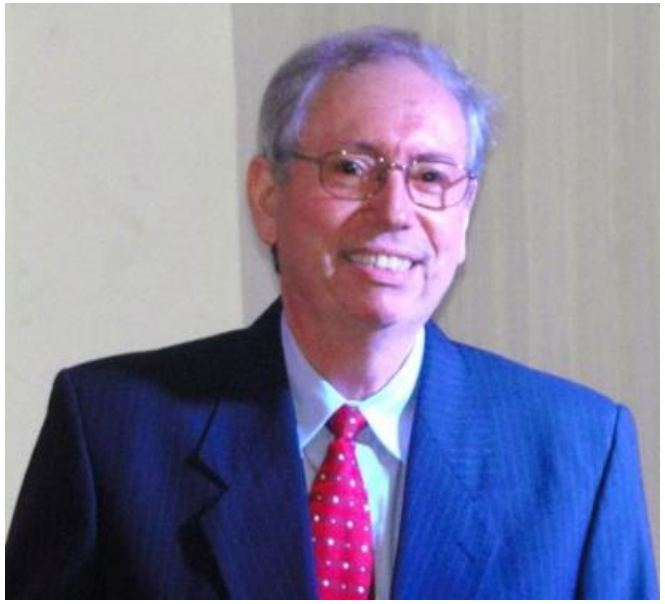
Duchenne Muscular Dystrophy with severe cardiomyopathy and unusual intraventricular conduction disturbance

Andrés Ricardo **Pérez-Riera, M.D. Ph.D.**
Design of Studies and Scientific Writing Laboratory in the ABC School of Medicine, Santo André, São Paulo, Brazil
https://ekgvcg.wordpress.com



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

Male, 23-year-old patient. Carrier of Duchenne muscular dystrophy (DMD), with late onset (it started at 12 years of age; the most cases starts at 3 or 4), and with slow progression, characterized by progressive muscular weakness, mainly the lower limbs. Currently, he cannot stand on his own, he is wheelchair user.

Family history: a brother with the same pathology.

Current complaint: progressive dyspnea.

Physical examination: severe skeletal chest deformity by significant scoliosis. Obesity, proximal weakness.

Cardiovascular: irregular heart rhythm with high heart rate (120 bpm in average) and frequent PVC, S4, systolic murmur +/4 in the mitral area.

Lungs: clean.

No peripheral edema in the lower limbs.

Muscular atrophy with calf hypertrophy and ischiotibial muscle contraction.

Questions:

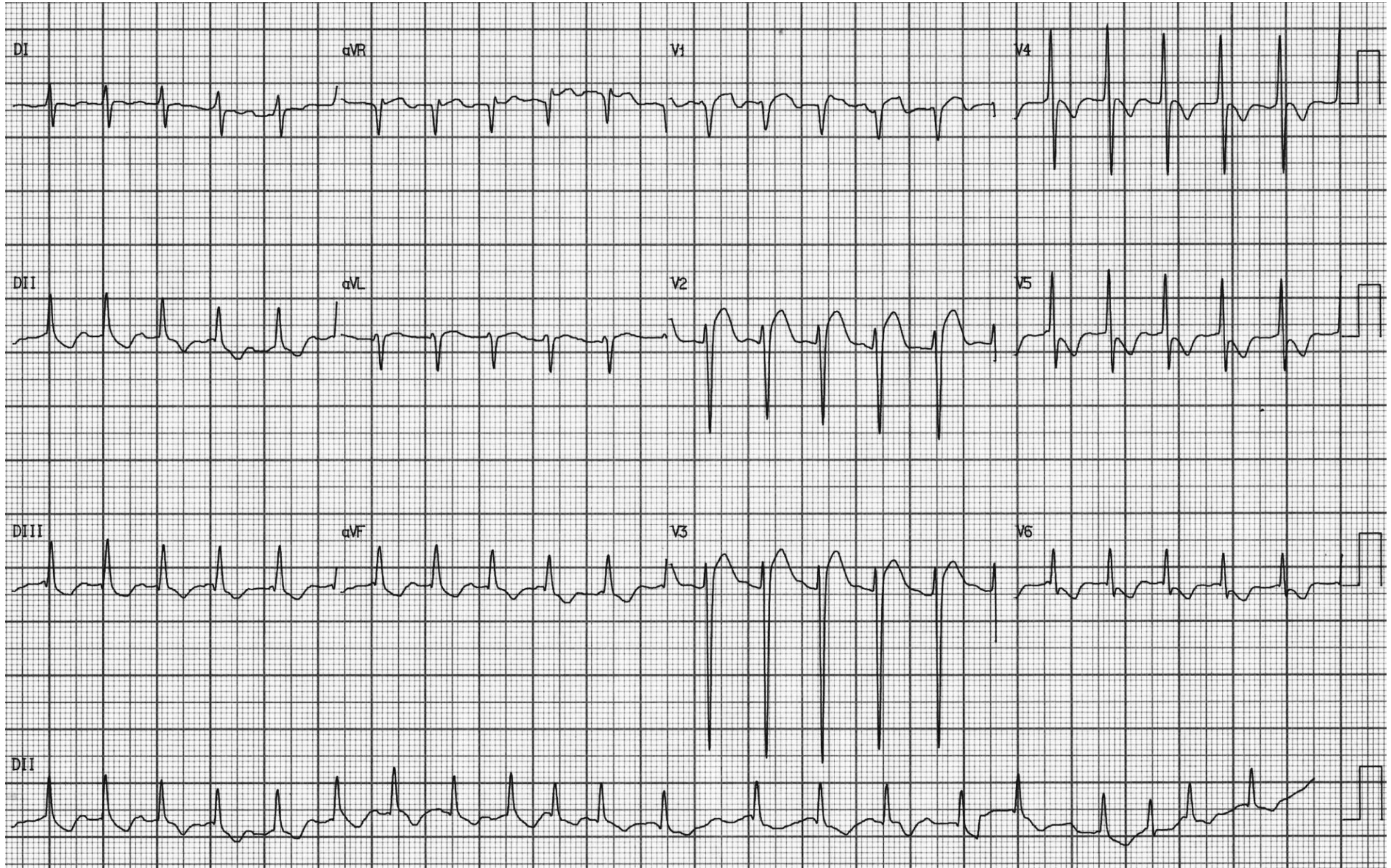
1. What is the diagnosis of ECG-1?
2. What is the diagnosis of ECG-2/VCG and why?
3. Why are ST segment elevation seen in the right precordial leads?

Português: Relato de caso

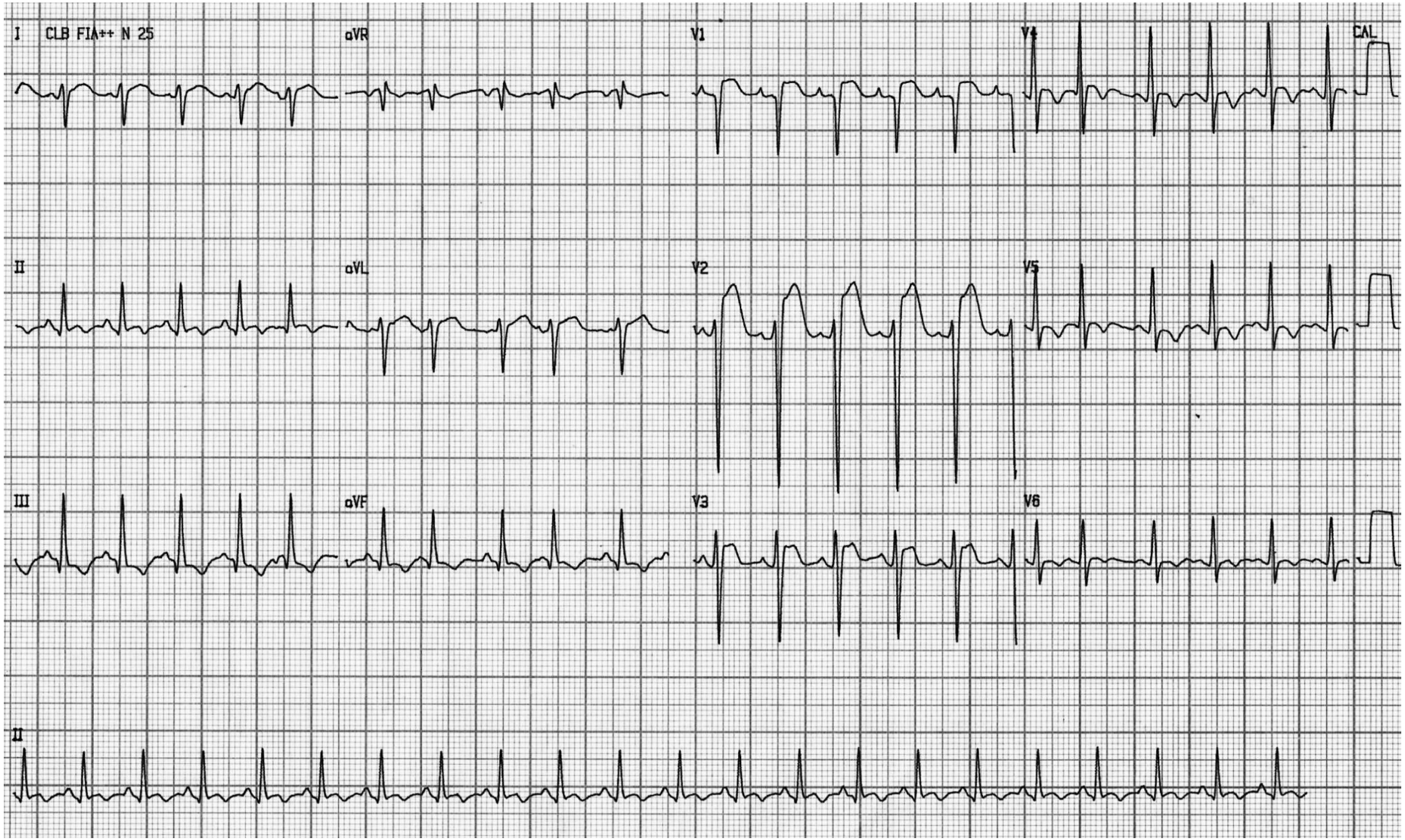
23 anos, sexo masculino. Sabe ser portador de distrofia muscular tipo Duchenne de inicio tardio (iniciou com 12 anos de idade: a maioria dos casos iniciam com 3 ou 4 anos) e de progressão lenta caraterizada por fraqueza muscular progressiva principalmente dos membros inferiores. Atualmente abásico cadeirante.
Antecedentes familiares: um irmão com a mesma patologia
Queixa atual: dispneia progressiva
Exame físico:
Deformidade esquelética torácica severa por escoliose importante. Obesidade, fraqueza proximal.
Cardiovascular: RCI com frequência cardíaca elevada (120bpm em media) e frequentes extra-sístoles B4 SS+/4 FM
Pulmões limpos
Sem edema periférico nos membros inferiores.
Atrofia muscular com hipertrofia da panturrilha e contratura do músculo isquiotibial

Perguntas:
1. Qual o diagnóstico do ECG-1?
2. Qual o diagnóstico do ECG-2/VCG e por quê?
3. Por que são observadas elevação do segmento ST nas derivações precordiais direitas?

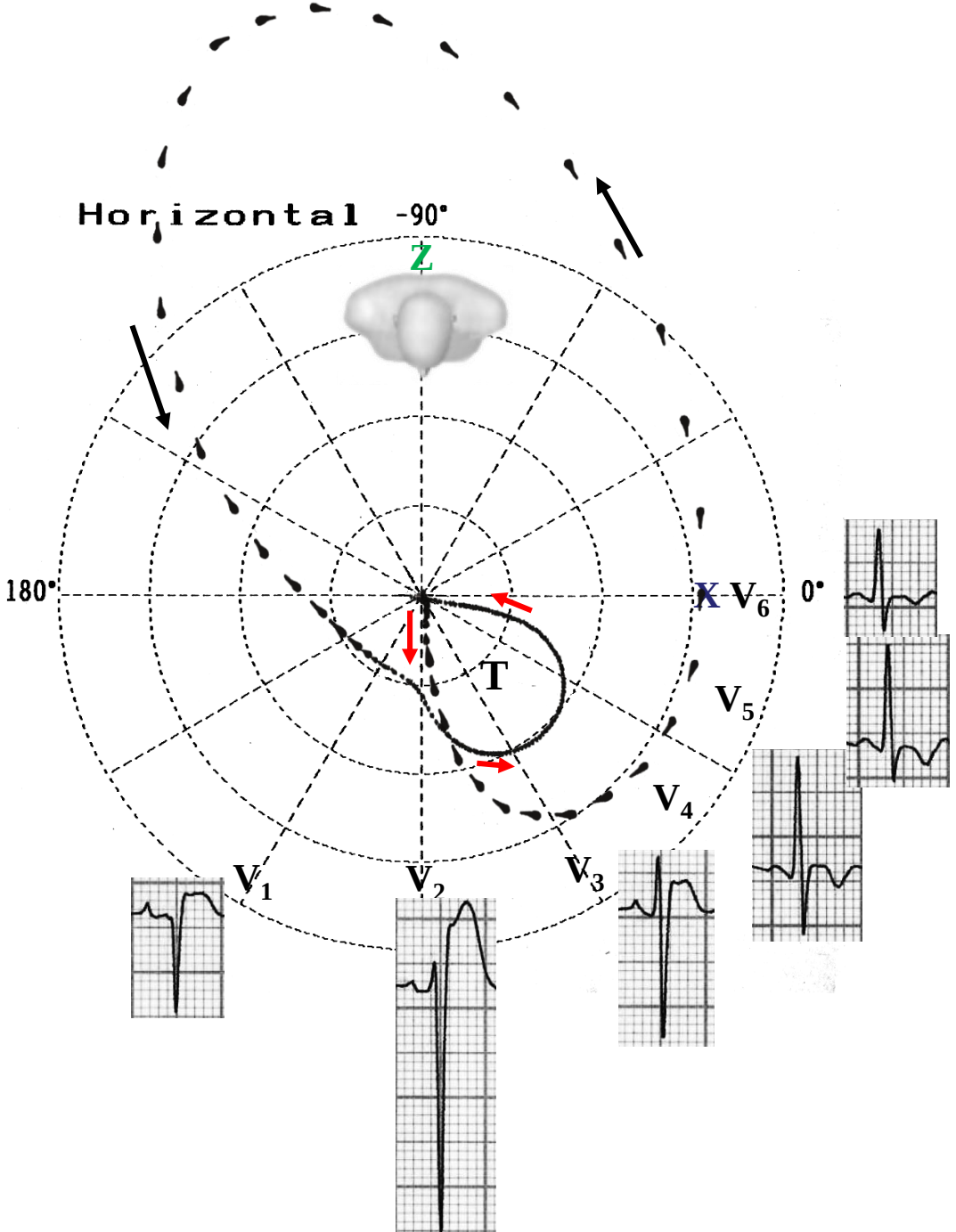
ECG-1



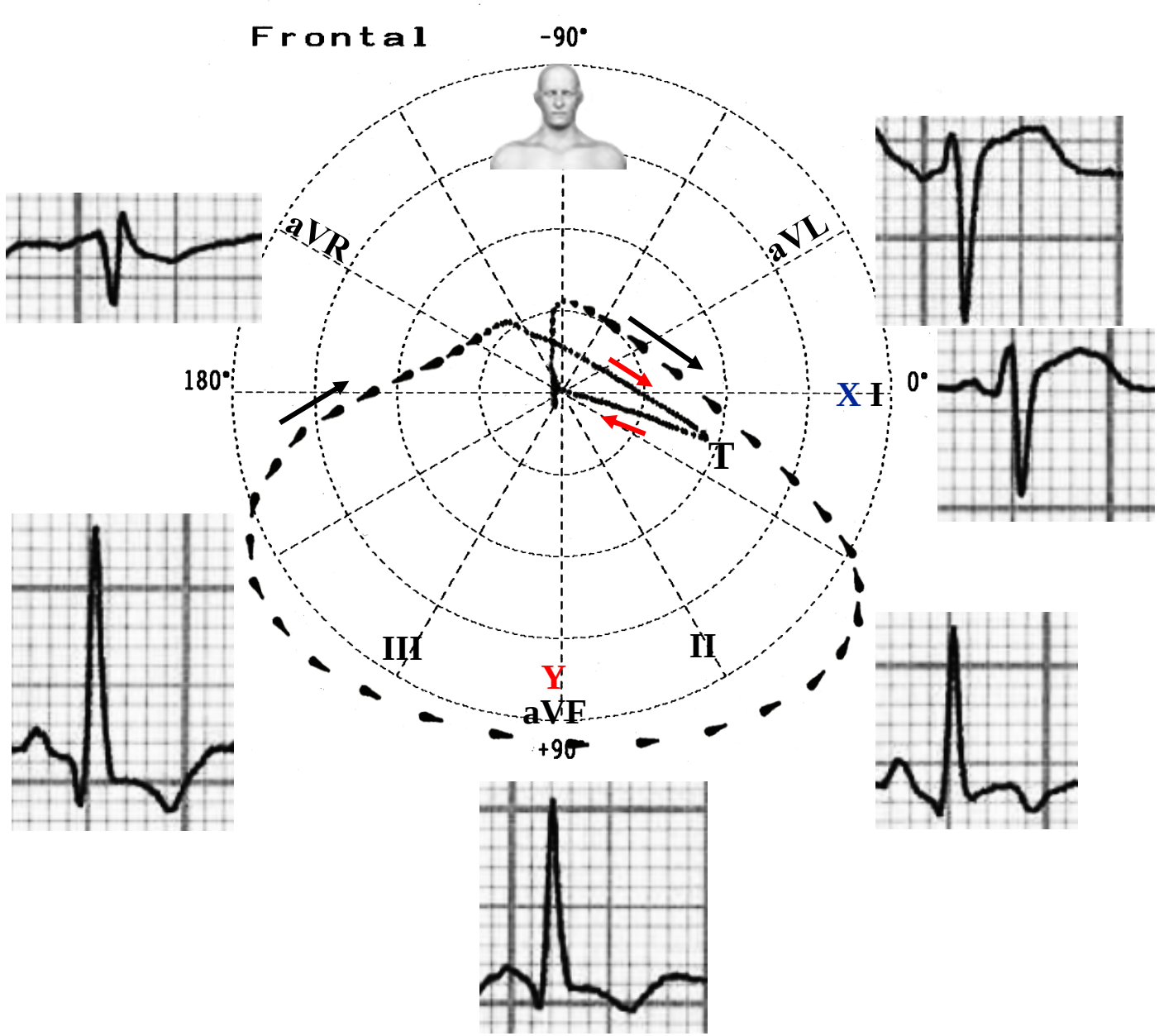
ECG-2



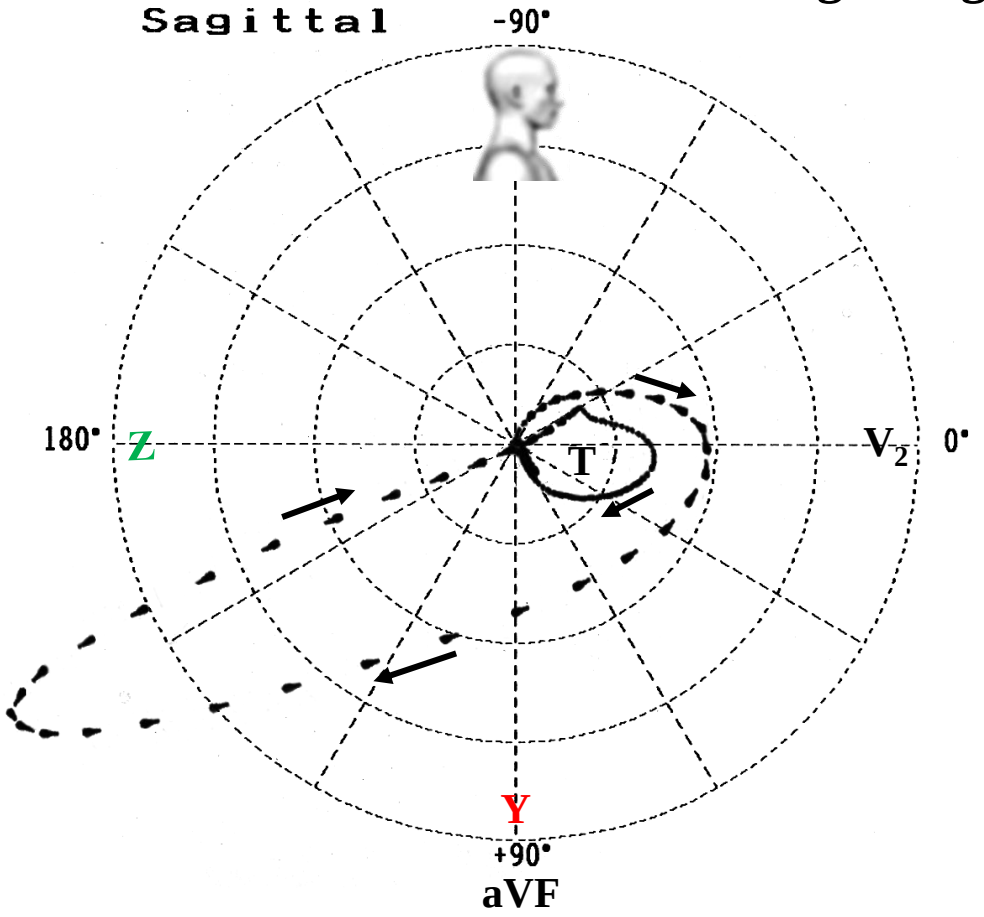
ECG-2/VCG correlation in the Horizontal Plane

