an early stage of the disease (**von Scheidt 1991; Schiffmann 2006**). These and recently published data indicate that the observed ECG surrogates in conjunction with a fibrotic substrate may be associated with the increased propensity of FD patients to develop ventricular arrhythmias (**Desnick 1976**). Unfortunately, the prevalence of life-threatening arrhythmia in patients with FD is not well documented so far. This might be due the paucity of studies involving large populations. NS-VT has been reported to occur in 38% of men with FD .>50 years in a study with 78 consecutive patients. While none of these patients had evidence of CAD as an underlying cause, some already had advanced LVH(and possibly fibrotic areas) and might therefore have been susceptible to VTs (**Dobrovolny 2005**). Results from the International Fabry Outcome Survey with 714 patients depicted the prevalence of palpitations or documented arrhythmias (not further specified) as 15 and 21%, respectively, in untreated men and women. The average age of these two groups was 26 and 45 years, respectively. Although these numbers suggest that arrhythmias might occur earlier than the development of LVH, it is important to note that the prevalence of LVH even in these two groups was 33 and 21%, respectively (**Kampmann 2002**). However, an earlier analysis demonstrated that QTc prolongation and pronounced repolarization abnormalities are present before echocardiographic signs of LVH are detectable (**von Scheidt 1991**). These data indicate that conduction abnormalities do not exclusively occur as a result of the latter but may result from a FD-specific disease myocardial fibrosis. As a matter of fact, these alterations, mainly found in the lateral leads V5 and V6, fit very well with the region where late enhancement (a sign for focal fibrosis) in MRI can be seen first. ST/T-alterations have already been reported in patients with FD However, they have been rather misinterpreted as infarct associated lesions in the past since macrovascular coronary artery disease is very rarely encountered in these patients (**Kampmann 2005; DeGraba 2000**). While the detection of fibrotic areas by one single ECG parameter did not emerge feasible, it is nevertheless reasonable to state that replacement fibrosis is very unlikely when no ST- or T-alterations are observed (**Pochis 1994**). The importance of this finding is manifold. First of all, in “ECG negative” FD patients, the cost and time consuming process of a CMR tomography might not be necessary. Second, as the presence of fibrosis evidently plays a crucial role in terms of a higher incidence of VTs and poor prognosis in patients with ischemic and non-ischemic cardiopathies, these findings might have a major impact on further diagnostic and therapeutic strategies (**Murata 1999**). process and that the temporal as well as the causal interrelationship between the development of conduction abnormalities and/or arrhythmias and LVH with or without fibrosis remain unclear.

Chest Rx

Cardiomegaly may be readily evident on a chest radiograph.

Echocardiography may be indicated to investigate a possible source of emboli. Echocardiograms may reveal valvular abnormalities, ventricular hypertrophy, and flow abnormalities., increased papillary muscle (**Silbiger 2016**), end diastolic LV wall ≥ 12 mm, and LV wall is > 13 mm (**Matsui 1977**).

RVH is common in patients with FD(≈31% of cases FD) and correlates with disease severity and LVH. RVH, however, does not significantly affect RV systolic function: systolic tissue Doppler velocities (RV S_a, septal S_a, and lateral S_a, respectively). Patients with Fabry cardiomyopathy have better RV systolic function compared with those with cardiac amyloidosis with similar levels of RV thickness. The combination of low LV S_a values and normal RV S_a values might be helpful in the differential diagnosis of infiltrative heart disease. Compared with control subjects with cardiac amyloidosis, patients with Fabry cardiomyopathy showed better indices of RV systolic function (**Graziani 2017**).

Two-dimensional speckle strain imaging: Loss of base-to-apex in global and segmental longitudinal and circumferential strain CS gradient may be a specific LV deformation pattern of Fabry cardiomyopathy in patients with and without LVH (**Labombarda 2017**).

Laboratory Studies in Fabry Disease

Microscopic examination of urine may show lipid-laden epithelial cells.

Electrolyte imbalances reflecting renal failure may be seen.

When an acute stroke is suspected on clinical grounds, customary laboratory tests, such as determination of the complete blood count (CBC), electrolytes, prothrombin time, and activated partial thromboplastin time, should be ordered. A search for the etiology of the symptoms should commence. The level of globotriaosylceramide (Gb_3 or GL-3), a glycosphingolipid, may be elevated.

Enzymatic analysis performed by using plasma or leukocytes may show a deficiency of α-galactosidase A.

levels of Gb_3 and α-galactosidase A may be normal in female (heterozygote) FD patients. Therefore, genetic and/or molecular diagnosis is necessary to confirm Fabry disease if the disease is suspected based on clinical features of proteinuria and acroparesthesias that were invariably present in men and women with Fabry mutation and cryptogenic stroke. Men with FD mutation tend to have more clinical features when presenting with stroke.