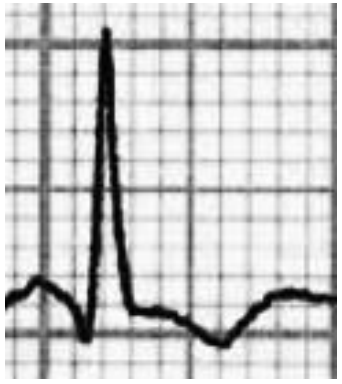


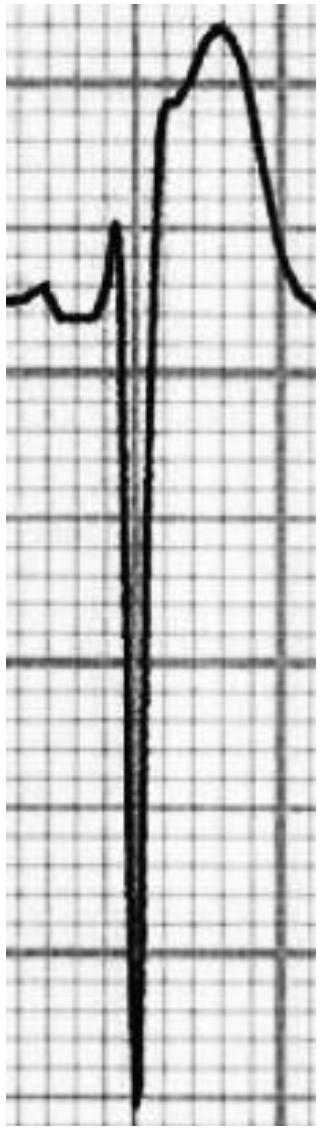
ECG-2/VCG correlation in the Frontal Plane



ECG-2/VCG correlation in the Right Sagittal Plane







Colleagues opinions

Portuguese

Caros colegas Raimundo e Andrés: O caso é muito interessante e inusitado para ECG de Duchene. O habitual é observar o diagnóstico de BDPIRE os ondas R de grande voltagem em V1 devido a comprometimento muscular na região dorsal, o que aliado à clínica faria o diagnóstico.

Vamos às perguntas:

1. **Para mim os diagnósticos do ECG 1 são: BDPIRE, isquemia subepicárdica *em face lateral e discutível lesão subepicárdica anterior (para justificar o supra de ST.***
2. ***O VCG esclarece as coisas, na minha ótica: Nos planos H e F fica patente o diagnóstico de BDPIRE pela proximidade dos cometas no final da alça de QRS. Por outro lado, a localização anterior e á direita (+ 150 graus) do ÂQRS, revela a perda de massa muscular em região posterior. A Isquemia miocárdica, que revela a miocardiopatia (o miocárdio 'r músculo estriado) que explica a dispneia. O VCG confirma a isquemia, pela forma arredondada e simétrica da alça de T nos três planos.***
3. ***Resta explicar o supra de ST nas precordiais. Duas possibilidades: real comprometimento miocárdico e, já que a alça de QRS retorna ao ponto de partida, que a deformidade torácica explique este achado.***

Abraços afetuosos do

Professor Hélio Germiniani MD PhD "República de Curitiba" Brasil.

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English

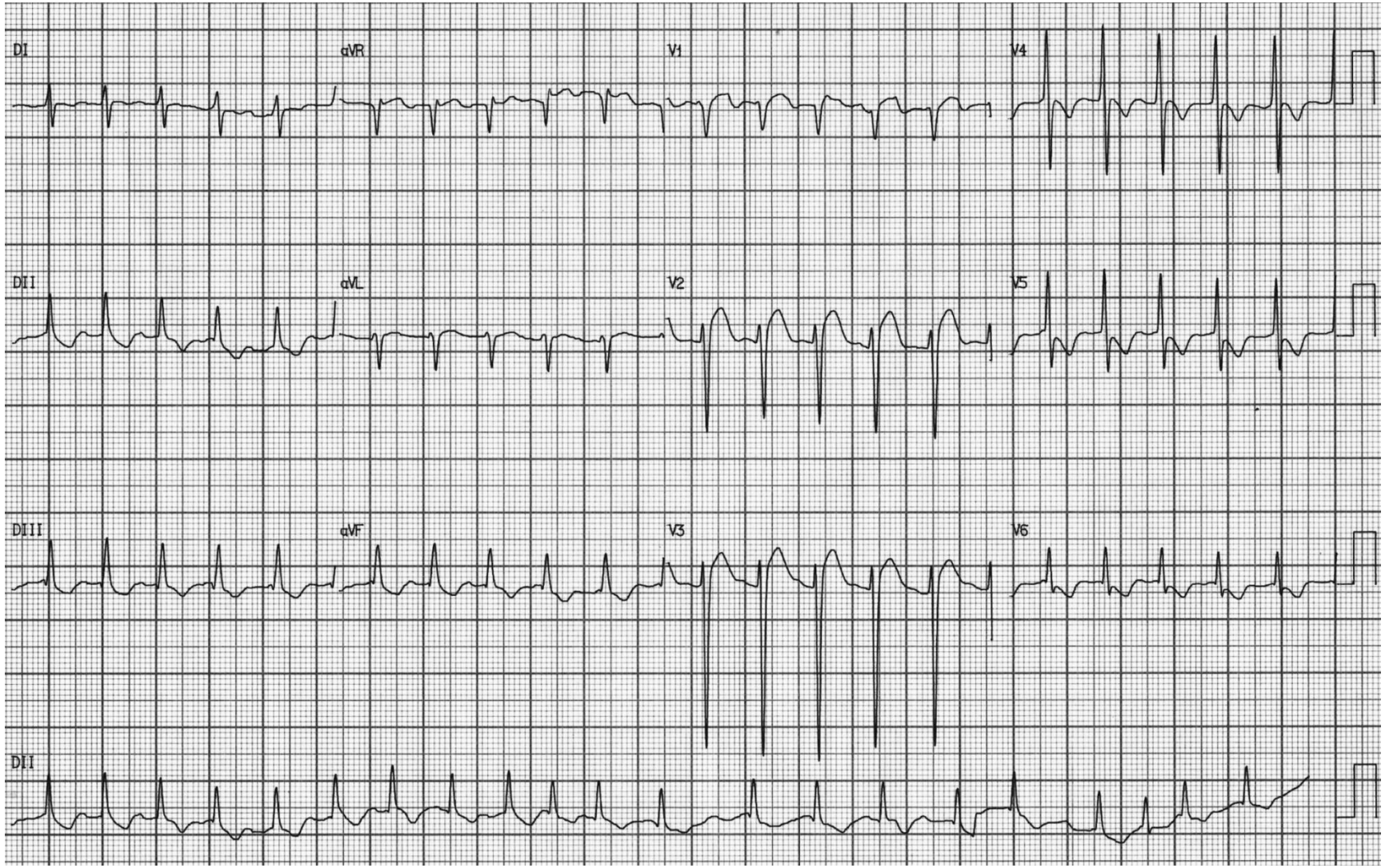
Dear colleagues, Raimundo and Andrés,

The case is very interesting and unusual for ECG of Duchenne dystrophy. The usual is to observed the diagnosis of LPFB and R waves of great voltage in V1 due to muscular compromise in the dorsal region, which together with the clinical symptoms would constitute the diagnosis. About the questions: 1) The way I see it, the diagnoses of ECG1 are: LPFB, subepicardial ischemia in the lateral side and arguably, anterior subepicardial lesion (to justify ST elevation). 2) The VCG further clarifies things, from my point of view: in the H and F planes, the diagnosis of LPFB diagnosis is evident from the dashes at the end of the QRS loop. On the other hand, the anterior and right location (+150 degrees) of AQRS reveals loss of muscle mass in the posterior region. Myocardial ischemia, revealing cardiomyopathy (myocardial striated muscle ‘r), which explains dyspnea. The VCG confirms ischemia, by the rounded and symmetrical shape of the T loop in the three planes. 3) It remains to explain ST elevation in the precordial leads. Two possibilities: a real myocardial involvement, and as the QRS loop returns to the starting point, the chest deformity may explain this finding.

Warm regards by Hélio Germiniani

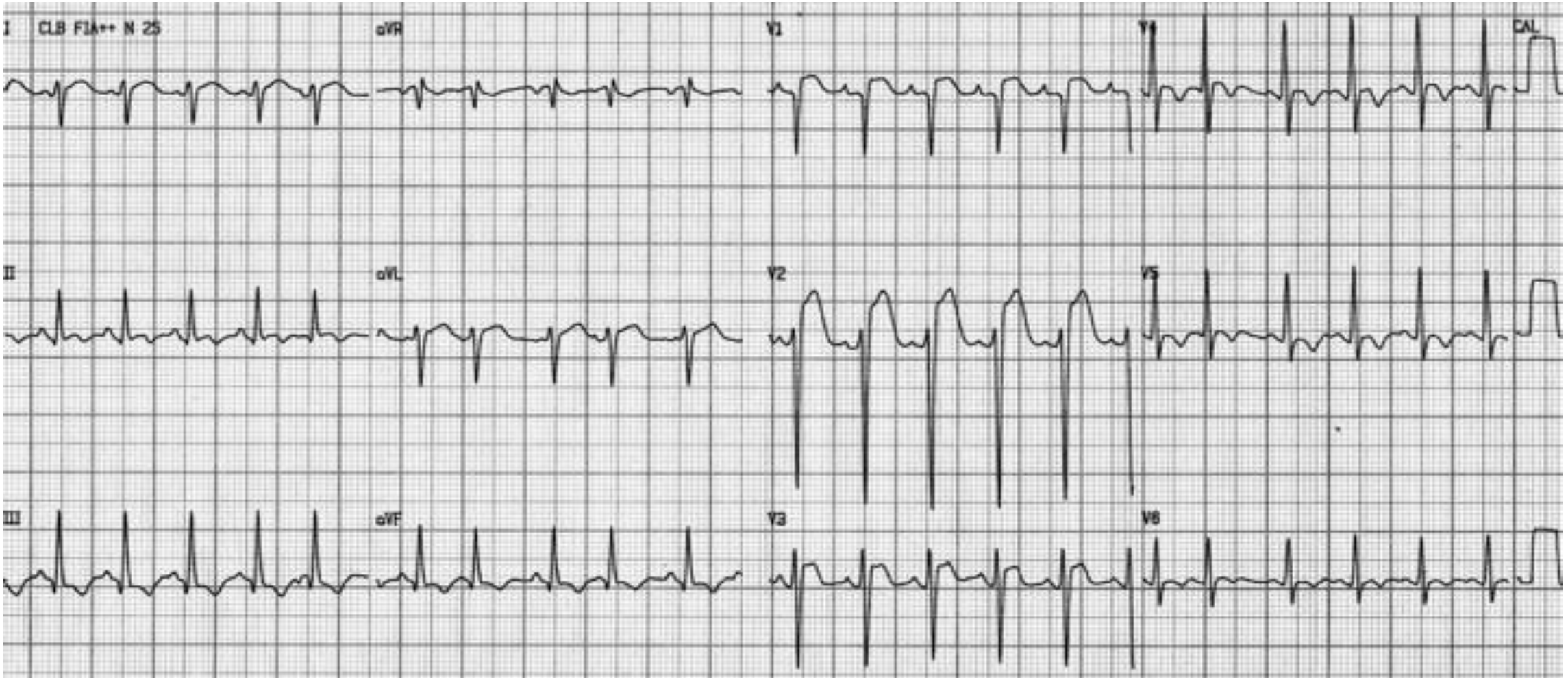
Final comments
By Andrés Ricardo Pérez-Riera
&
Raimundo Barbosa-Barros

ECG-1



ECG diagnosis: Irregularly irregular rhythm, no P waves, absence of an isoelectric baseline, QRS axis + 100°, variable ventricular rate with high heart rate response (mean HR 145bpm): **nonvalvular atrial fibrillation(AF).** The irregularity of the ventricular action associated with AF, therefore, indicates changes of refractoriness of the AV junctional tissues from cycle to cycle. This can best be attributed to varying degrees of penetration of "blocked" atrial impulses into parts of the AV junction, and to the effect of such concealed conduction on the propagation of subsequent impulses. ST segment elevation convex(STSE) upward in right precordial leads and negative ST/T from V4-6 and inferior leads. An interesting observation is the detection of myocardial injury at a very young age in patient with Duchenne cardiomyopathy (**Silva 2007**).

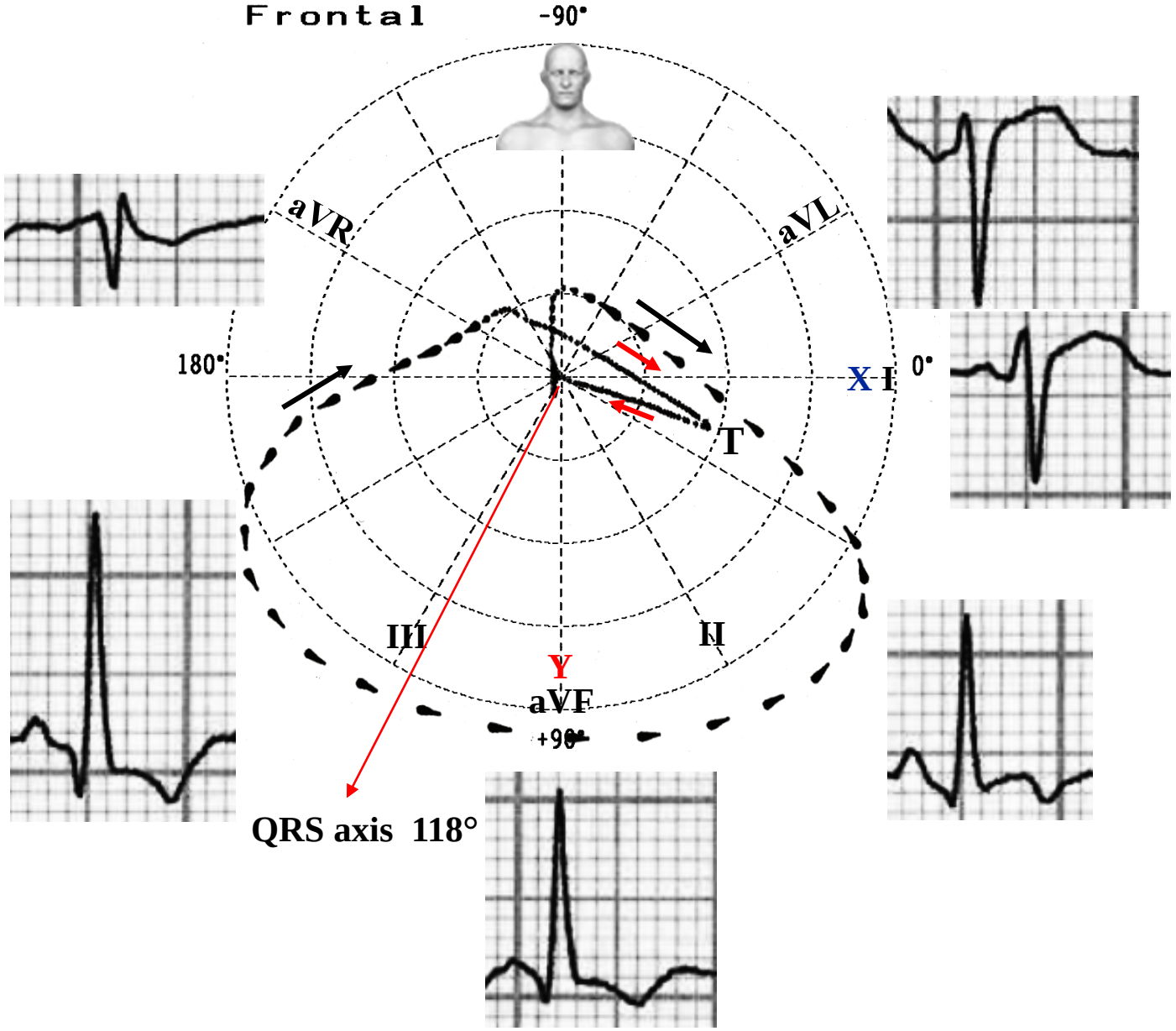
ECG-2



ECG diagnosis: Sinus tachycardia (HR= 136bpm), QRS axis +118° (closer to +120º (III) than +60º when closer to the latter, it would indicate an incomplete form of LPFB.), rS in I and aVL, qR in III, aVF, and II. The initial q wave in III is greater than the q wave in II and aVF. RIII>RII, R wave peak time in aVF > 35ms, very deep S wave in V2 consequence of posterior dislocation and to the right of the final forces of QRS loop.and Rs in V5-V6. ST segment elevation convex upward in right precordial leads and negative T waves form V4 to V6 and inferior leads.

Conclusion: Sinus tachycardia + Left Posterior Fascicular Block(LSFB) + diffuse primary repolarization (injury and ischemia: Intrinsic myocardial disease?). *"Primary"* ST-T Wave abnormalities (ST-T wave changes that are independent of changes in ventricular activation and that may be the result of global or segmental pathologic processes that affect ventricular repolarization).