Plasma lyso-Gb_3 level, and urinary analogue levels of lyso-Gb_3 at m/z (+16), (+34), and (+50) adjusted for gender and age had a positive association with the left ventricular mass index, and/or the Mainz Severity Score Index (**Auray-Blais 2017**).

Cardiovascular magnetic resonance (CMR) Magnetic resonance studies using gadolinium have provided new insights into the development of Fabry cardiomyopathy. In patients with LVH, such studies have demonstrated late enhancement areas, corresponding to myocardial fibrosis, occurring frequently within the midwall of the inferolateral basal segments(old Posterior). It appears that this finding characterizes late stages of LV involvement and is associated with decreased regional functioning, as assessed by strain and strain-rate imaging The RV also appears to be affected by storage and hypertrophy. However, the functional impact of right ventricular infiltration and hypertrophy is low, and right ventricular failure almost never complicates the course of the disease.

Diastolic dysfunction is a common feature of FD. In contrast to genuine restrictive cardiomyopathies, however, restrictive pathophysiology is found only rarely, mostly in extremely advanced stages of the disease that are associated with pronounced fibrosis. End-stage cardiac involvement may then present with restrictive pathophysiology. Today, the use of CMR is widespread in clinical practice. The increased need to evaluate of subtle myocardial changes, coronary artery anatomy, and hemodynamic assessment has prompted the development of novel CMR techniques including T1 and T2 mapping, non-contrast angiography and four dimensional (4D) flow.

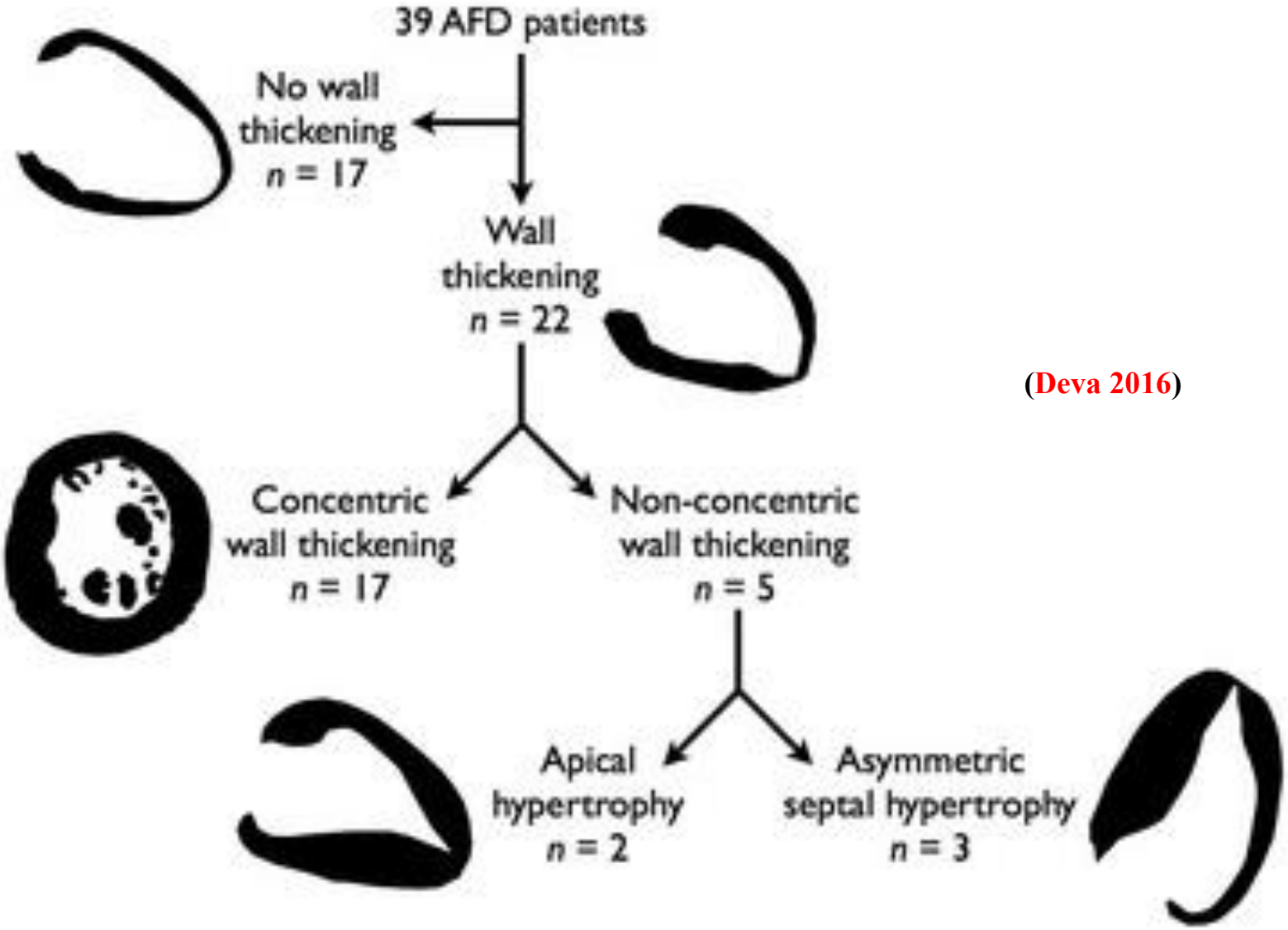
T1 mapping is suitable for diagnosing pathologies affecting extracellular volume such as myocarditis, diffuse myocardial fibrosis and amyloidosis, and is a promising diagnostic tool for patients with iron overload and Fabry disease.