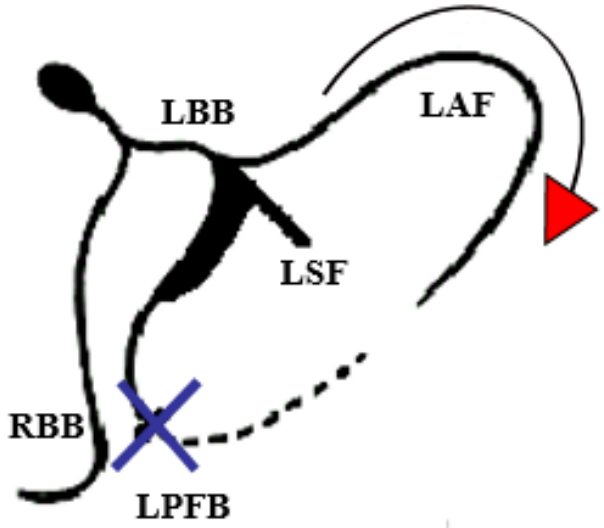
ECG/VCG correlation in the Frontal Plane

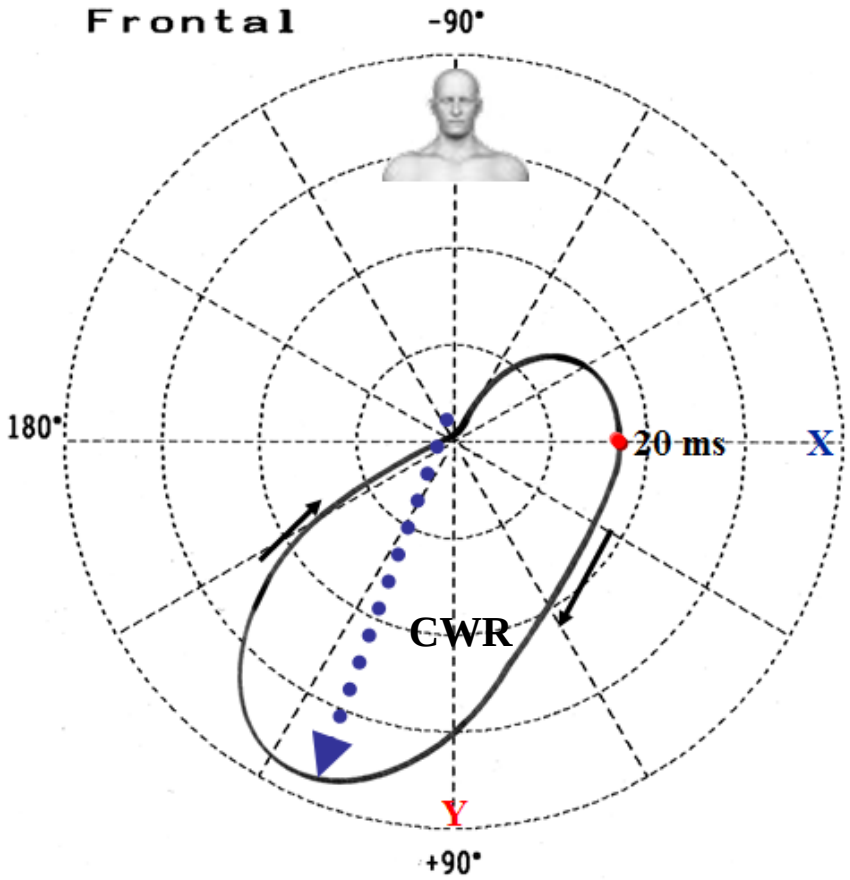


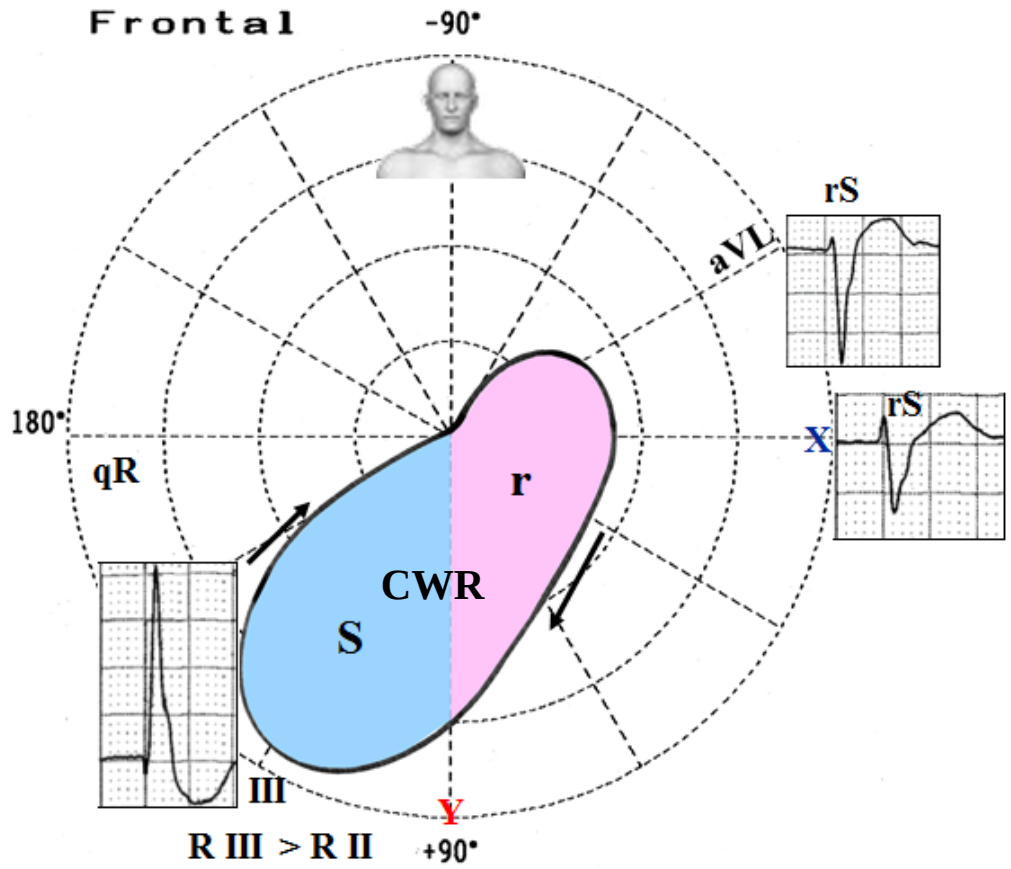
Isolated LPFB in the absence of associated RBBB is a rare ECG finding. In view of its anatomy and the fact that it receives a dual blood supply, the left posterior fascicle of the left bundle branch appears to be less vulnerable than the anterior fascicle or the right bundle.. In summary, the greater vulnerability of the LAF in comparison to the LPF has the following causes **1) Anatomical:** (**Rosenbaum 1970; Demoulin 1972; Strickland 1972**.) a) Less diameter (LAF: 3 mm; LPF: 6 mm).b) Greater extension (LAF: 35 mm; LPF: 30 mm) **2) Electrophysiological:** As a consequence of its greater extension and less diameter, the depolarization and repolarization of LAF is slower than LPF, i.e. the "QT of LAF" is greater than the one of LPF, a fact that makes it more vulnerableñ **3) Vascular:** Posteroinferior fascicle always irrigated by the two systems of the ADA and RCA. **4) Topographic:** The LPF runs through a more protected area, with less pressure mechanic impact. The LAF runs diagonally through the LVOT by the subendocardium. This region is subject to a great turbulence and high pressure, which justifies the greater vulnerability of the LAF when compared to the LPF, which runs through an area in the LV Inflow Tract (LVIT), which is much less exposed to turbulence, which explains the rarity of the LPFB. Mechanical disruption of the LPF can produce rarely isolated LPFB (**Brenes 1970; Medrano 1970 a; 1971b; 1972c; Rokey 1984**).

See ECG/VCG analysis of FP in the next slide.....

ECG/VCG correlation in LPFB: QRS loop in the FP







Characterization of QRS loop in the frontal plane: Vector of initial 20 ms heading above and to the left; efferent limb to the left; clockwise rotation (CWR); greater area of QRS loop located in the right inferior quadrant; maximal vector heading below and to the right near +110º (from +80º to +140º); QRS loop of "broad" aspect (“fat” loop); afferent limb located in the right inferior quadrant. Typical QRS loop in the frontal plane that explains the rS pattern in I and aVL. Typical QRS in the frontal plane that explains the qR pattern in III with notch in the descending limb of the R wave and R wave in III > R in II. Notch in the descending limb of the R wave in III (middle-final notch). CWR: Clock Wise Rotation.

Left Posterior Fascicular Block VCG criteria in the Frontal Plane: (Brohet 1977)

I. The LV activation is conducted via the left anterior fascicle (LAF), which ends in the endocardial surface of upper, lateral wall in the the anterolateral papilar muscule of the mitral. The initial 10 to 20 ms electrical vector is therefore directed upwards and leftwards (near -45°) with discrete delay (the initial 10 to 25 ms). When LPFB is associated to inferior MI, superior initial forces of ≥25 ms (≥ 12.5 dashes above the orthogonal X lead. 1 dash = 2 ms) (**Castellanos 1972**). This initial activation cause small r waves in the lateral leads (I and aVL) and small q waves in the inferior leads qIII >II).

II. Broad QRS-loop, with clockwise rotation. Cooksey, Dunn and Massie(**Cooksey, Dunn, Massie. 1977**) wrote that occasionally, it may be in "eight" with a counterclockwise terminal portion (10%).

III. Maximal vector near +118º (between +80º to +140º)

IV. Opposite direction of the initial forces (left anterosuperior fascicle) and the maximal vector (right posteroinferior fascicle): the angle between these two vectors averaged 152°.(**Brohet 1977**)

V. Almost all the loop is located below the X line (0 to ±180º) in the inferior quadrants.(**Benchimol 1971**)

VI. ≥ 20% of the QRS-loop located in the right inferior quadrant. When in association to CRBBB, ≥40% (95% of cases)

VII. Afferent limb heading below and slightly to the left, and the efferent one to the right.

VIII. Middle-terminal portion of the QRS loop (vector of 60 ms to 100 ms) with delay. It may possibly reach the right superior quadrant

IX. QRS loop duration up to 110 ms if in isolation. In association to Complete RBBB≥120 ms (**Castellanos 1971**).

X. Normal ST-T vectors in isolated LPFB: T loop with clockwise rotation, heading below and to the left. If in association to Complete RBBB: alteration secondary to ventricular repolarization.(**Varriale 1972**)

Left Posterior Fascicular Block ECG criteria in the Frontal Plane

1. **Frontal plane axis between +90º and 180º in adults.** The difficulty with pure electrocardiographic diagnosis of LPFB arises in the range of between +90 and +110°. Here, we are unable to distinguish electrocardiographically the cases with suspected LPFB without right ventricular loading diseases from the cases with disease predisposing to such overload but without RVH. According to Simonson,(**Simonson 1961**) the upper limit for rightward deviation of the mean QRS axis in the age group of 40-59 years is +87.90 with a standard error of 2.91. It could be postulated that all cases with a mean QRS axis of ≥+90° associated with S1Q3 pattern and relatively R tall voltage in leads III and aVF represent impaired conduction in the region of the posterior fascicle of the left bundle branch. Indeed the distribution of the S1Q3R3 pattern in the range of QRS axis between +90 and +180° is paralleled by the distribution of proven RVH, clinical right loading without hypertrophy, inferoseptal myocardial scar or infarction, and even RBBB.

I. **rS pattern in leads I and aVL:** is the rule

II. **qR pattern in III, aVF and II:** Q wave is always present in III and may be small or absent in II or aVF.

III. **$S_1Q_3R_3$ pattern with right-axis deviation without right ventricular hypertrophy and with or without inferior wall myocardial infarction.** Right bundle-branch block is a frequent occurrence in the spectrum of right-axis deviation (RAD) whether $S_1Q_3R_3$ is present or not. (**Strickland 1972**)

IV. **Notch in the descending limb of the R wave in III** (middle-final notch): frequent and hallmark

V. **RIII > RII ratio:** SÂQRS closer to +120º (III) than +60º (II), when closer to the latter, it would indicate an incomplete form of LPFB.

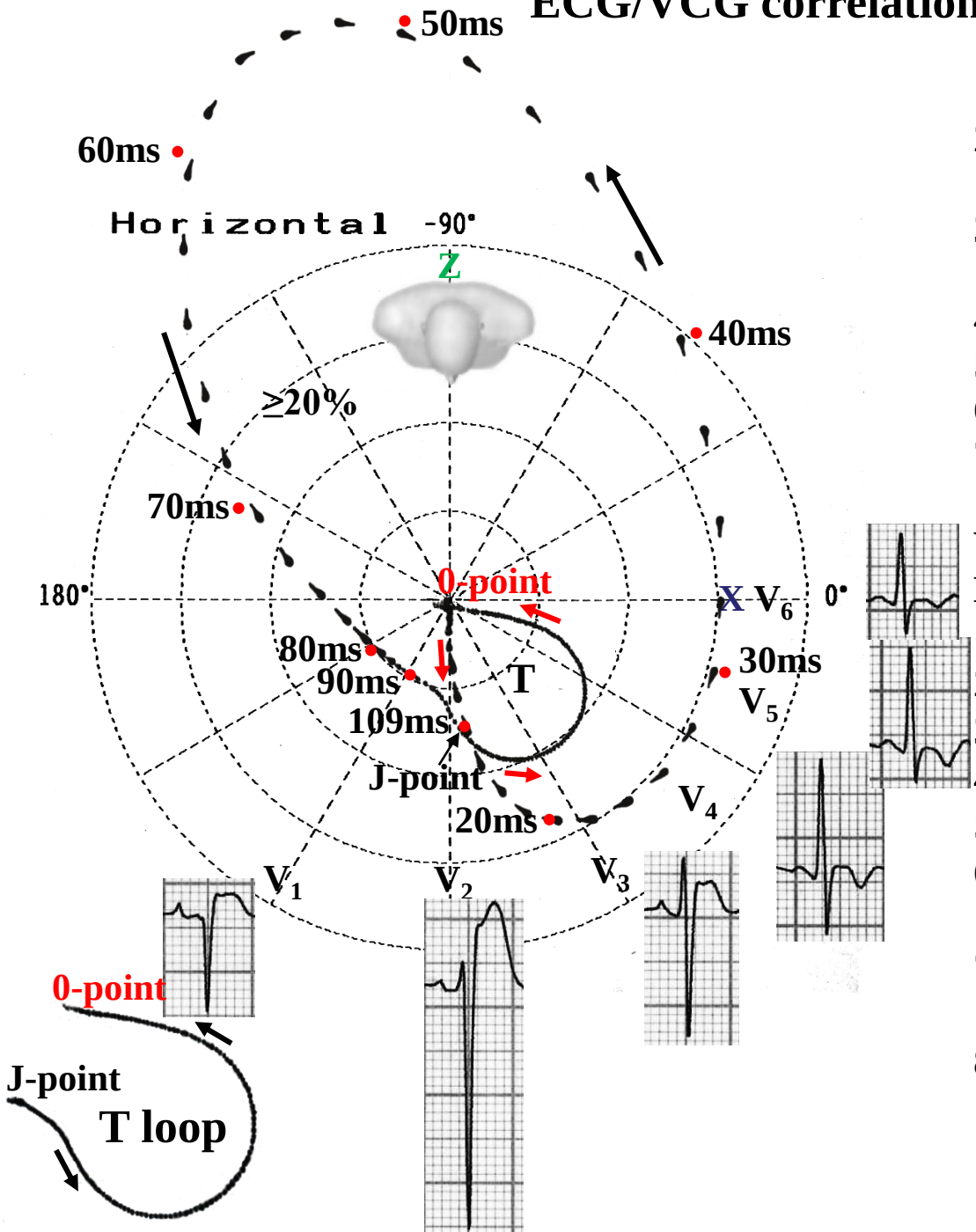
VI. **Q wave size:** The q wave in III is always greater than the q wave in II and aVF. If there is association with inferior infarction, the Q wave duration > 40 ms. (**Castellanos 1972**)

VII. **QRS duration** >120 ms if isolated (without RBBB) and ≥ 120ms when associated with RBBB(> 95% of cases)

VIII. **Ventricular activation time in aVF**: prolonged (≥35ms).(**Rusconi 1980**)

IX. **AV conduction disturbance:** Rosenbaum et al.(**Rosenbaum 1970 a;b**) noted disturbed AV conduction in 83% of his cases with RBBB and LPFB.

ECG/VCG correlation in the Horizontal Plane



ECG

1. V_1 and V_2: rS pattern, QS rarely.
2. Very deep S wave in V_2 consequence of posterior dislocation and to the right of the final forces of the QRS-loop.
3. Scant progression of growth of R wave in precordial leads: dislocation to the left of the transition area (V4).
4. V_5 and V_6: Rs patterns.
5. Increased R-wave peak time of V_5 and V_6 (> 50 ms)
6. Disappearance of q wave in V5 and V6 when LPFB occurs.
7. Primary T-loop: rounded and with symmetric afferent/efferent limb speed.

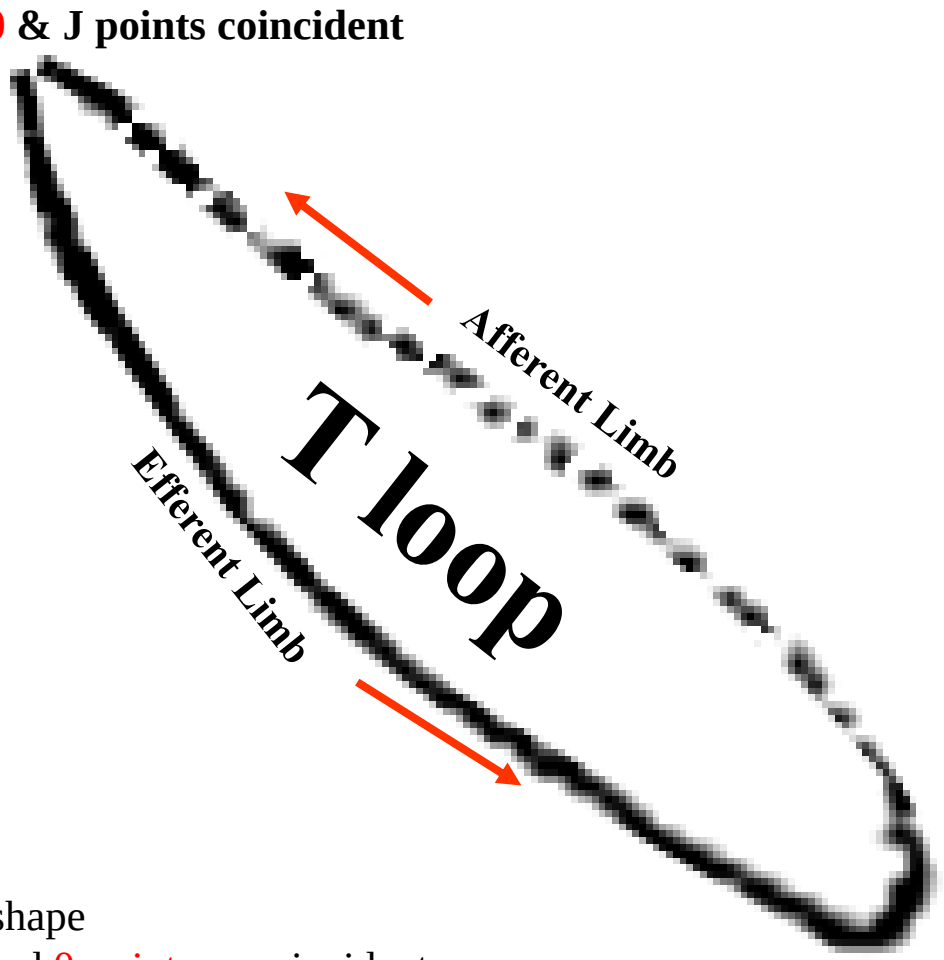
VCG

Horizontal Plane

1. Initial 10 to 20 ms vector heading to the front and to the left;
2. QRS loop very similar to RVH of type C(**Fernándes 1972**);
3. Counterclockwise rotation of QRS loop;
4. Greater area of QRS loop located in the left posterior quadrant;
5. Maximal vector of QRS around -60^0 to -110^0;
6. Final portions with delay (60 ms to 100 ms) and located in the right anterior quadrant;
7. ≥20% of the area of the QRS loop located in the right posterior quadrant (**Pryor 1972**);
8. T loop to the front and the left ($+60^\circ$), counterclockwise rotation(normal) rounded with similar afferent and efferent limbs speed: primary T-loop(ischemic) See in next 2 slides the differences between normal T-loop and ischemic T-loop……

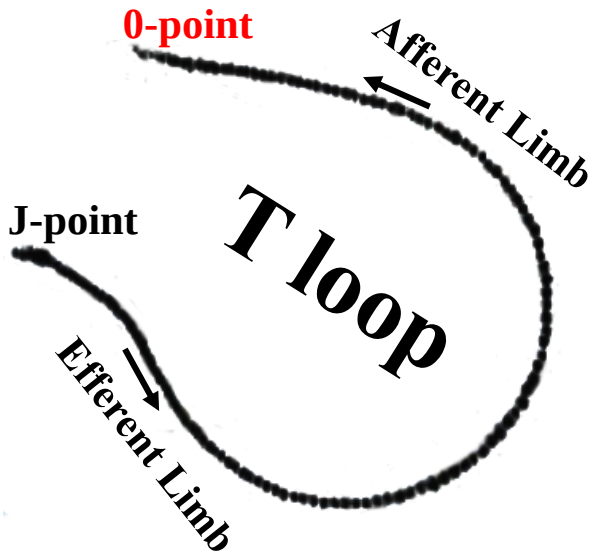
	Normal T-loop	Ischemic T-loop
Shape/morphology	Elliptic tendency	Rounded
The maximal normal T-loop magnitudes in the three planes	**FP**: 0.75 mV. **HP**: 0.75 mV. **RSP**: 0.70 mV.	Smaller
T-loop rotation	**FP**: variable: clockwise or counterclockwise. **HP**: Counterclockwise exclusively. Clockwise rotation in this plane indicates heart disease. **RSP**: clockwise. **LSP:** counterclockwise.	**HP**: Clockwise rotation indicates heart disease.
The J-point and 0-point relationships	Both together with exception of early repolarization	When ST is elevated, the J and **0 point** do not coincide (injury vector)
Velocity of recording of its efferent and afferent limbs	The efferent limb is always recorded more slowly than the afferent one	Both limbs recorded slowly with similar speed
Location	**FP:** in left inferior quadrant. **HP:** in left anterior quadrant. **RSP:** in anteroinferior quadrant.	Variable.
QRS/ ST-T angle	< 75°. Usually smaller in the FP than in the HP.	Wider

Normal T-loop in the HP



Elliptic shape
J-point and 0-point are coincident
Efferent limb is registered slowly than afferent one (comets more separated one another)
Efferent limb corresponds to the initial portion of the T-wave
QRS/ ST-T angle <75°

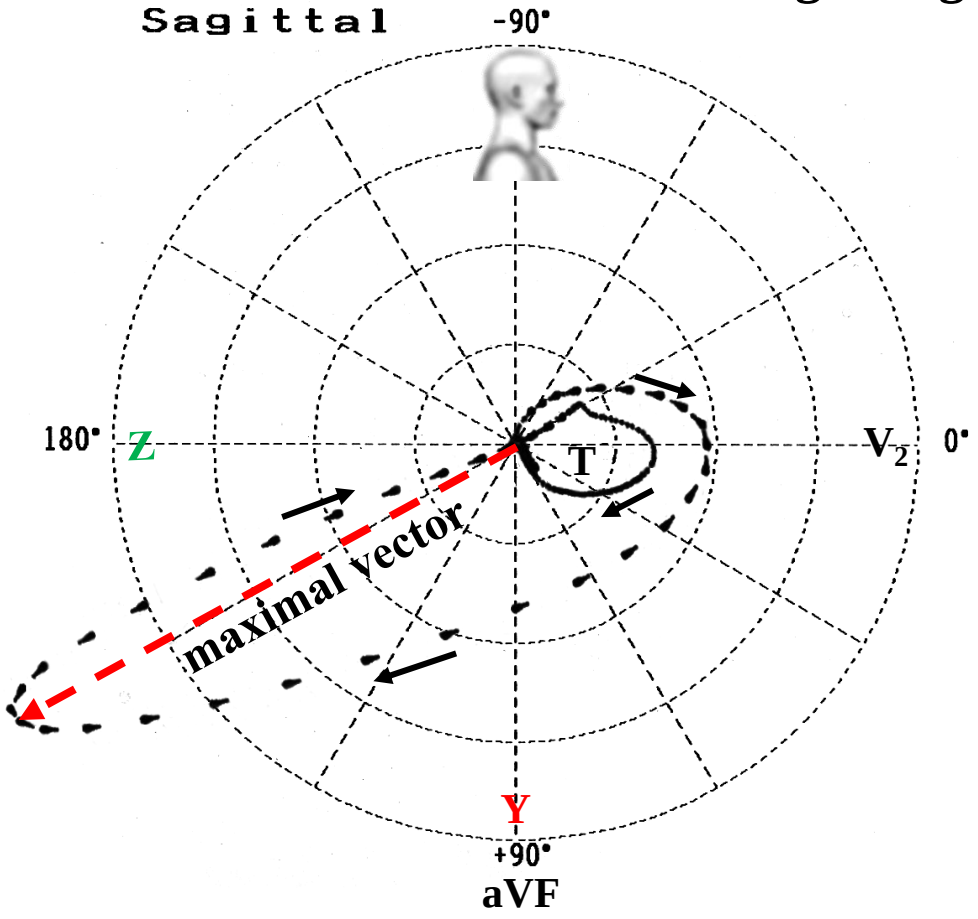
Ischemic T-loop in the HP

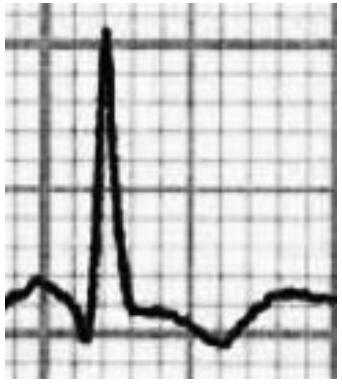


- Round in configuration
- Smaller
- J-point and 0-point are not coincident: ST-segment elevation
- Efferent and afferent limbs have similar speed
- Wide QRS/ ST-T angle: The T sÊ loop is opposite to QRS loop.

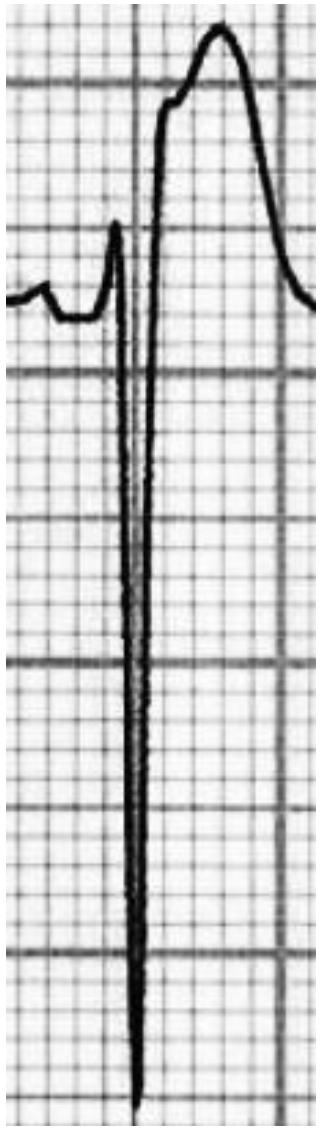
ECG/VCG correlation in the Right Sagittal Plane

Vector of initial 10 to 20 ms directed to the front and above with discrete delay; most of the QRS-loop located in the inferoposterior quadrant; QRS loop of clockwise rotation; maximal vector(dotted red line) around +140º; end delay and initial delay and T loop heading to the front and below with clockwise rotation: **LPFB** and rounded: primary T-loop (ischemic)





Initial q wave in inferior lead: **LPFB**



V_1 and V_2 with rS pattern and very deep S wave of V_2 (28mm!) consequence of posterior dislocation and to the right of the final forces of QRS-loop: **LPFB.**

Left Posterior Fascicular Block (LPFB): possible causes (Pryor 1971; Elizari 2007; Hecht 1973; Nishida 2007; Rosenbaum 1973)

It is the most rare block of all intraventricular blocks. Very rare without association with others blocks.

1. Coronary artery disease (**Rizzon 1975**): LPFB is a rare but clinically important intraventricular conduction disturbance. Its appearance is reliably connected with IMI and generally reflects severe three-vessel CAD), left main coronary arterial stenosis or double vessel disease **(Demoulin 1979)** requiring invasive investigation (**Godat 1993; Janion 2007**). Of a cohort of 830 patients referred for invasive investigation of certain or suspected CAD, 163 patients had an old inferior MI. 9 patients (5.5%) showed the LPFB pattern; 8 of these had three-vessel disease. The diagnosis of IMI had been made only in one case before entry of the patient into the hospital, since LPFB generally masks IMI. Prospective study: 2502 ECGs were investigated. Six LPFBs were detected (0.24%), all associated with IMI and 4 of them with three-vessel CAD. It is concluded that LPFB is a rare but clinically important intraventricular conduction disturbance. Its appearance is reliably connected with IMI and generally reflects severe three-vessel CAD, requiring invasive investigation (**Godat 1993**). During the acute phase of ischemia (**Patenè 2009; 2010: Garcia-Brugos 1993**) or transient during exercise treadmill testing (**Madias 1999**). During the acute phase of MI: 0.2% to 0.4% (**Demoulin 1979**). A case of transient LPFB and various intraventricular conduction disturbances associated with acute anterolateral MI was reported by Ogawa et al (**Ogawa 1976**) and transient mode consequence of occlusion of the RCA (**Hasegawa 2016; Cantor 1992**). Scott (**Scott 1971**) think that the S1Q3 (McGinn-White) pattern in acute cor pulmonale could be a form of transient LPFB. We think that it is not possible because the diagnosis of LPFB requires absence of RVH. Isolated LPFB is a very rare finding but the evidence of transient right axis deviation with a LPFB pattern has been reported during AMI as related with significant RCA obstruction and collateral circulation between the left coronary system and the posterior descending artery (**Sclarovsky 1986; Patanè 2011**). The incidence, in-hospital evolution, and long-term follow-up were studied in patients who developed acute deviation of the mean (frontal) QRS axis to the right during an AMI. Among 3,160 patients evaluated, 13 (0.41%) developed LPFB and 57 (1.8%) developed an incomplete form of LPFB, the right axis deviation (RAD) group (CHF) and mortality (38.5 %). Follow-up revealed a statistically significant higher incidence of cardiac symptomatology (angina pectoris and CHF) in the RAD group than in the control group, mainly in patients in whom RAD persisted > 24 hours (**Lewin 1984; Lopes 1974**). LPFB and basalinferior MI accounted for Q waves in leads II, III and aVF. However, R amplitude in these same leads is increased after LPFB but decreased after basalinferior MI. The mean QRS axis in the frontal plane was shifted toward the vertical in LPFB but little changed or shifted slightly away from the vertical in basalinferior MI. When LPFB and inferobasal MI coexist, there may be masking, imitation or enhancement of the effects of one lesion by the presence of the other (**Watt 1982**). Recently, Hasegawa et. al (**Hasegawa 2016**) showed a transient ischemic right axis deviation in the Frontal Plane in a case of IMI/myocardial ischemia.

   Transitory **LPFB during contrast injection in the RCA and in acquired ventricular septal defect:** in cases of inferior wall MI, complicated

by rupture of the inferior septum, resulting in isolated LPFB (**Rokey 1984**). Intermittent right axis deviation has been also rarely reported in the presence of LBBB also during AF and with acute myocardial infarction. Isolated LPFB is a very rare finding and transient right axis deviation associated with a LPFB pattern has been also rarely described associated with acute myocardial infarction. Changing axis deviation with changing bundle branch block and new-onset of AF during acute MI has been also reported. Changing axis deviation with intermittent RBBB in a patient admitted with acute MI has been also described (**Patanè 2009**);

2. Systemic hypertension and severe CAD in association (**Glancy 2010**);
3. Lenègre's disease, progressive cardiac conduction defect (PCCD) or "idiopathic" sclerosis of the intraventricular His system: by mutation in the SCN5A gene, the same gene affected in the Brugada Syndrome (**Dianzumba 1977**);
4. Lev disease or progressive idiopathic sclerosis of the "cardiac skeleton". With a clinical behavior similar to Lenègre disease, however, it occurs in elderly patients (**Elizari 2007**);
5. Heavy calcifications of the left side of the cardiac skeleton (**Demoulin 1979**);
6. Aortic valve disease: Aortic stenosis(calcific aortic stenosis and congenital bicuspid aortic stenosis) associated or not with aortic insufficiency. Aortic insufficiency: attributed to the mechanical effect of jet regurgitation on the posterior portion of the left septum, the site that the thick LPF goes through (LV inflow tract);
7. Dissecting aneurysm (**Scott 1971**);
8. Supravalvar aortic stenosis;
9. Coarctation of the aorta;
10. Dissecting aortic aneurysm;
11. Massive calcification of the "cardiac skeleton";
12. Transcatheter aortic valve replacement; was observed in 1 case form 271 consecutive procedures in patients with symptomatic, severe aortic stenosis (**Laynez 2011**);
13. Chronic chagasic myocarditis: the most frequent one in Latin America. Additionally, given recent migration trends, there is a large population at risk in the United States (**Traina 2017**);
14. Cholera and myocarditis with antitoxine choleric antibodies (AcTCA) (**Leon 1997**);
15. Cardiomyopathies, myocarditis (e.i diphtheritic myocarditis);
16. Infiltrative myocardial diseases: sarcoidosis, amyloidosis.hemochromatosis;
17. Interventricular septum tumor (**Cola 1992**);

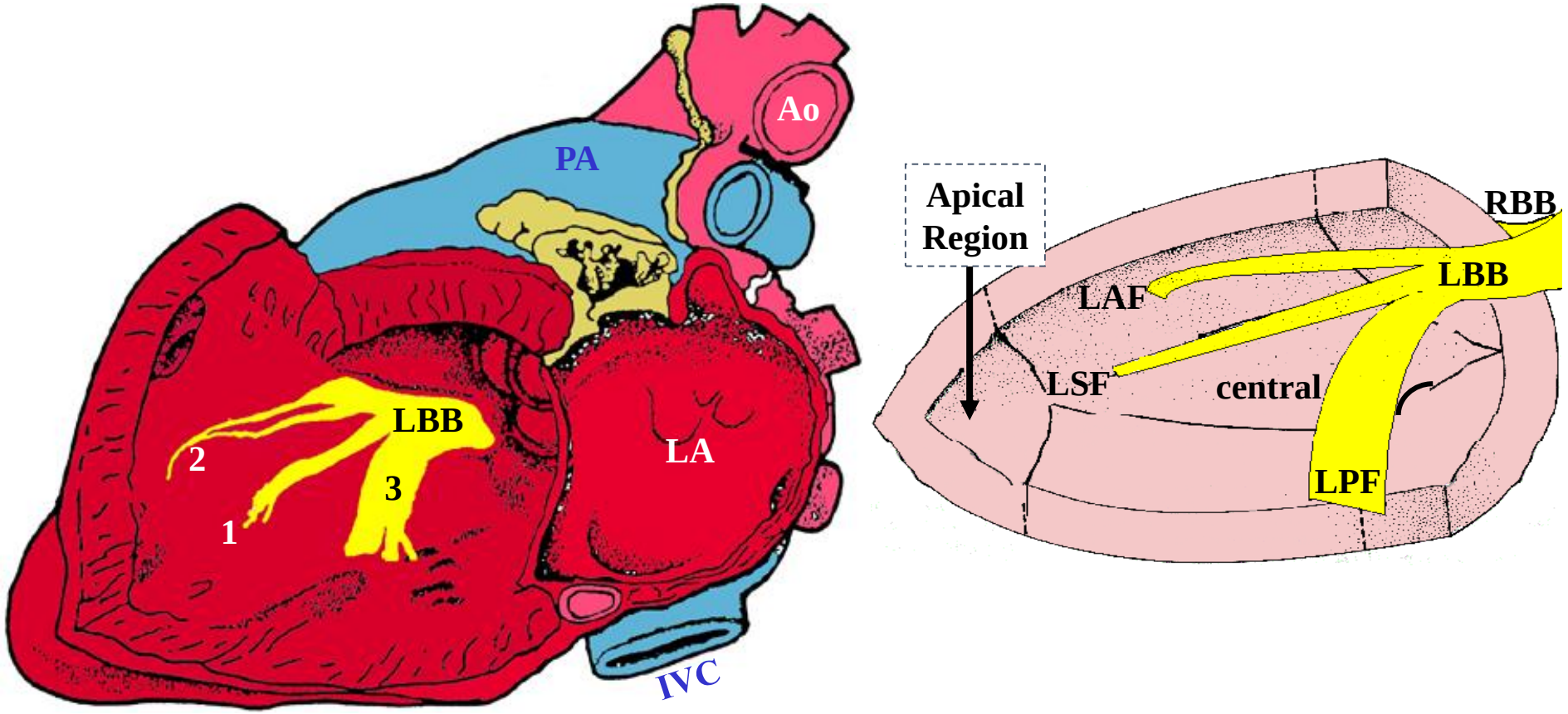
18. Hyperpotassemia (**O'Neil 1976**);
19. Systemic sclerosis (scleroderma). Consequence of some degree of myocardial **fibrosis** (**Follansbee 1985**);
20. Ventricular septal defect (**Rokey 1984**);
21. High-dose of interleukin-2 (**Singla 2008**);
22. Left posterior fascicular block caused by Duchenne Muscular Dystrophy **(Perlof 1984) (The present case)**;
23. Hereditary: pseudo LPFB? (**Lorber 1988**) right axis deviation: ECG pattern of pseudo left posterior hemiblock and incomplete right bundle branch block.

Wolff-Parkinson-White Syndrome Mimics a Conduction Disease RBBB associated with LPFB (Marrakchi 2014)

Transient forms of LPFB: Intermittent right axis deviation in the presence of complete LBBB. The most plausible explanation is the coexistence of LPFB and predivisional LBBB. Bobba et al **(Bobba 1972)** described transient LPFB in four cases induced by exercise test. The occurrence of transient LPFB patterns is related to the development of acute, transient injury in the inferobasal wall of the LV (inferodorsal) in the presence of segmental or widespread CAD and chronic inferobasal damage. In the presence of LPFB, a progressive change of the SÂQRS from a normal axis to the right, up to +120° in the same or subsequent tracings in a short period, can only be explained by increasing the degrees of LPFB. When a partial or incomplete LPFB is present and the SÂQRS direction can be considered normal in clinical practice, it is difficult or even impossible to reach a diagnosis. That is, small degrees of block in the divisions of the LPFB totally overlap normal variants **(Elizari 2012)**. Another differential diagnosis of LPFB is with inferior or posteroinferior fascicular block of the RBBB. The block in the divisions of the free RV wall are ECG/VCG changes, secondary to physiological delay or to true dromotropic disorders in the territory of one of the three fascicles of the RBB, in isolation in the RV free wall. To speak about blocking it is necessary the presence of dromotropic disorder or slowing of ventricular activation process because in its absence can not call it so properly. These blocks cause localized or regional delay on basal portion of RV on its free wall. Zonal right ventricular blocks correspond to block of the superoanterior division of the right bundle on RV free wall (on RVOT) or inferoposterior zone (on RVIT) of the right free wall ventricle.(differentia diagnosis with LPFB). Others denominations: Parietal focal blocks (**Masini 1952; Alzamora-Castro 1953; Rossi 1954; Noseda 1963**); right focal blocks; peripheral branch block of the right bundle; peripheral blocks of the right branch; right peripheral fascicular blocks **(Pastore 1983);** right peripheral blocks; distal RBBB; divisional blocks of the RBB; fascicular block of the His bundle; delayed activation of the wall of the RV.

Fascicular Blocks of the Left Intraventricular His system

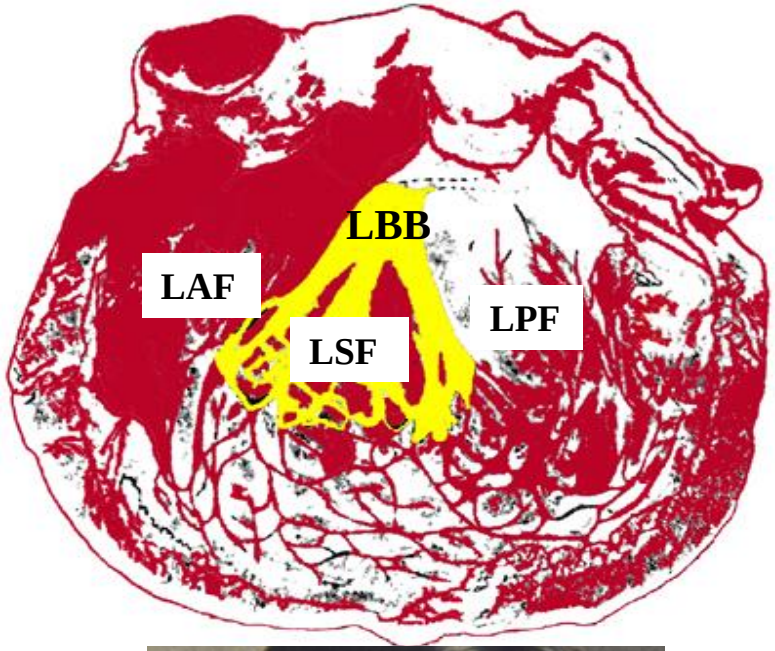
The left intraventricular His system is made up by three fascicles:

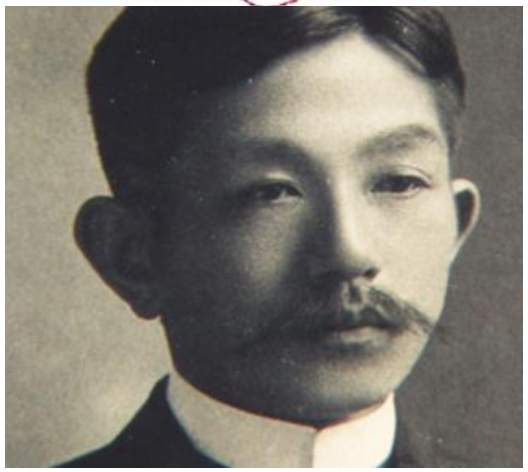


1) Left Septal Fascicle (LSF)
2) Left Anterior Fascicle (LAF)
3) Left Posterior Fascicle (LPF)

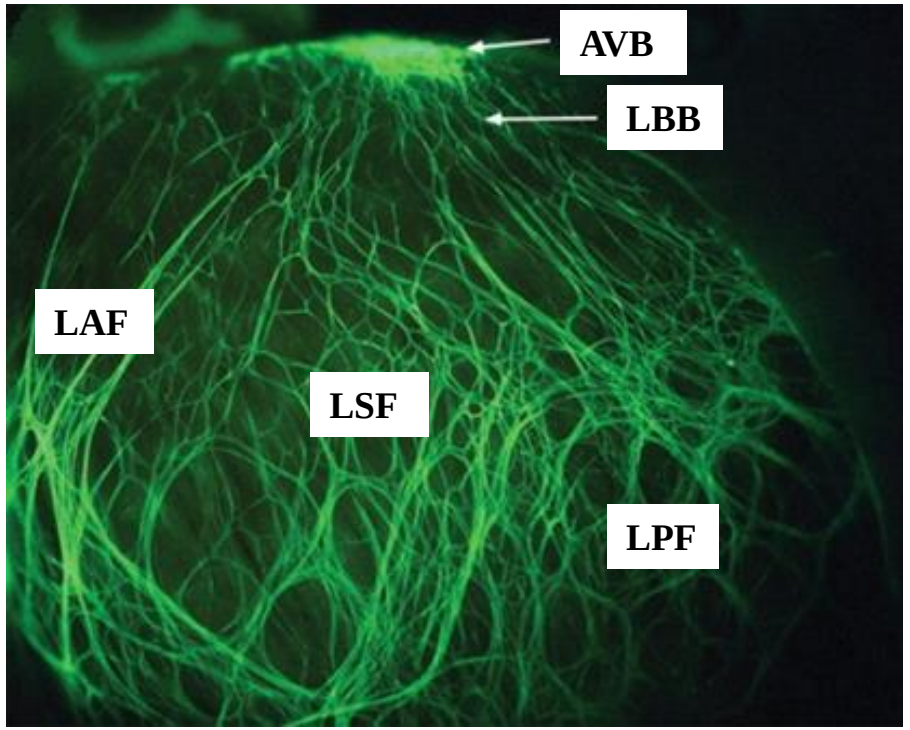
Left lateral view of the intraventricular His system with the three fascicles of the Left Bundle Branch (LBB). Left Septal Fascicle- 1 (LSF); Left Anterior Fascicle - 2 (LAF); Left Posterior Fascicle -3 (LPF).