T2 mapping is useful in depicting acute myocardial edema and estimating the amount of salvageable myocardium following an ischemic event. Novel angiography techniques, such as the self-navigated whole-heart or the quiescent-interval single-shot sequence, enable the visualization of the great vessels and coronary artery anatomy without the use of contrast material.

The 4D flow technique overcomes the limitations of standard phase-contrast imaging and allows for the assessment of cardiovascular hemodynamics in the great arteries and flow patterns in the cardiac chambers. The future of CMR is heading toward a more reliable quantitative assessment of the myocardium, an improved non-contrast visualization of the coronary artery anatomy, and a more accurate evaluation of the cardiac hemodynamics.

Although it is known that FD can mimic the morphologic manifestations of HCM on echocardiography, there is a lack of CMR literature on this. There is limited information in the published literature on the distribution of myocardial fibrosis in patients with FD, with scar reported principally in the basal inferolateral mid wall. Concentric thickening and inferolateral mid-myocardial scar are the most common manifestations of FD, but the spectrum includes cases morphologically identical to apical and HCM subtypes of HCM and these have more apical and mid-ventricular LV scar. Significant LVH is associated with ventricular arrhythmia (**Deva 2016**).

Breakdown of FD cohort according to presence of wall thickening and the various morphological phenotypes



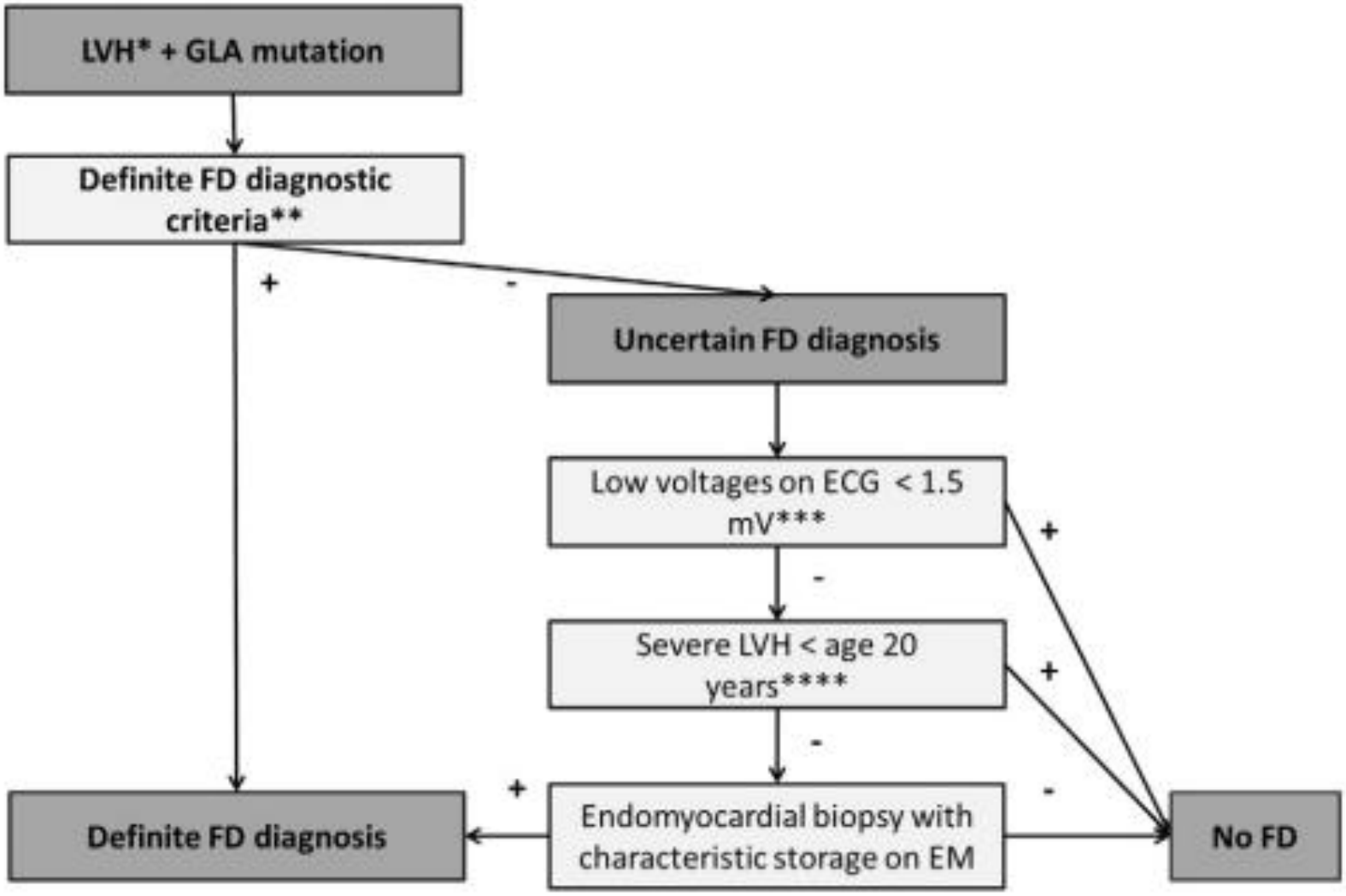
(Deva 2016)