From the beginning of last century (1906), Tawara showed the left His system as trifascicular (Tawara 1906)





Classical outline by Sunao Tawara (1906) that proves the trifascicular nature of the left His system (**Tawara 1906**)



Sunao Tawara studied at the Imperial University in Tokyo, graduating there in 1901, Igaku Hakushi 1908. The years 1903 to 1906 he spent in Marburg studying pathology and pathological anatomy with Karl Albert Ludwig Aschoff (1866-1942). It was here he undertook his important works on the anatomy and pathology of the heart. When returning to Japan he was appointed extraordinary professor of pathology in Fukuoka, becoming *ordinarius* of this specialty in 1908.

Mauricio B. Rosenbaum and his Argentine school “spread” in literature the concept of the bifascicular nature of the left His system that is accepted until today by most authors

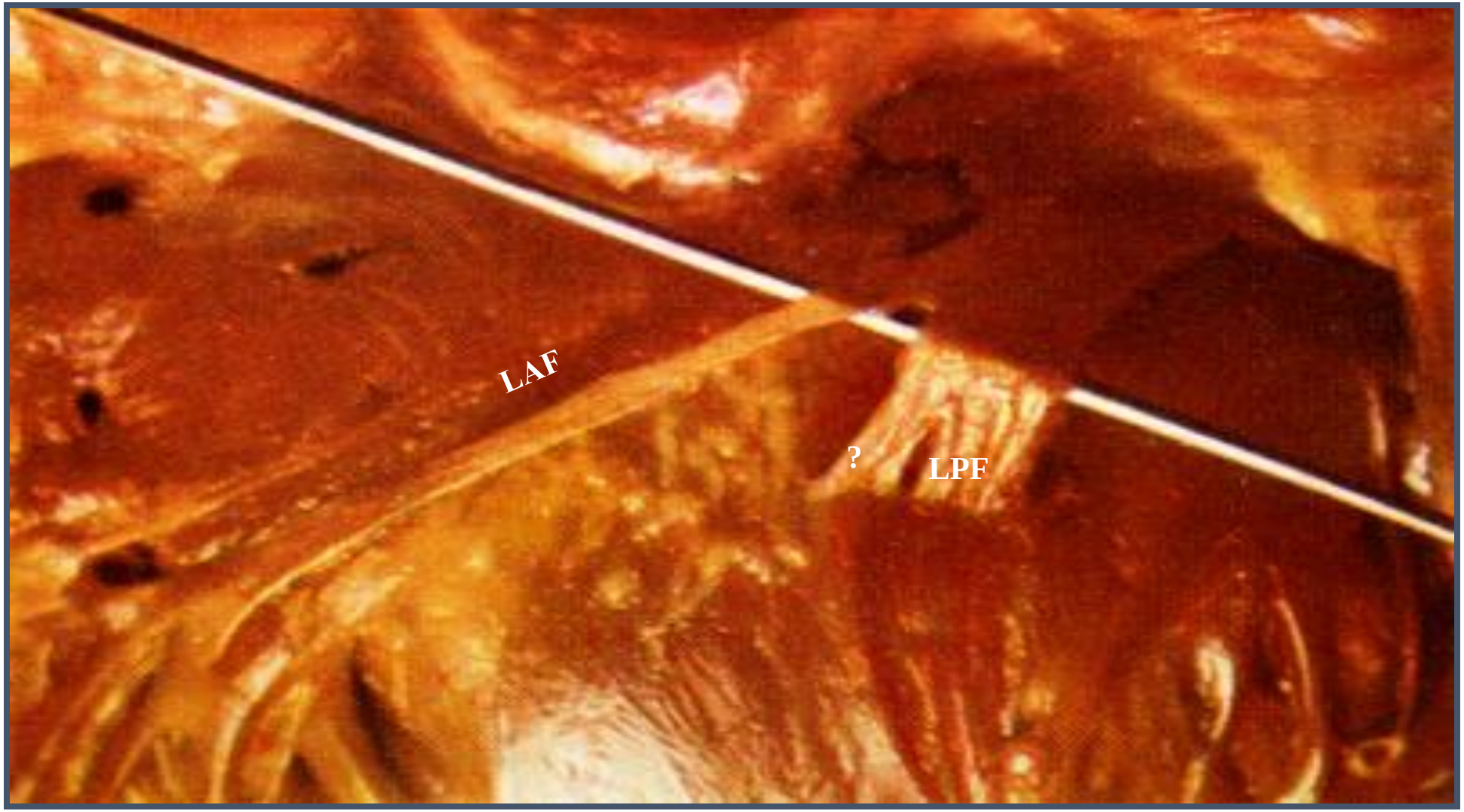
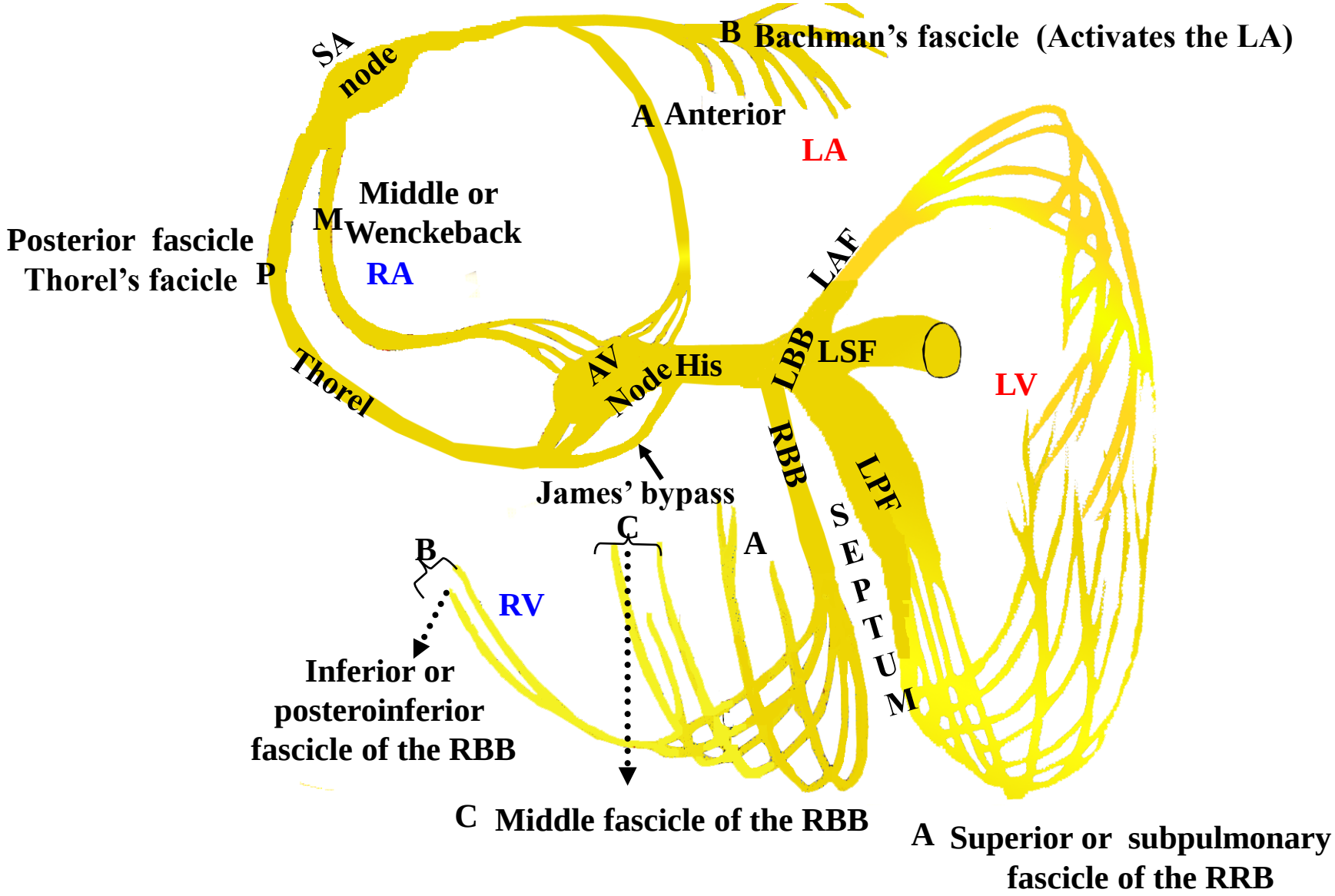


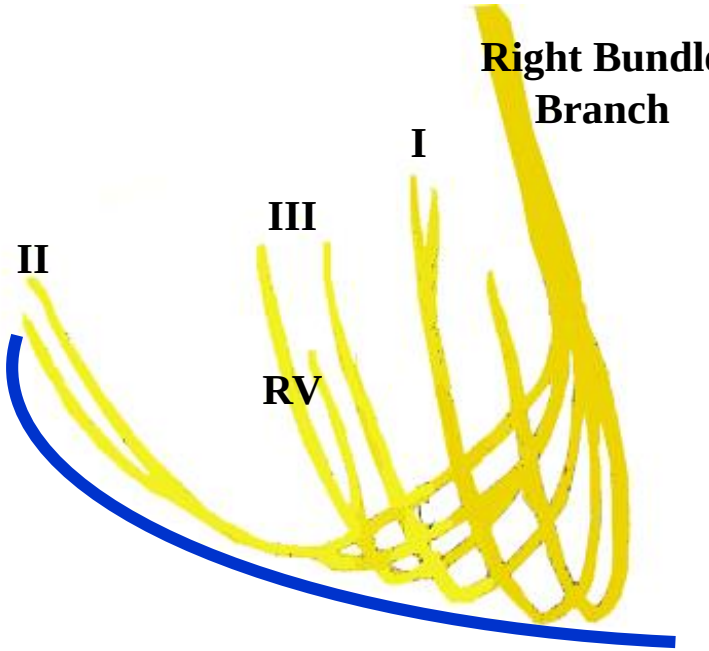
Image from the classical book by Rosenbaum (**Rosenbaum 1968**), where the dissected left branch is shown lifted with a scalpel at the place of its division. According to the interpretation of the great master, the left branch splits into two. On the contrary, we think it splits into three, because the LPF originates the LSF.

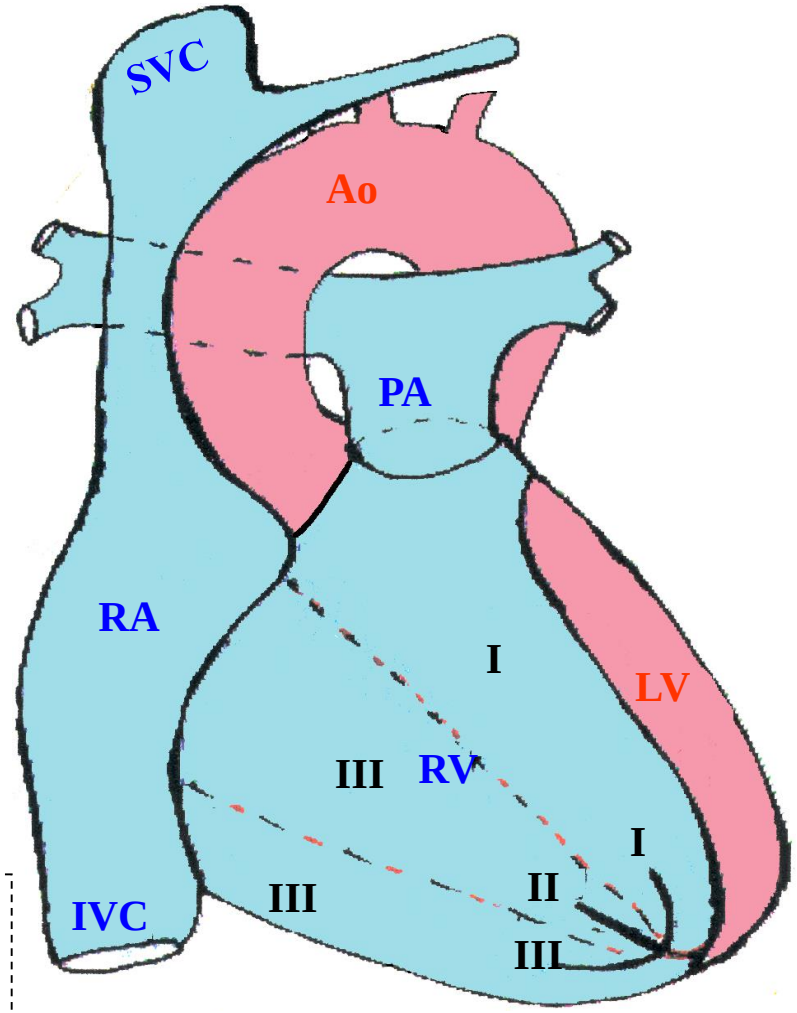
Components of the cardionector system of sinoatrioventricular & intraventricular conduction system



You can see the SA node, atrial internodal bundles (anterior, middle and posterior), AV node, His bundle and its divisions (3 left and 3 right) (**Magri 1956**).

Distribution of the three fascicles of the right branch of the His bundle in the RV free wall (Lev 1964-1968; Mahaim 1931; Lenègre 1958)





I - Territory of superior or subpulmonary fascicle
II – Territory of inferior or posteroinferior fascicle
III – Territory of middle fascicle

Distribution of three divisions of the right branch in the RV free wall.

The LPFB diagnosis is always clinic/electrocardiographic it is necessary absence of:

I. **Extremely vertical heart position:** loosely descriptive of the hearts electrical axis when this is directed at approximately +90°. As a cardiac electrical position, recognized in the ECG when the QRS complex in lead aVL resembles V1 while that in aVF resembles V6. The heart is considered vertical if lead aVL contained QS or rS pattern (Rotation of the heart about Its anteroposterior axis). A right heart axis is present when lead I is negative and aVF positive. (between +90º and +180º): A vertical heart in slender subjects (ectomorphic biotype);

II. Right ventricular hypertrophy/enlargement

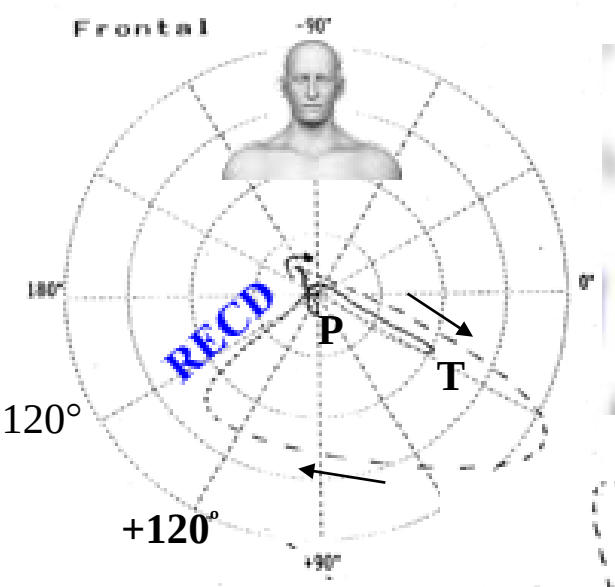
III. Large lateral wall myocardial infarction.

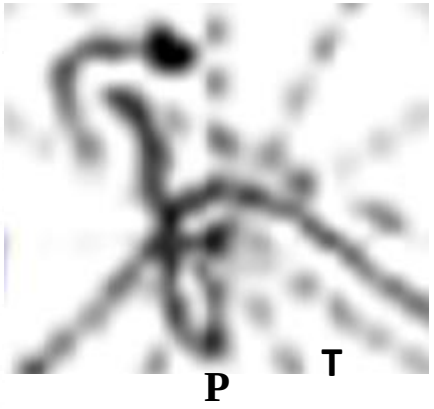
IV. Tricyclic antidepressant overdose

V. Right Posterior Subdivision Block of the right bundle branch: it is another differential diagnosis of LPFB. We called right end conduction delay type II (**RECD) type** II or Right Posterior Subdivision Block or Right Inferior Fascicular Block. This block is characterized by presenting **RECD** located in the right inferior quadrant in the territory of the inferior fascicle of the right branch. It corresponds to the territory of the right inferior fascicle (RIFB) of the right bundle branch. The differential diagnosis occurs with LPFB. Many of the cases described in literature as LPFB are, the way we see it, RECD type II, and since their electro-vectocardiographic differences are very subtle, the diagnosis must always be clinic-electrovectocardiographic. SÂQRS between + 70° and + 110°; normal QRS duration; SI – RII - RIII pattern, with RII and RIII of voltage not increased (usually ≤10 mm), never reaching 15 mm (essential element for the differential diagnosis with LPFB); RII ≥ RIII (in LPFB RIII > RII); prolonged ventricular activation time on V5R, V3R and V4R (and aVF in horizontal hearts). This is because these leads are located opposite the blocked area; aVR of the QS type; possible notch in the descending ramp on inferior leads; S wave of V_2 and/or V_3 of increased depth; persistent with notched S wave in V_5 and/or V_6; and in V_1: rS, RS or rSR' with S of V_1 and V_2 possibly broadened. See next slides…….

The diagnosis of LPFB cannot always be made from the ECG alone, except in cases of transient or intermittent LPFB. Common findings in transient LPFB are: A shift of the main QRS forces inferiorly and slightly to the right, between +90° and +120°, which generates a relatively tall R wave in leads III, II, and aVF, with RIII>RII, qIII.> qII, ventricular activation time in aVF ≥ 35ms, and a deep S wave in leads I and aVL, A definite change in the direction of the initial 20ms QRS vectors, which is shifted superiorly and to the left. This changes are responsible for the occurrence of an SI qIII pattern, which simulates a fictitious clockwise rotation of the heart on the longitudinal axis, a displacement of the precordial transition zone to the left and a small widening of the QRS interval ≤ 2ms (**Bobba 1972**).

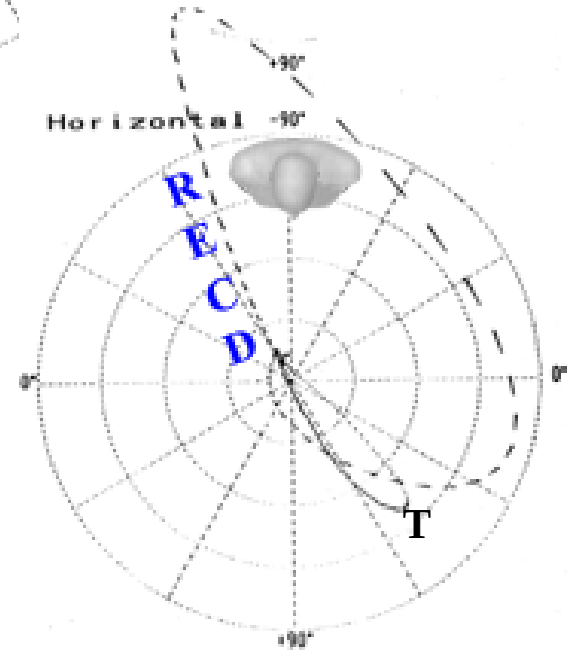
B) VCG criteria: Right End Conduction Delay **(RECD)** in the territory of inferior or posteroinferior fascicle:





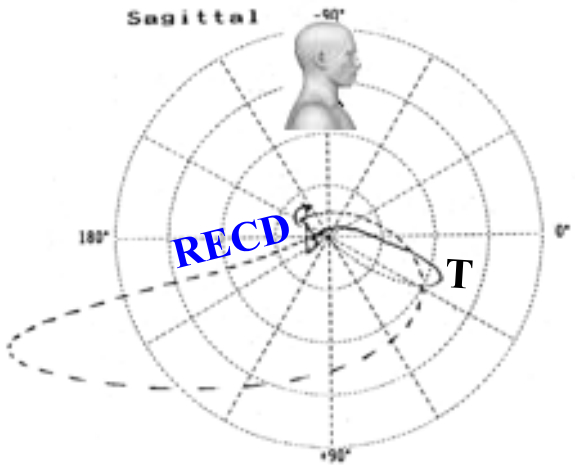
Frontal Plane:

1) Initial vectors always to the right, above or below;
2) QRS loop with clockwise rotation (CW);
3) Predominant location in the inferior quadrants;
4) Rapid change from left to right between 30ms and 50ms;
5) **Right End Conduction Delay(RECD)** to the right and below between +120° and +150°.



Horizontal Plane:

1) QRS loop of counterclockwise rotation;
2) Marked posterior dislocation (Remembers right ventricular overload type C);
3) Rapid change from left to right between 30 and 50 ms;
4) **RECD** to the right and downwards.

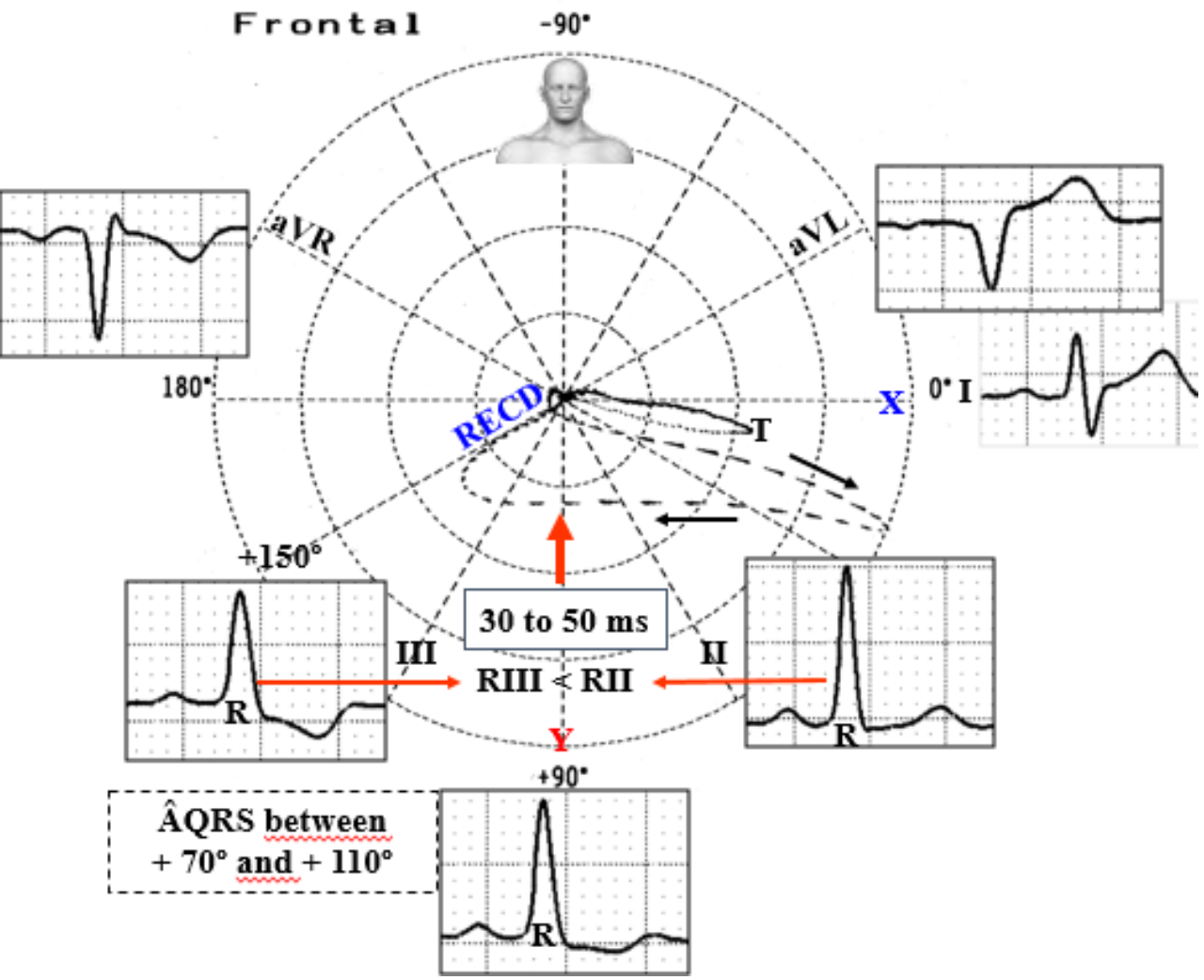


Right Sagittal Plane:

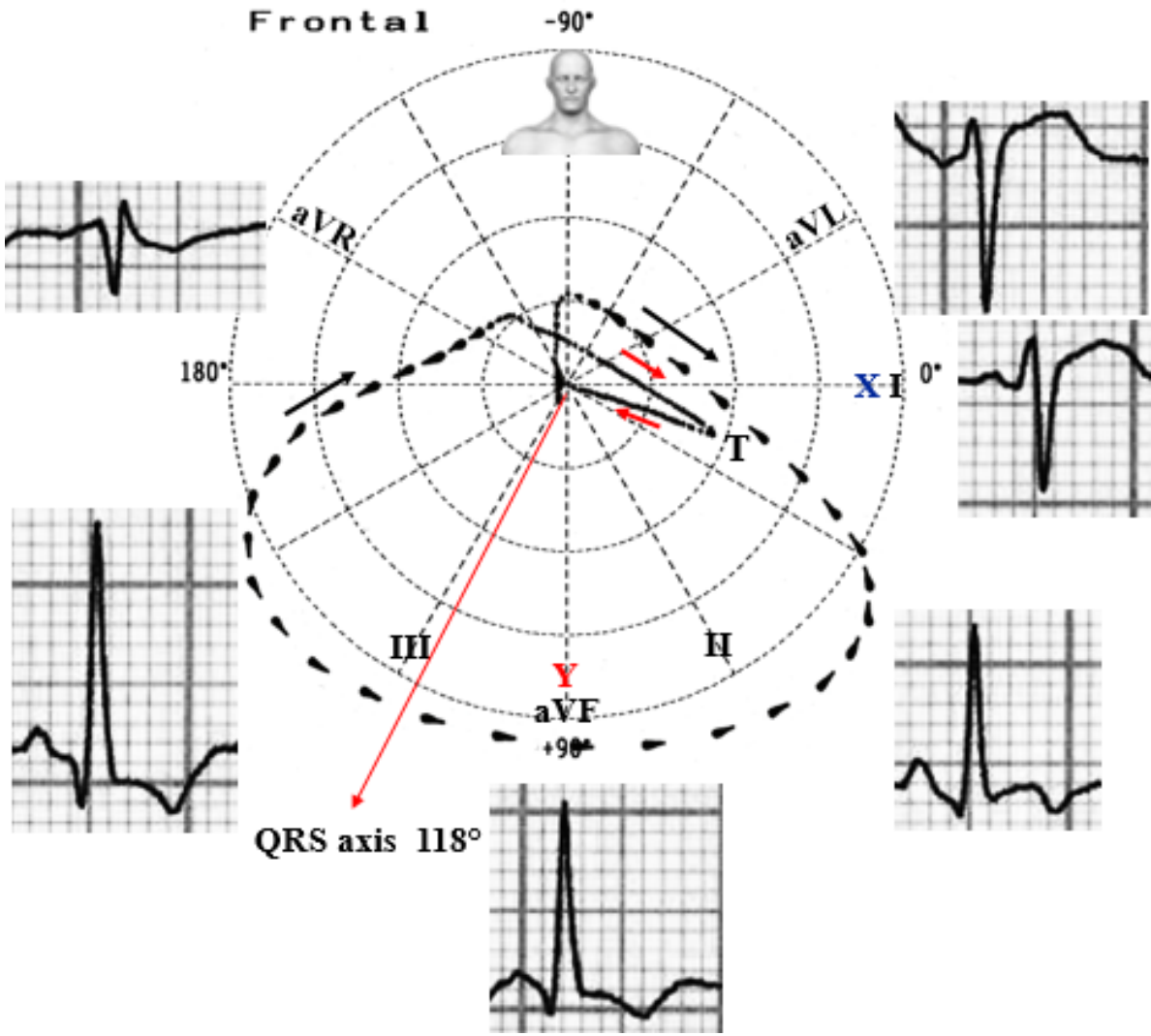
1) Initial vectors upward or downward;
2) Clockwise rotation;
3) Marked posterior/inferior dislocation;
4) **RECD** downward and backward.

ECG/VCG differential diagnosis in the Frontal Plane

RECD type II or Right Posterior Subdivision Block of the RBB



Left Posterior Fascicular Block of the LBB

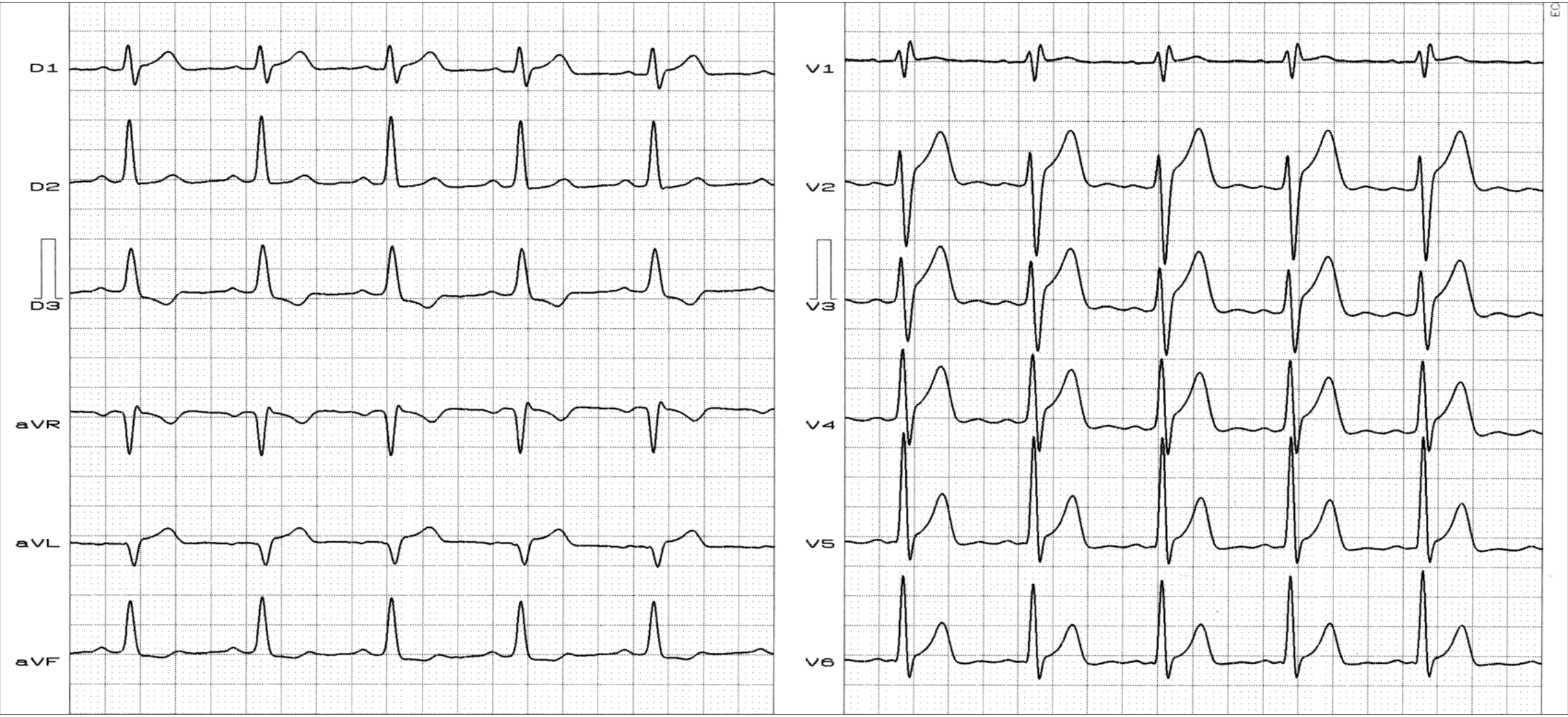


See in next slide the differential diagnosis ……..

Differential diagnosis between RECD type II and Left Posterior Fascicular Block (LPFB)

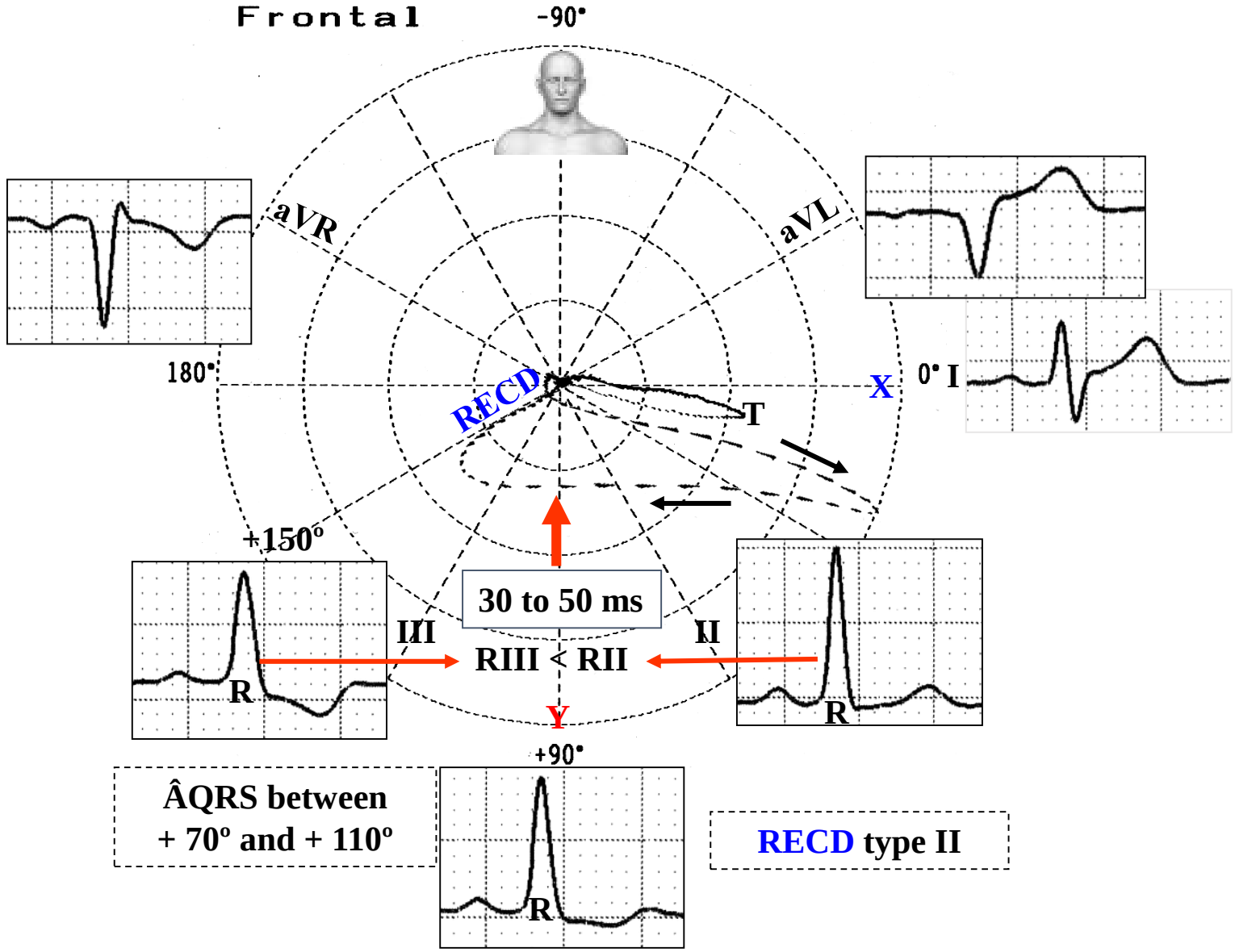
	RECD type II or Right Posterior Subdivision Block	LPFB
PR interval	Normal.	Frequent prolongation.
Association with inferior infarction	No.	Frequent.
Voltage of RII and RIII	≤ 10 mm.	≥ 15 mm.
RII/RIII voltage ratio	RII >RIII.	RIII > RII.
Notch in the descending ramp of R wave of inferior leads	Absent.	Constant middle-final notch.
Ventricular activation time in aVF, V5 and V6	Normal.	Increased: up to 30 ms.
Ventricular activation time in aVL	Normal.	Decreased: up to 15 ms.
QRS loop in the FP	Clockwise rotation and with characteristic rapid passage from left to right between 30 and 50 ms. RECD on inferior right quadrant.	Clockwise, aspect of “fat” loop and maximal vector close to + 120°.

Name: BMB; **Sex:** M; **Age:** 20 yo; **Race:** White; **Weight:** 78 Kg; **Height:** 1.81 m; **Biotype:** Athletic; **Date:** 18/09/2004; **Medication in use:** none



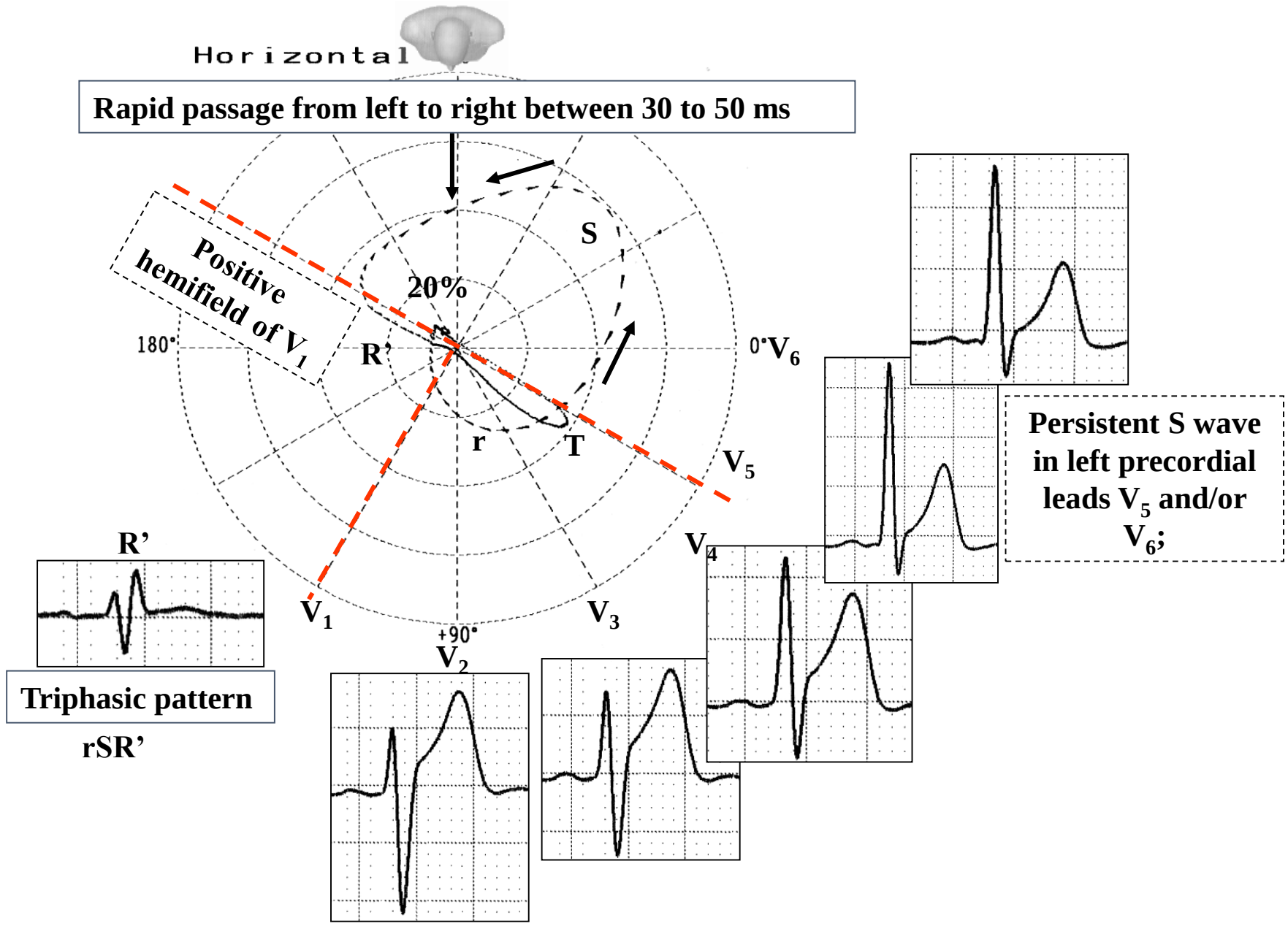
Clinical diagnosis: Healthy patient. He came to the office to have his aptitude for the practice of sports evaluated.
ECG diagnosis: SÂQRS: + 85º. RII > RIII. SAT: + 5º to the front and the left. Morphology of IRBBB: rSR' in V1.
Conclusion: ECG of **RECD** type II. ECG/VCG correlations are observed on next slides.