Diagnosis clue points (Azevedo 2017)

1. FD diagnosis should be considered in all cases of unexplained left ventricular hypertrophy (LVH), even in its milder forms;
2. Screening in subjects with LVH reveals a high prevalence of FD. Often, a diagnosis is uncertain because characteristic clinical features are absent and genetic variants of unknown significance (GVUS) in the α-galactosidase A (GLA) gene are identified. This carries a risk of misdiagnosis, inappropriate counselling and extremely expensive treatment (**Smid 2014**).
3. A complete evaluation of patients with unexplained LVH is important to find diagnostic red flags of treatable causes of LVH, such as FD;
4. Cascade family screening is paramount to the earlier diagnosis and treatment of other affected family members;
5. The FD phenotype is highly variable in heterozygote females, even within the same family.
6. The new screening criteria: atypical HCM, history or presence of documented arrhythmia, short PR interval defined as <120 ms on ECG, and symptoms of autonomic dysfunction (**Seo 2016**).
7. The diagnosis can usually be confirmed in males if there is low α-Gal A activity in leukocytes or plasma
8. Molecular genetic analyses of the GLA gene is the most accurate method of diagnosis female
9. Kidney biopsy may also be suggestive of FD if excessive lipid buildup is noted.

Summary of the nine criteria that were pre-selected based on the systematic review. with sensitivity and specificity calculation (Smid 2014)

Fabry diagnosis	Entry criteria	Sen.%	Spec.%	Exit criteria	Prev.
ECG	PR interval minus P wave duration > 40 ms (**Namdar 2012**) Corrected PR interval <144 ms (**Namdar 2012**)	82 82	99 90	Low voltages: Sokolow–Lyon index of ≤1.5 mV total QRS amplitude in I, II, III < 1.5 mV (**Hoigne 2006, Namdar 2012**)	0
Echocardiography	• Increased papillary muscle • LV wall ≥ 12 mm • When LV wall is > 13 mm (39)	75 100	86 ND		
CMR				▪ LVOTO ((**Kounas 2008; Pieroni 2006**) ▪ Pericardial effusion (**Hoigne 2006**) ▪ CMR Late enhancement in papillary muscles (**Pieroni 2006; Niemann 2011**)	0 0 0



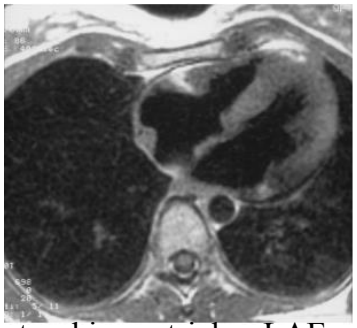
Proposal for a diagnostic algorithm for subjects presenting with isolated LVH and an uncertain diagnosis of FD. *LVH: left ventricular hypertrophy defined as an MWTd N 12 mm, **see before Table, ***low voltages on ECG defined as the total sum of the amplitude of the QRS complex in I, II, III b 1.5 mV [34], ****severe LVH was defined as a MWT N 15 mm. Abbreviations: EM: electron microscopy, FD: Fabry disease, GLA: α-galactosidase A gene.

Differential Diagnosis

FD must be high on the list of differential diagnoses when a young man presents with signs and symptoms of stroke, along with other characteristic lesions. Conditions that mimic the symptoms of FD

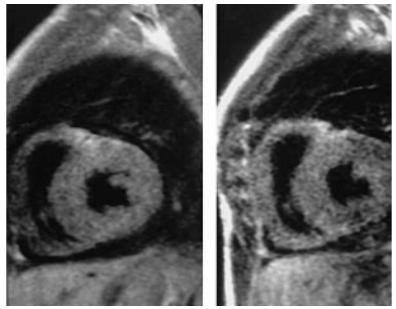
I. Acute Stroke
II. Basilar Artery Thrombosis
III. Cardioembolic Stroke
IV. Cavernous Sinus Syndromes
V. Dissection Syndromes
VI. Lacunar Syndromes
VII. Posterior Cerebral Artery Stroke
VIII. Transient Global Amnesia
IX. Hypertensive heart disease (HHD).
X. Aortic stenosis (AS)
XI. Hypertrophic cardiomyopathy mainly non-obstructive HCM: papillary muscle anomaly in NO-HCM (specificity 92%) (**Hoigné 2006**)
XII. Cardiac amyloidosis (CA): ECG documentation of low QRS voltages is often one of the first clues of CA. Orthostasis and/or pericardial effusion for CA (specificity 93%) The 46% of the patients affected by CA have mild or moderate pericardial effusion. A pleural effusion (mild) is present in 50% of CA patients and in none with HCM or FD. Typical appearance of CA with MRI spin-echo sequence shows hypertrophic ventricles, enlarged left and right atrium, thickened interatrial septum, and posterior atrial wall (A).

A



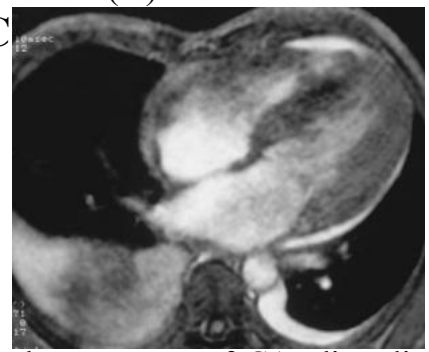
Hypertrophic ventricles, LAE and RAE, thickened interatrial septum, and posterior atrial wall

B



MRI variable echo (20 to 60 ms) sequences of CA: decreased signal intensity of infiltrated myocardium compared with skeletal muscle (top right).

C

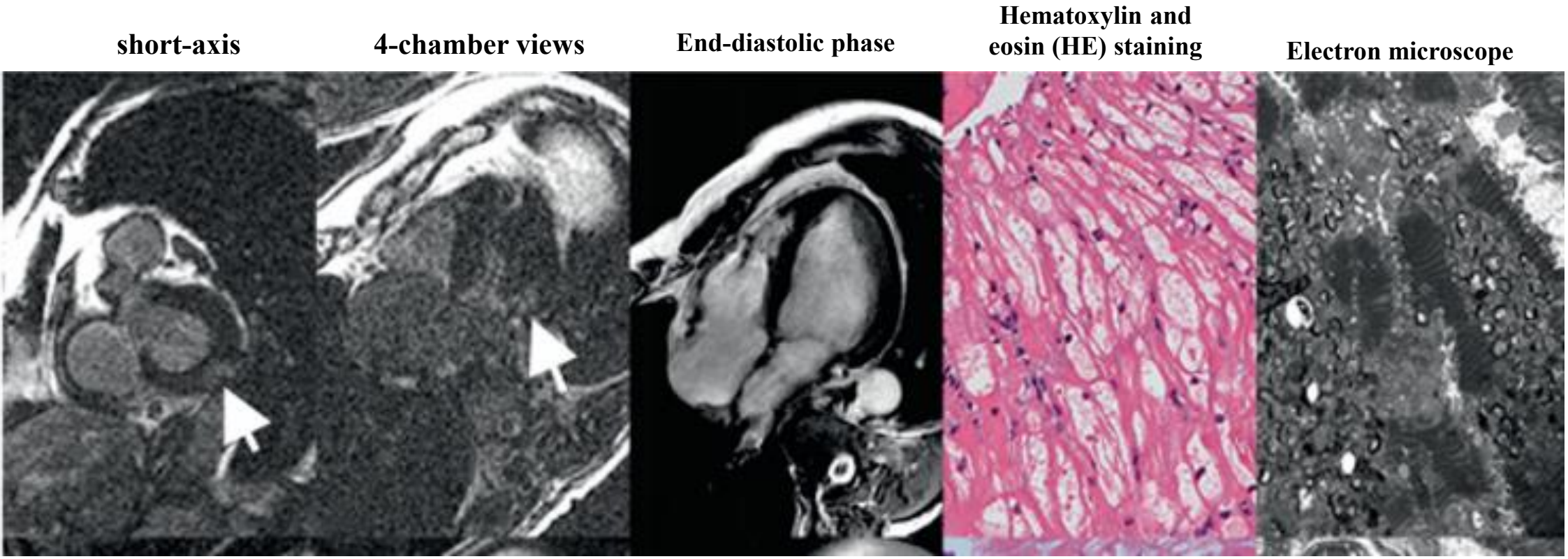


MRI gradient echo sequence of CA: diastolic image shows LAE and RAE associated with nondilated and noncompliant ventricles: mild pleural and pericardial effusions