ECG/VCG correlation on Frontal Plane

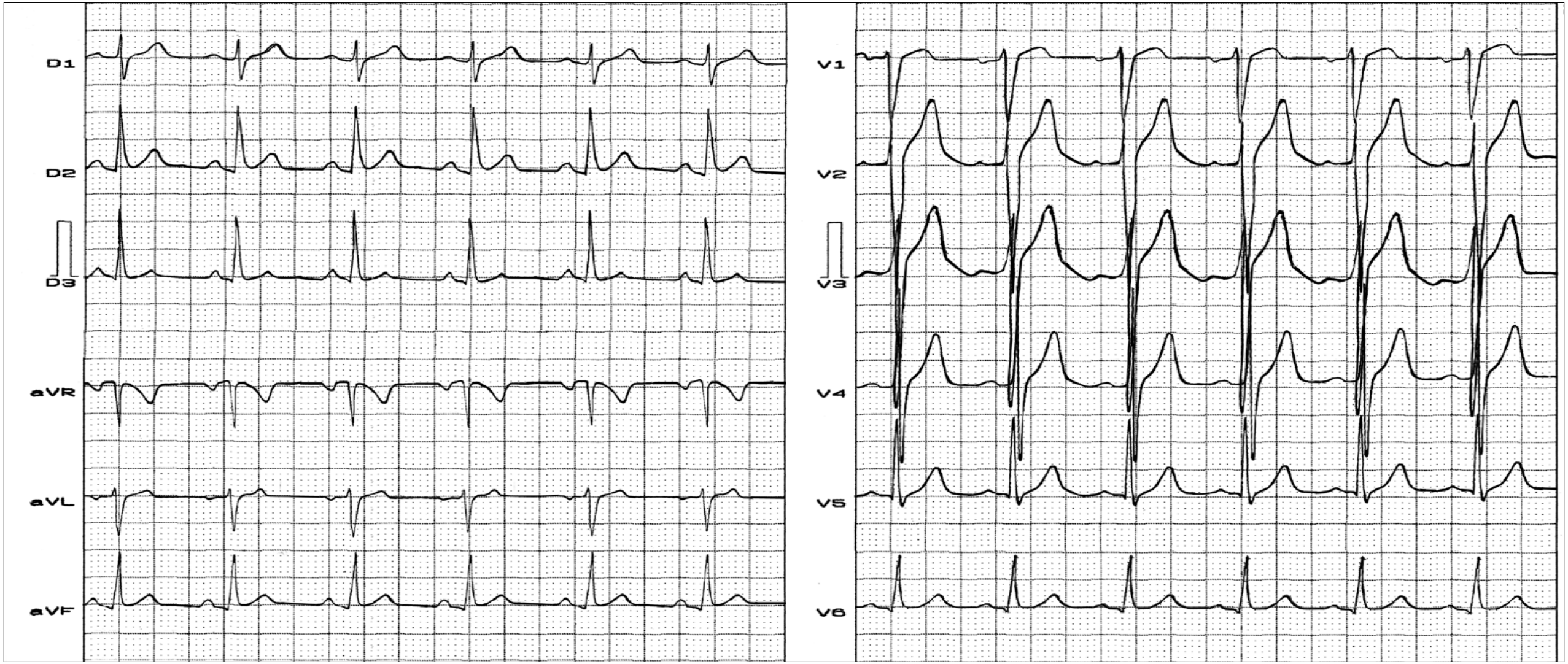


QRS loop located on inferior quadrants, CW rotation, rapid passage from left to right between 30 to 50 ms SÂQRS between + 70º and + 110º and **RECD** located on inferior right quadrant.

ECG/VCG correlation in horizontal plane of RECD type II



Name: CJO; **Sex:** M; **Age:** 22 y/o; **Ethnic group:** Caucasian; **Weight:** 70 Kg; **Height:** 1.71 m; **Biotype:** Athletic; **Date:** 15/05/2001

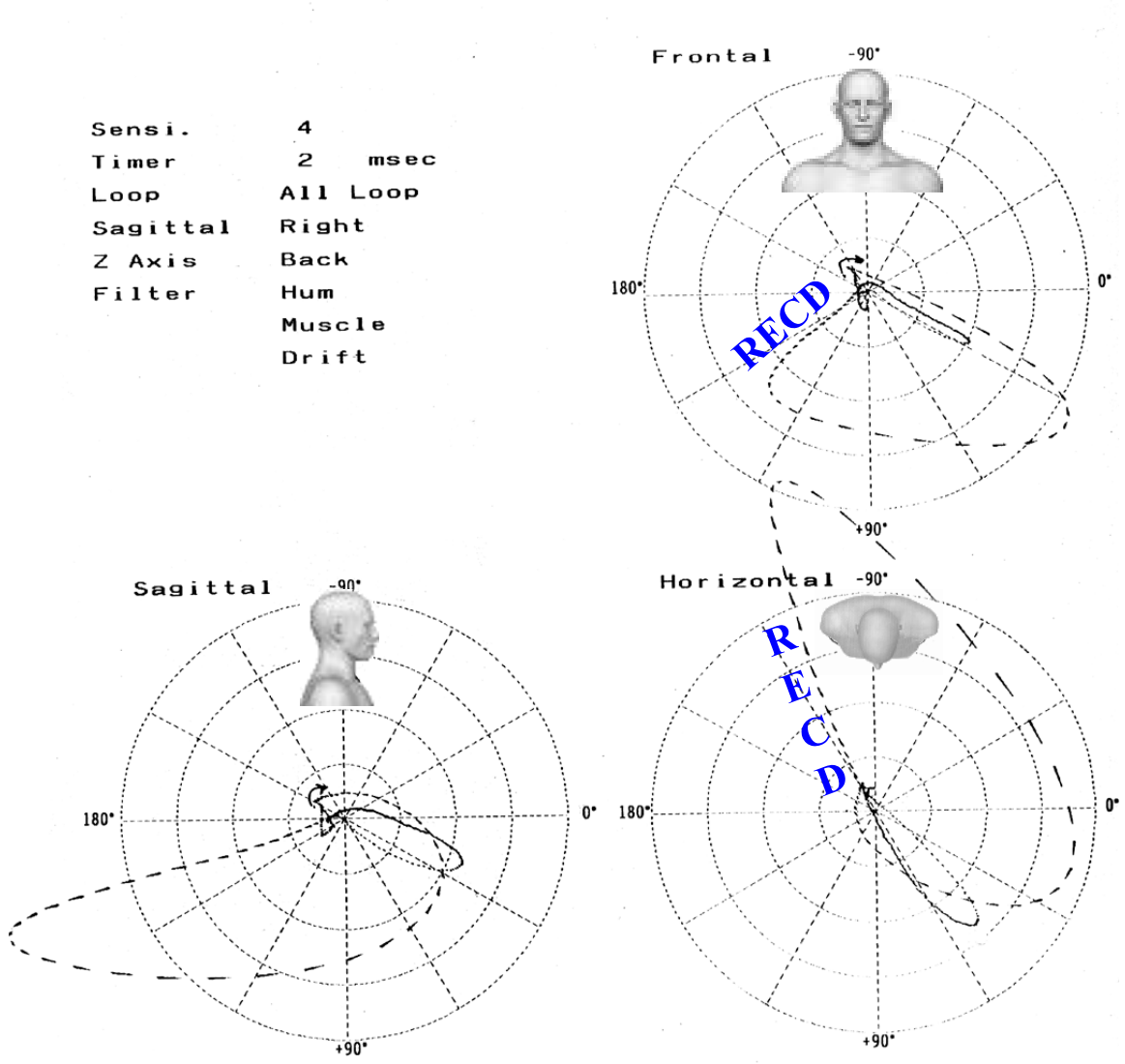


Clinical diagnosis: CM: preoperative evaluation for abdominal surgery, physical examination background: nothing important. ECHO nothing important. Chest X rays: nothing important.

ECG diagnosis: SÂQRS: +95º. SI-RII-RIII pattern (RIII < 15 mm). I and aVL: rS.

II and III: qR. Descending ramp of R wave is slightly slow. It may present diagnostic doubt with LPFB.

Name: CJO; **Sex:** M; **Age:** 22 y/o; **Ethnic group:** Caucasian; **Weight:** 70 Kg; **Height:** 1.71 m; **Biotype:** Athletic; **Date:** 15/05/2001



VCG of RECD type II.

Duchenne muscular dystrophy Overview

Duchenne muscular dystrophy (DMD) is an recessive X-linked mediated, musculoskeletal disorder that affects only males. It is the most common and severe form of muscular dystrophy (MD) where there is failure to manufacture dystrophin. Clinically, it is characterized by progressive muscle wasting leading to premature death. DMD is a inherited noninflammatory but progressive muscle disorders without a central or peripheral nerve abnormality. The disease affects the muscles with definite fiber degeneration but without evidence of morphologic aberrations. Mutation of the X linked chromosome prevents the production of dystrophin. Dystrophin is a cytoskeleton protein found in the skeletal and cardiac muscle that helps maintain sarcolemmal stability by connecting the cytoskeleton of each muscle fiber to the underlying basal laminal layer. As a result of the mutation of the DMD gene on the short arm of the X chromosome, there is a deficiency of dystrophin in the muscle fibers. This shortage of dystrophin leads to a disruption in the linkage between the subsarcolemmal and the extracellular matrix which will cause muscle fibers to become damaged over time after having to repeatedly contract and relax. Ultimately, resulting in necrosis. Once the muscle fibers have been structural damaged muscle weakness will set in. Because DMD results in muscle weakness due to a defect or damage in the muscle fibers it is considered a myopathy. Myopathy literally means muscle disease, and is indicative of DMD because the weakness experienced by the patient is a result of the wasting muscle fibers and not because of lesions or damages of the upper motor neurons, lower motor neurons, peripheral nerves, neuromuscular junction, or motor pathway. Symptoms of DMD include a waddling gait, enlarged calves, muscle weakness, thoracic deformity, cardiomyopathy and restrictive pulmonary disease and eventually paralysis. There is no known cure for DMD and life expectancy is estimated to be 25 /35 years. The final cause of death is usually respiratory /cardiac failure.

DMD affect 1:3500 to 1:6000 male births worldwide, causing severe disability and death due to cardiopulmonary failure associated with dilated cardiomyopathy and restrictive pulmonary disease (**Engel 1994**).

Incidence

The incidence of MD varies, depending on the specific type of MD under consideration. DMD is the most common MD and is sex-linked, with an inheritance pattern of 1 case per 3500 live male births (**Emery 1993; Dubowitz 1995**). ≈ 30% of cases occurs as a result of spontaneous new mutations (**Emery 1991**). Becker MD is the second most common form, with an incidence of 1 case per 30,000 live male births (**Shapiro 1993**). Other types of MD are rare. For example, limb-girdle dystrophy occurs in only 1.3% of patients with MDs.

The incidence of MDs internationally is similar to that of the US for most of the dystrophies, except for the oculopharyngeal type, which is more common in French Canadians (**Pratt 1986**). Distal MD tends to occur more in Sweden, high esteem for his work in faradism and for his contributions to the understanding of muscle diseases, one of the most severe and classic forms of DMD, now bears his name.

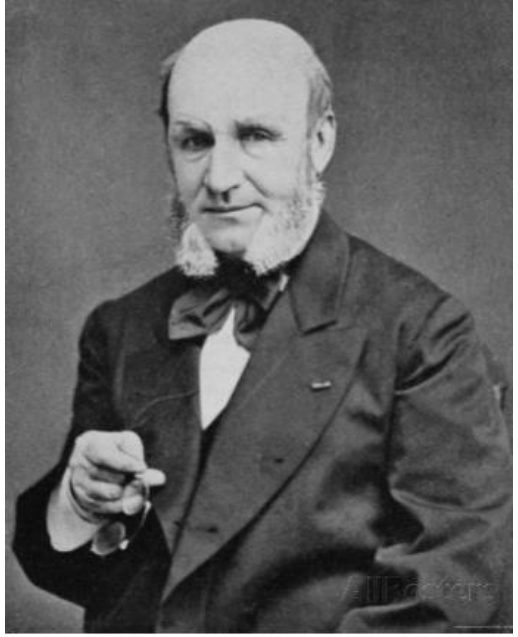
Brief history

The first historical account of DMD was reported by Gaetano Conte in 1836 (Conte (1798–1858). He was a 19th-century physician who practiced in the vicinity of Naples. He reported to the Annals of the Ospedale degl'Incurabili di Napoli on two brothers with a so far unknown kind of **muscular paralysis** (**Conte 1836**), a condition that, a quarter of a century later, was systematically studied by the British physician Edward Meryon (1807–1880) (**Meryon 1852**). Somewhat later, in 1868, Guillaume Amand Duchenne de Boulogne (1806–1875), then practicing at the L'hôpital de la Pitié Salpêtrière, described the disease as **pseudo-hypertrophic muscular paralysis**.

In 1891 the internist Wilhelm Erb (**Erb 1891**) of Heidelberg distinguished this entity from other cases of juvenile paralysis by calling it a **progressive muscular dystrophy**.

History has assigned the name of Duchenne to this most common and most severe form of MD that is characterized by X chromosomal recessive inheritance. Alan and Marcia Emery (**Emery 1995**) have written a commendable monograph on the history of this disease with special emphasis on the question as to what extent these predecessors (Gaetano Conte) should be considered as 'the discoverer'. For a long time the achievements of these forerunners had been forgotten even by experts in the history of medicine. In the case of Gaetano Conte, it was the cardiologist Giovanni Nigro who retrieved the memory of his great Neapolitan fellow countryman. He reprinted the paper of 1836 in facsimile (**Nigro 1986**) after he had founded the Academy in 1981 and, the year after, endowed the prize, which henceforth should keep alive the remembrance of 'the Italian discoverer of DMD. The prize is regularly awarded in three classes, i.e. for basic research, for clinical research, and for social achievement in the field of neuromuscular disorders. Occasionally, an 'extra prize' has also been awarded as required, subject to the classification of the awardee. The award consists of a gold medal and the sum of 1000 Euros. In 1852, Meryon (**Meryon 1864**) reported in vivid details a family with four boys, all of whom were affected by significant muscle changes but had no central nervous system abnormality when examined at necropsy. Meryon subsequently wrote a monograph on DMD and even went on to suggest a sarcolemmal defect to be at the root of the disorder. He further suspected that the disorder is genetically transmitted through females and affects only males.

Guillaume Benjamin Amand Duchenne "de Boulogne" (September 17, 1806 in Boulogne-sur-Mer – September 15, 1875 in Paris) was a French neurologist who was already famous for his application of faradism (the use of electric currents to stimulate muscles and nerves) in the treatment of neurologic disorders when he wrote about his first case of DMD (**Duchenne 18**68). The disease is named for the pioneering 19th Century. Although already known for his work in electrophysiology, Duchenne cemented his name in medical history with his contributions in the field of myopathies. In 1861, Duchenne described and detailed the first documented case of DMD. A few years later after becoming the first to obtain muscle biopsies from a living patient, Duchenne gave an account of thirteen other affected children. In 1868, he gave a comprehensive account of 13 patients with the disease, which he called **"paralysie musculaire pseudo-hypertrophique."**



Guillaume Benjamin Amand Duchenne de Boulogne (1806-1875)

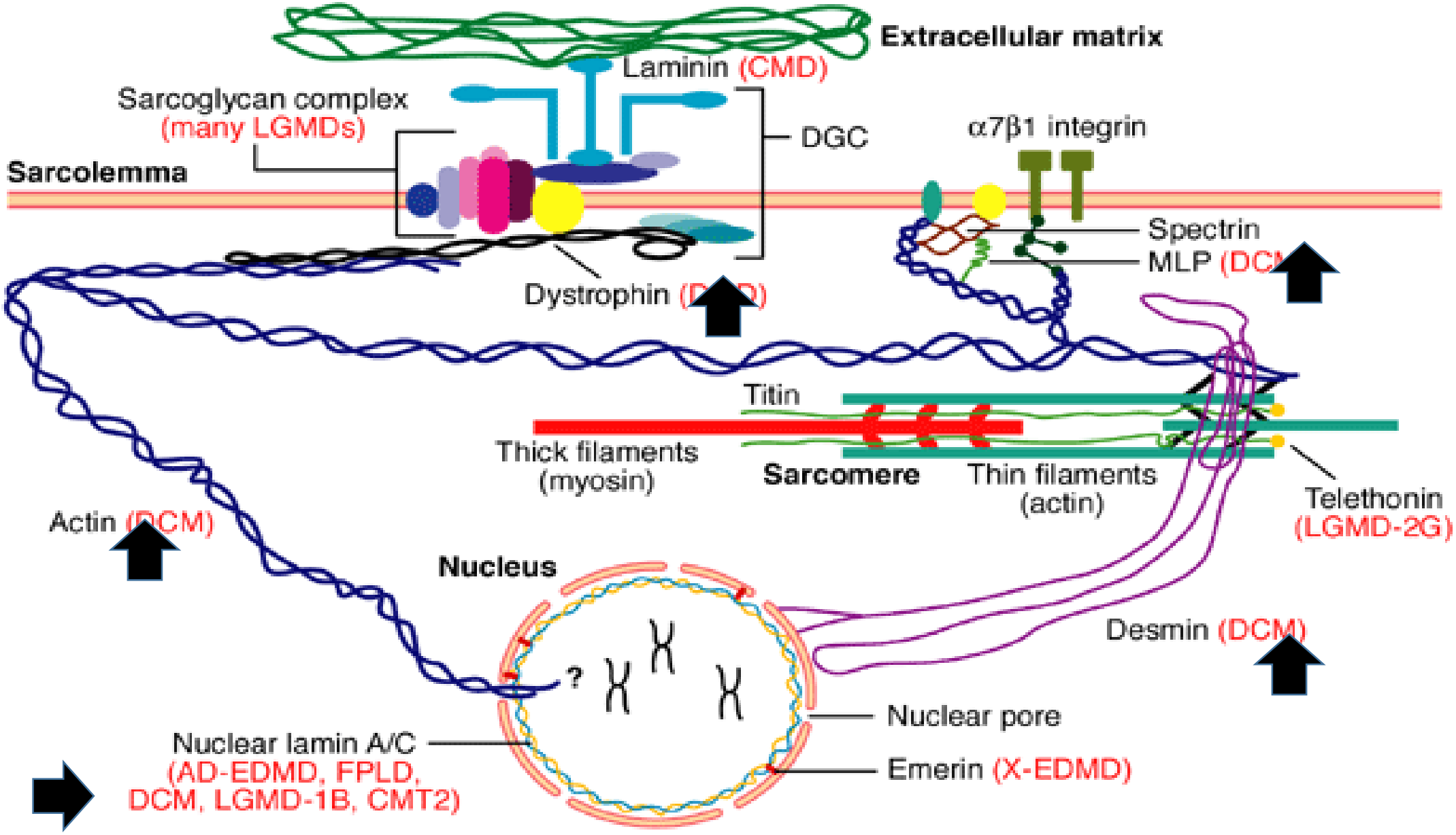
The advancement of molecular biology techniques illuminates the genetic basis underlying all MD: defects in the genetic code for dystrophin, a 427-kd skeletal muscle protein (Dp427). These defects result in the various manifestations commonly associated with DMD, such as weakness and pseudohypertrophy. Dystrophin can also be found in cardiac smooth muscles and in the brain (accounting for the slight mental retardation associated with this disease) (**Erb 1891**). Minor variations notwithstanding, all types of DMD have in common progressive muscle weakness that tends to occur in a proximal-to-distal direction, though there are some rare distal myopathies that cause predominantly distal weakness. The decreasing muscle strength in those who are affected may compromise the patient's ambulation potential and, eventually, cardiopulmonary function. In addition, structural soft-tissue contractures and spinal deformities may develop from poor posturing caused by the progressive muscle weakness

Pathophysiology

Multiple proteins are involved in the complex interactions of the muscle membrane and extracellular environment. For sarcolemmal stability, dystrophin and the dystrophin-associated glycoproteins (DAGs) are important elements (**Waite 2009; Banks 2009**). The dystrophin gene is located on the short arm of chromosome X near the p21 locus and codes for the large protein Dp427, which contains 3685 amino acids. Dystrophin accounts for only approximately 0.002% of the proteins in striated muscle, but it has obvious importance in the maintenance of the muscle's membrane integrity (**Hoffman 1987**).