XIII. Cardiac Hereditary haemochromatosis (HH) is an autosomal recessive genetic disorder related to proteins involved in iron transport, resulting in iron load and deposition of iron in various tissues of the body. Homozygosity for p.Cys282Tyr or p.Cys282Tyr/p.His63Asp compound heterozygosity. In addition to HFE gene, mutations in the genes that encode hemojuvelin (HJV), hepcidin (HAMP), transferrin receptor 2 (TFR2) and ferroportin (SLC40A1) have been associated with regulation of iron homeostasis and development of HH. It is characterized by an excessive absorption and progressive accumulation of iron in the liver, the pancreas, the heart, and the joints. This iron overload leads to complications including liver cirrhosis (and related complications such as liver failure and hepatocellular carcinoma), cardiac failure, cardiac arrhythmias, impotence, diabetes, arthritis, and skin pigmentation. For 55% of patients. Cardiac involvement in hemochromatosis affects mainly the myocardium: iron overload of the myocytes reduces left ventricular distensibility. Heart failure is the most frequent manifestation of cardiac involvement. Diagnosis of cardiac involvement depends essentially on Doppler echocardiography showing abnormal LV filling and, later, ventricular dilatation with LV systolic dysfunction. Cardiac MRI with measurement of T2* relaxation times can help quantify myocardial iron overload. Age at onset of symptoms and specific organ involvement in HH depend on the type of mutation. diagnosis was based on familial genetic survey or fortuitous abnormal results of blood samples. An initial serum level of ferritin >1000 µg/L was a factor of severity for 50% of patient, transferrin saturation (TS) > 45%, serum ferritin (SF)> 200 µg/L in females and > 300 µg/L in males; or in advanced stages (TS) > 50% in females and TS > 60% in males, in the absence of secondary causes. Some patients with primary iron overload may not present mutation during this genetic approach. Phlebotomy (venesection or 'blood letting') is the currently recommended treatment for hereditary haemochromatosis. The optimal treatment of hereditary haemochromatosis remains controversial.

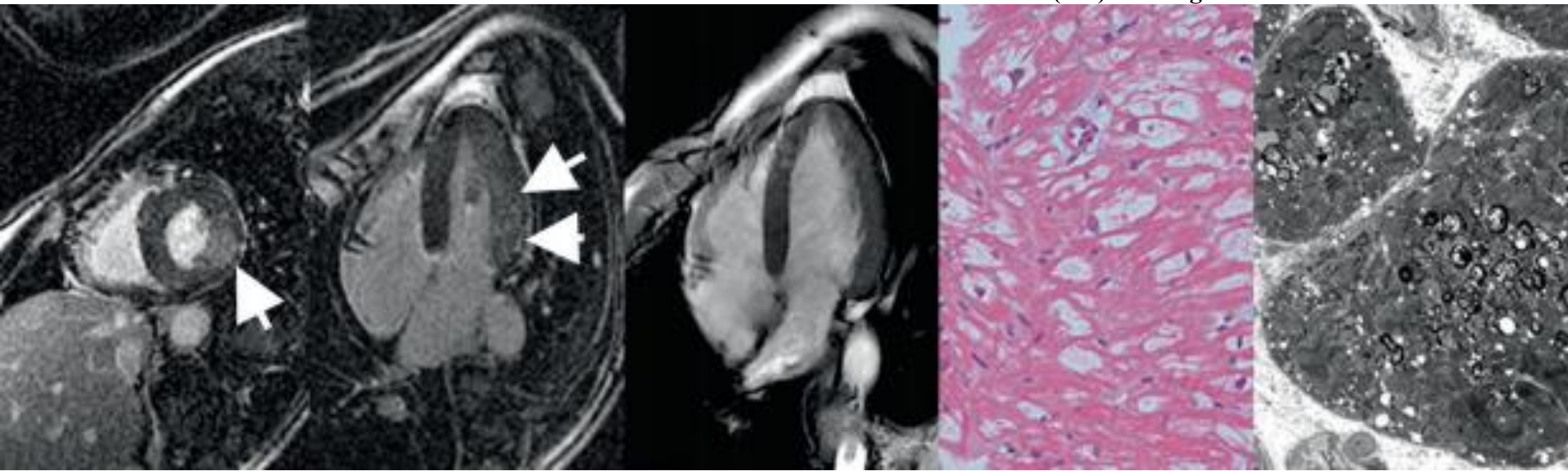
The cardiac variant of FD may be defined as a cardiomyocytic storage disorder, thus, mimicking the clinical features of O-HCM and especially NO-HCM. In patients with unexplained LVH the diagnosis of a cardiac variant of FD is performed by light- and electron microscopic evaluation of endomyocardial catheter biopsy specimens and/or serologic investigations (decreased activity of α-galactosidase A in plasma or leucocytes). A combined analysis of PR interval minus P-wave duration in lead II, QTc duration, and Sokolow-Lyon index proved highly sensitive and specific in the differentiation of FD, CA, and HCM compared to HHD and AS. Analysis of these easy-to-assess ECG parameters may be of substantial help in the diagnostic workup of these 5 conditions. A QTc <440 ms in combination with a PR interval minus P-wave duration in lead II <40 ms was 100% sensitive and 99% specific for the diagnosis of FD, whereas a QTc duration >440 ms and a Sokolow-Lyon index ≤1.5 mV were found to have a sensitivity and specificity of 85% and 100%, respectively, for the diagnosis of amyloidosis and differentiation from HC, AS, and HHD. Moreover, a novel index PR interval minus P-wave duration in lead II multiplied by QTc duration/Sokolow-Lyon index) proved to be highly diagnostic for the differentiation of CA and FD (**Namdar 2012**).

Case 1



Case 1, a 60-year-old man with a normal LVMI of 45.2 g/m^2. Images with LGE are shown as short-axis and 4-chamber views; arrows indicate fibrosis. The end-diastolic phase demonstrated that there was no evidence of LVH ; The end-diastolic phase demonstrated that there was no evidence of LVH. Endomyocardial biopsy showed diffuse vacuolization on hematoxylin and eosin (HE) staining and abundant membrane-bound lamellar myelin bodies ("zebra" or "onion-skin" appearance) on electron microscope. GE-CMR ¼ gadolinium-enhanced cardiac magnetic resonance; LGE ¼ late gadolinium enhancement.

Case 2



A 58-year-old man with an LVMI of 36.1 g/m$^{2.}$ Images with LGE are shown as short-axis and 4-chamber views; arrows indicate fibrosis. The end-diastolic phase demonstrated that there was no evidence of LVH. Endomyocardial biopsies showed diffuse vacuolization on hematoxylin and eosin (HE) staining and abundant membrane-bound lamellar myelin bodies ("zebra" or "onion-skin" appearance) on electron microscope. GE-CMR ¼ gadolinium-enhanced cardiac magnetic resonance; LGE ¼ late gadolinium enhancement.

Brain MRI or computed tomography (CT) scans should be obtained to visualize the site and extent of infarction.
MR angiography (MRA), CT angiography (CTA), or 4-vessel cerebral angiography should be performed to identify large-vessel dilated arteriopathy, stenosis, or occlusion.
In patients with acute ischemic stroke, diffusion-weighted MRI may be used to identify early lesions, and perfusion-weighted MRI can be performed to identify perfusion defects.
Electrocardiography may show conduction abnormalities and evidence of previous myocardial infarctions
MR spectroscopy, arterial spin tagged MR imaging, and positron emission tomography (PET) scanning have been performed on an experimental basis to understand the pathophysiology of FD.

Neurologic Examination

A detailed neurologic examination may reveal peripheral neuropathy or nystagmus, internuclear ophthalmoplegia, dysarthria, aphasia, hemiparesis, and sensory loss caused by stroke lesions, especially in the posterior circulation
Skin Biopsy and Histologic Findings
Skin biopsy with cells showing increased lipid content is suggestive of FD.
Lipid-laden cells have been described in endothelial cells, epithelial cells, muscle fibers, and ganglion cells
Nerve conduction studies may show decreased conduction velocities and prolonged distal latencies.
Prenatal diagnosis can be made by using samples of chorionic villi and amniotic cells.
Treatment should be initiated before irreversible end-organ damage has occurred.
Asymptomatic children with FD mutations should be followed closely.
The management of FD requires a multidisciplinary approach.
Aggressive efforts to diagnose the etiology of stroke are necessary to plan secondary prevention strategies. In this context, unusual presentations, with multiple organ involvement or lack of traditional vascular risk factors, should lead to the consideration of FD. Traditional secondary stroke prevention strategies are still necessary.

Prognosis

Life expectancy is reduced by an average of 15 years in female patients and 20 years in male patients (**MacDermot 2001**) Males was 58.2 years, compared with 74.7 years. Females 75.4 years compared with 80.0 years in the general population, according to registry data from 2001 to 2008. The most common cause of death was cardiovascular disease, and most of those had received kidney replacements. After a first stroke, recurrent. stroke is frequent, with a median interval to first recurrence of 6.4 years in hemizygotes.

Treatment strategies

involve combined efforts from multiple specialties. The diagnosis and care of these patients usually is best handled at tertiary care centers.

Acute strokes may be managed adequately in community hospitals in the initial phases. Further care can be accomplished by means of consultation with tertiary care centers.

Research to replenish deficient enzymes by means of gene transfer via adenovirus is in its early stages.

Pharmacologic Therapy

Antiplatelet agents, including aspirin, ticlopidine, clopidogrel, and aspirin-dipyridamole, are used routinely to prevent recurrent ischemic strokes of thrombotic type in Fabry disease, but their effectiveness in this setting has not been proved.

Administration of the anticoagulant warfarin, which is often used to prevent cardioembolic strokes, may be necessary if embolic events that stem from cardiac causes are a concern. Painful neuropathies may be treated with a variety of medications. Carbamazepine and phenytoin have been used anecdotally in FD.

Intravenous enzyme replacement therapy (ERT) Two enzymes, agalsidase-α (Replagal) and agalsidase-beta (Fabrazyme), reportedly help in normalizing renal function, cardiac function, and cerebrovascular flow. Whether therapy with these enzymes changes the natural history of strokes attributable to FD is unclear. Medical regulatory requirements are different in various parts of the world, and the appropriate authorities should be consulted regarding the approval status of these enzymes. Enzyme replacement therapies (ERT) with agalsidase-α and -β were investigated to characterize their therapeutic effect on kidney function in FD patients with Classic phenotype. Mathematical disease progression modeling indicates that there is no clear therapeutic effect of ERT on kidney function in adult patients with Classic Phenotype of FD. Interpretation of these findings should take into account that this conclusion is not derivate of randomized and lacks a placebo controlled group. Further investigations are warranted to clarify whether earlier ERT initiation before 18 years of age, higher ERT dose or more intensive therapies can preserve kidney function (**Nowak 2017**). The first treatment for FD was approved by FDA on April 24, 2003. Fabrazyme Corporation (β-agalsidase was licencsed to the Genzyme Corporation. It is an enzyme replacement therapy (ERT). The pharmaceutical company Shire manufactures α-agalsidase under the brand name Replagal as a treatment for FD.

ERT with agalsidase α every two weeks. Over the past 15 years, intravenous replacement therapy of the deficient α-agalsidase A enzyme has been well-established retarding the progression of a multisystemic disease and organ involvement. Despite this innovative treatment approach, premature deaths still do occur. The response to ERT varies considerably and appears to depend on

- Gender: male patients with FD respond more actively to ERT than do female patients with FD. Pathway analysis revealed that oxidative phosphorylation pathway-related genes are downregulated under ERT. ERT has a role to protect the proteins from oxidative damage and such deactivation of oxidative phosphorylation is one of direct pharmacodynamic actions of ERT (**Ko 2016**).

- Genotype (classic or later onset/non-classic)
- Stage of disease or age: Chronically ill patients with need for regular infusion therapy may benefit from a home care setting. Home-based infusion therapy as exemplified by agalsidase α-ERT in FD is a viable option for patients who received uneventful infusions within the hospital (**Beck 2013**).
- Agalsidase inhibition by anti-agalsidase antibodies.
- Plasma BNP levels: may be useful for evaluating the effectiveness of ERT for heterozygous FD, even in patients who demonstrate no improvement in echocardiographic parameters of cardiac structure and function (**Masugata 2009**).

Early ERT treatment at young age, a personalized approach, and adjunctive therapies for specific disease manifestations appear to impact on prognosis and are currently favored with the expectance of more effective intravenous and oral treatments in the short future (**Oder 2016**).

Renal and Fetal Liver Transplantation

Renal failure is a clear indication for renal transplantation. However, renal transplantation may not alter the course of disease progression in other organ systems.

Human-induced pluripotent stem cell-derived cardiomyocyte (hiPSC-CM) models of cardiac storage disorders

Several cardiac storage disorders (CSDs) have been modeled using patient-specific hiPSC-CMs, including Anderson-Fabry disease, Danon disease, and Pompe disease. These models have shown that patient-specific hiPSC-CMs faithfully recapitulate key phenotypic features of CSDs and respond predictably to pharmacologic manipulation. hiPSC-CMs generated from patients with CSDs are representative models of the patient disease state and can be used as an in vitro system for the study of human cardiomyocytes. While these models suffer from several limitations, they are likely to play an important role in future mechanistic studies of cardiac storage disorders and the development of targeted therapeutics for these diseases.

Fetal liver transplantation has been tried in a small number of patients. In the limited group of patients tested, no changes in serum or leukocyte α-galactosidase A levels were reported. Clinical use of this experimental procedure should be undertaken with caution, since published literature on the topic is sparse.

Consultations in Stroke, Renal Failure, and Neuropathy: Consultation with a neurologist is recommended if Fabry disease is suspected as a cause of stroke or if the usual causes of stroke are not present. In addition, a neurologist can better handle painful neuropathies that are not amenable to treatment in the primary care setting. If an embolic event is thought to have caused a stroke, a cardiologist's expertise can be sought for diagnostic and therapeutic options. A nephrologist should be consulted if a patient has renal failure.

Sessions with a physical therapist and an occupational therapist can be helpful in rehabilitative efforts.

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