Dystrophin aggregates as a homotetramer at the costomeres in skeletal muscles, as well as associates with actin at its N-terminus and the DAG complex at the C-terminus, forming a stable complex that interacts with laminin in the extracellular matrix. Lack of dystrophin leads to cellular instability at these links, with progressive leakage of intracellular components; this results in the high levels of creatine phosphokinase (CPK) noted on routine blood workup of patients with DMD. Less-active forms of dystrophin may still function as a sarcolemmal anchor, but they may not be as effective a gateway regulator because they allow some leakage of intracellular substance. This is the classic Becker dystrophy. In both DMD and Becker MD, the muscle-cell unit gradually dies, and macrophages invade. Although the damage in MD is not reported to be immunologically mediated, class I human leukocyte antigens (HLAs) are found on the membrane of dystrophic muscles; this feature makes these muscles more susceptible to T-cell mediated attacks. Selective monoclonal antibody hybridization was used to identify cytotoxic T cells as the invading macrophages; complement-activated membrane attack complexes have been identified in dystrophic muscles as well. Over time, the dead muscle shell is replaced by a fibrofatty infiltrate, which clinically appears as pseudohypertrophy of the muscle. The lack of functioning muscle units causes weakness and, eventually, contractures. Other types of MDs are caused by alterations in the coding of one of the DAG complex proteins. The gene loci coding for each of the DAG complex proteins is located outside the X chromosomes. Gene defects in these protein products also lead to alterations in cellular permeability; however, because of the slightly different mechanism of action and because of the locations of these gene products within the body, there are other associated effects, such as those in ocular and limb-girdle type dystrophies. Equinovarus contractures start as flexible dynamic deformities and advance to rigid contractures. This altered anatomy prevents normal ambulation, proper shoe wear, and transfers (how patients can be picked up to transfer out of their chair). Once wheelchair-bound, patients with DMDs tend to develop worsening contractures and rapidly progressive scoliosis. For each 10° of thoracic scoliosis curvature, the forced vital capacity (FVC) decreases by 4% (**Hoffman 1987**). In a patient with an already-weakened cardiopulmonary system, this decrease in FVC could rapidly become fatal.

Striated muscle cell proteins implicate in muscular dystrophies, dilated cardiomyopathy and lipodystrophy, and their protein-protein interactions



Etiology

Classification of types of muscular dystrophy

The etiology of MD is an abnormality in the genetic code for specific muscle proteins (**Merlini 012**). They all are classified according to the clinical phenotype, the pathology, and the mode of inheritance. The inheritance pattern includes the sex-linked, autosomal recessive, and autosomal dominant MDs. Within each group of heritable MDs, several disorders exist. These are characterized by the clinical presentation and pathology.

Heritable MDs include the following: Sex-linked MDs - Duchenne, Becker, Emery-Dreifuss; Autosomal dominant MDs - Facioscapulohumeral, distal, ocular, oculopharyngeal and autosomal recessive MD – Limb-girdle form

Genetic defects and dystrophin

In the X-linked forms of MD, such as the DMD and Becker dystrophies, the defect is located on the short arm of the X chromosome (**González-Herrera 2009**). Hoffman and coworkers identified the locus of the defect in the Xp21 region, which includes approximately 2 million base pairs (**Hoffman 1987**). The gene codes for Dp427, which is a component of the cytoskeleton of the cell membrane.

Dystrophin is distributed not only in skeletal muscle but also in smooth and cardiac muscles and in the brain.

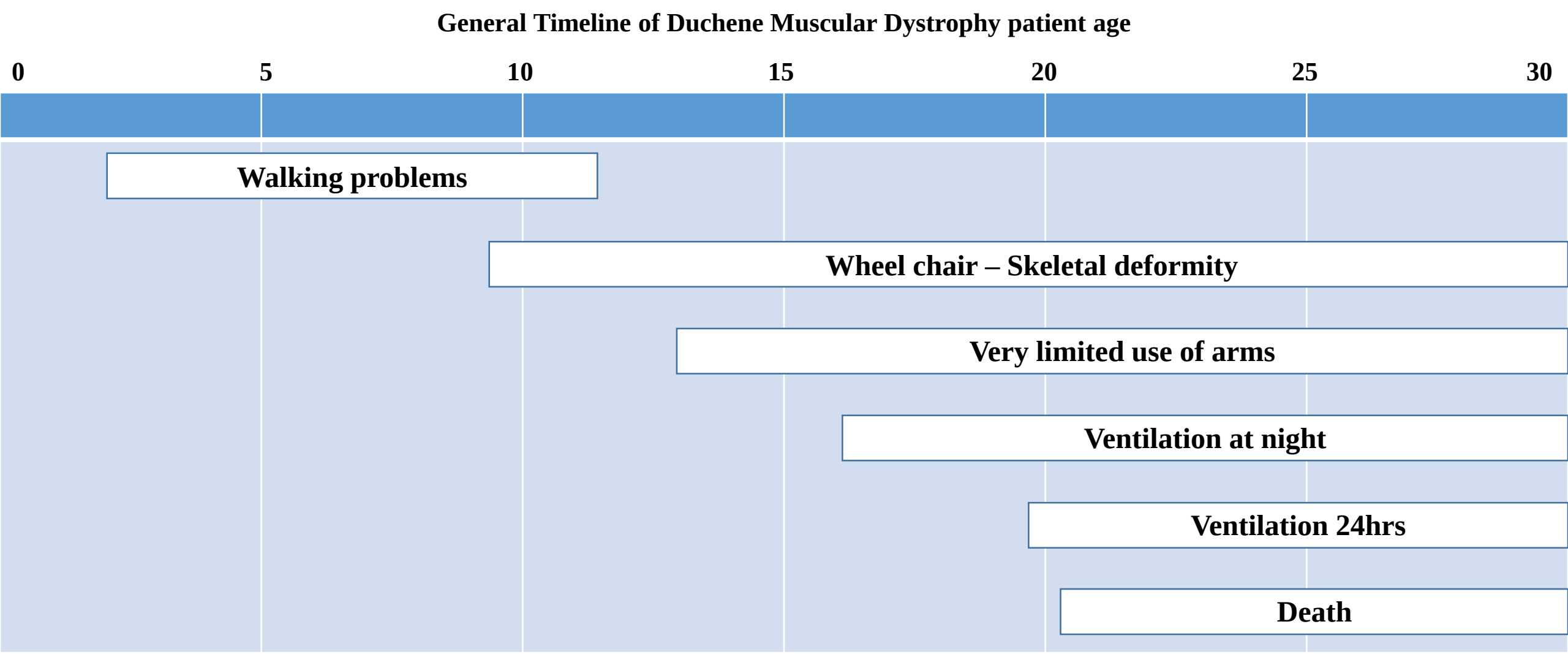
The large size of the dystrophin gene explains the ease at which spontaneous new mutations can occur, as in DMD. The large size also allows mistakes in protein synthesis to occur at multiple sites.

Defects that interfere with the translation reading frame or with the promoter sequence that initiates synthesis of dystrophin lead to an unstable, ineffective protein, as in DMD. Disruption of the translation process further down the sequence leads to production of proteins of lower molecular weight that, although present, are less active and result in the milder variety of Becker MD.

Like DMD, Emery-Dreifuss MD is a sex-linked recessive disorder, but its defect is localized to the long arm of the X chromosome at the q28 locus (**Dickey 1984**). Some authors, however, have cited case reports of similar findings in Emery-Dreifuss that were transmitted in an autosomal dominant pattern (**Miller 1985**). However, this finding is more of an aberration than a normal observation in Emery-Dreifuss MD.

In autosomal recessive conditions such as limb-girdle MD, the genetic defect is localized to the 13q12 locus.

In the autosomal dominant facioscapulohumeral MD, the defect is at the 4q35 locus. In distal MD, it is at the 2q12-14 loci (**Dobrowski 1986**).


General Timeline of Duchene Muscular Dystrophy patient age
0
5
10
15
20
25
30
Walking problems
Wheel chair – Skeletal deformity
Very limited use of arms
Ventilation at night
Ventilation 24hrs
Death

History and Physical Examination

In DMD, unless a sibling has been previously affected to warrant a high index of suspicion, no abnormality is noted in the patient at birth, and manifestations of the muscle weakness do not begin until the child begins to walk. Three major time points for patients with Duchenne MD are when they begin to walk, when they lose their ability to ambulate, and when they die (**Donders 2009**).

The child's motor milestones may be at the upper limits of normal, or they may be slightly delayed. Some of the delays may be caused by inherent muscle weakness, but a component may stem from brain involvement. Although the association of intellectual impairment in MD has long been recognized, it was initially thought to be a result of limited educational opportunities (**Prosser 1969**). Psychometric studies have since revealed a definitively lower intelligence quotient (IQ) in patients with DMD despite equalization of educational opportunities (**Leibowitz 1981**). The average IQ in patients with DMD is 85 points on the Wechsler Adult Intelligence Scale (WAIS), compared with 105 points in healthy populations (**Pane 2012**). In addition to mental deficits, another milestone delay is the patient's age at ambulation. Children with DMD usually do not begin to walk until about age 18 months or later.

74% of children with DMD manifested the disease by age 4 years. By age 5 years, awareness increases as the disease is manifested in all affected children when they experience difficulty with school-related activities (eg, getting to the bus, climbing stairs, reciprocal motions during activities) (**Dubowitz1995**).

Cardiac features of DMD

The role of cardiac involvement in DMD has been recognized for decades. Although the extent of involvement varies, cardiac disease is present by 20 years of age in essentially all boys with DMD. Cardiac involvement, manifest as dilated cardiomyopathy, has been described in up to 90% of all DMD patients, and at least 20% of them died of heart failure, and in up to 60% of carriers (**Finsterer 2003**). Progression of LV dysfunction in DMD patients is often unrecognized due to lack of physical activities (**Heymsfield 1978**). It has been shown that the process of cardiomyopathy is in progress long before symptoms occur (**Ashford 2005**). Since a significant part of these patients died of heart failure, a diagnostic tool for early detection of cardiac involvement and early intervention is desired to guide therapy options, such as corticosteroids and afterload reduction agents (**Duboc 2005**). Preclinical cardiac involvement in 20% of cases by age six, with the onset of clinically apparent cardiomyopathy after 10 being common. but the ECG changes, ventricular arrhythmias, and ventricular late potentials associated with such conditions appear to be of little value in predicting mortality. The most common cardiac abnormality in DMD is dilated cardiomyopathy, which in its symptomatic phase is usually associated with congestive heart failure and significantly associated with premature death. The absence of dystrophin, the metabolic defect that causes DMD, leads to a peculiar cardiomyopathy which initial involvement of the **basal inferior wall of the left lateral wall of the** LV (old dorsal). involvement in the basal inferior(old posteroinferior) and basal lateral(old posterolateral) of the LV and **posteromedial papillary muscle of the mitral valve**. This has been hypothesized to be related to the increased axial stress that cardiac myocytes encounter in trophin in limiting sarcolemma damage (**Cziner 1993**). The absence of dystrophin, the metabolic defect that causes DMD, leads to a peculiar cardiomyopathy which initially affects the basal inferior e lateral wall of the LV. Patients with DMD develop **cardiac fibrosis** and dilated cardiomyopathy. Cardiac symptoms typically appear late in the course of the cardiomyopathy, in part because affected individuals are usually wheelchair-bound and often physically inactive. Cardiac symptoms appear more often in patients over 18 years of age. Disease tends to progress rapidly, leading to premature death, often before 25 years of age. No successful treatments for cardiomyopathy in these individuals have been reported.

The most common inciting event is a respiratory infection that progresses extremely rapidly despite its initial benign course. The resultant respiratory failure can easily occur from the underlying progressive nocturnal hypoventilation and hypoxia or from an acute cardiac insufficiency.

Other clinical findings in DMD include absent deep tendon reflexes in the upper extremities and patella (though the tendo Achillis reflex remains intact even in the later stages of this disease), pain in the calves with activity (<30% of patients), pseudohypertrophy of the calf (60%), and macroglossia (30%). Cardiopulmonary involvement is present from the beginning of the disease stages, but the findings are not so clinically obvious. Becker MD is similar to DMD, but because patients have some measure of functioning dystrophin, the manifestations of Becker MD occur later and are more mild. Patients tend to live past the fourth or fifth decades.

The child then walks on tiptoes because it is easier to stay vertical with an equinus foot position than on a flat foot, though no real tendo Achillis contracture exists at this early point. Gradually, noticeable difficulty with step taking by the child is observed. Frequent falls without tripping or stumbling often occur and are described as the feet being swept away from under the child. The child then begins having problems getting up from the sitting or supine position, and he or she can rise to an upright stance only by manifesting the Gower sign. The Gower sign is a classic physical examination finding in MD and results from weakness in the child's proximal hip muscles. To get up from a sitting or supine position, the child must first become prone on the elbows and knees. Next, the knees and elbows are extended to raise the body. Then, the hands and feet are gradually brought together to move the body's center of gravity over the legs. At this point, the child may release one hand at a time and support it on the knee as he or she crawls up their legs to achieve an upright position. Although the Gower sign is a classic physical examination finding in Duchenne MD, it is by no means pathognomonic; other types of MD and disorders with proximal weakness may also cause this sign.

While still ambulatory, the child may have minimal deformities, including iliopsoas or tendo Achillis tightness. Mild scoliosis may be present if the child has an asymmetrical stance. Upper-extremity involvement rarely occurs in the beginning, although proximal arm muscle weakness may be evident on manual strength testing. When upper-extremity involvement manifests in later stages of DMD, it is symmetrical and, along with distal weakness, usually follows a rapid worsening of the child's condition toward being wheelchair bound.

The second important phase in DMD is the loss of ambulation. This usually occurs between the ages of 7 and 13 years, with some patients becoming wheelchair bound by age 6 years. If children with MD are still ambulating after age 13 years, the diagnosis of DMD should be questioned, because these patients usually have Becker MD, the milder form of MD. In Emery's work (**Emery1993**), the 50th percentile for loss of ambulation in patients with DMD was age 8.5 years, with the 95th percentile at 11.9 years and the 99th percentile at 13.2 years. With the child's loss of ambulation, there is usually a rapidly progressive course of muscle or tendon contractures and scoliosis. Most authors recommend posterior spinal fusion at 20° when the vital capacity is at its best (**Thompson 2000**). However, some reports showed that respiratory function after spinal fusion did not significantly differ (**Kinali 2006**). The investigators concluded that respiratory failure resulted from muscle weakness and not the mechanical bellows of the chest cage, as was previously assumed. Other early features include a gait abnormality, which classically is a waddling, wide-based gait with hyperlordosis of the lumbar spine and toe walking. The waddle is due to weakness in the gluteus maximus and gluteus medius muscles and the patient's inability to support a single-leg stance. The child leans the body toward the other side to balance the center of gravity, and the motion is repeated with each step. Hip extensor weakness also results in a forward tilt of the pelvis, which translates to a hyperlordosis of the spine to maintain posture. DMD is a terminal disease in which death usually occurs by the third decade of life (mostly from cardiopulmonary compromise). Causes of death are acute pneumonia, cardiac arrest, acute respiratory distress and multi-organ failure. The main cause of death in DMD remains cardio-respiratory failure (**Van Ruiten 2016**).

Emery-Dreifuss MD is an uncommon sex-linked dystrophy that presents with early contractures and cardiomyopathy in affected patients; the typical presentation involves tendo Achillis contractures, elbow flexion contractures, neck extension contractures, tightness of the lumbar paravertebral muscles, and cardiac abnormalities. Death may occur in the fourth or fifth decade as a result of first-degree AV block, a condition that is usually not present at the initial presentation of this disease.

Autosomal dominant distal MD is a rare form of MD and tends to become apparent in those aged 30-40 years; it is more commonly found in Sweden than in any other country and can cause a mild weakness that affects the arms before the legs.

Autosomal dominant facioscapulohumeral dystrophy causes facial and upper-extremity weakness, and scapulothoracic motion is decreased, with winging of the scapula. This type of dystrophy can occur in both sexes and appear at any age, although it is more common in late adolescence.

Autosomal dominant oculopharyngeal dystrophy appears in those aged 20 to 30 years. The pharyngeal muscle involvement leads to dysarthria and dysphagia, which may necessitate palliative cricopharyngeal myotomy. The ocular component comprises ptosis, which may not become obvious until the patient's mid life.

None of the autosomal dominant conditions significantly affect longevity.

Complications

The complications of progressive muscle weakness include:

I. **Inability to walk.** Some people with muscular dystrophy eventually need to use a wheelchair. early wheelchair dependence in patients who develop minor musculoskeletal injuries (eg, ankle sprain) and those who are immobilized. Prolonged immobilization worsens the clinical weakness caused by MD and ultimately results in the patient's nonambulatory status.

II. **Shortening of muscles or tendons around joints (contractures).** Contractures can further limit mobility.

III. **Breathing problems.** Progressive weakness can affect the muscles associated with breathing. People with muscular dystrophy may eventually need to use a breathing assistance device (ventilator), initially at night but possibly also in the day.

IV. **Curved spine (scoliosis).** Weakened muscles may be unable to hold the spine straight.

V. **Heart problems.** MD can reduce the efficiency of the heart muscle(dilated cardiomyopathy, arrhythmias).

VI. **Swallowing problems.** If the muscles involved with swallowing are affected, nutritional problems and aspiration pneumonia may develop.

Laboratory Studies

A creatine phosphokinase (CPK) determination is the most specific test for muscular dystrophy (MD). Elevated CPK levels are indicative of muscle disease. Because the concentration of CPK is not significant in red blood cells, CPK levels are not affected by hemolysis. CPK is not affected by liver dysfunction, as are the other tested enzymes (eg, transaminases, aldolase, lactate dehydrogenase). High CPK levels represent leakage of the enzyme from the muscle cells only. This change is not exactly correlated with the severity of the disease.

All MDs result in some CPK elevation during the active phase of the disease. The finding of three elevated levels obtained 1 month apart is diagnostic for MD. Early in the disease process, CPK levels are 50-300 times greater than normal levels, but the levels tend to decrease as the muscle mass decreases. The CPK level is highest in Duchenne MD, with less elevation noted in Becker MD.

Enzyme levels that may be elevated but can be altered by liver dysfunction include the following: Transaminase levels; Lactate dehydrogenase levels and Aldolase levels. The multiplex polymerase chain reaction (PCR) assay may be useful. PCR was developed by Chamberlain et al (**Chamberlain 1988**), who noted that deletions of the dystrophin gene tend to cluster around two hot-spot regions: at exons 3-30 and at exons 44-55 (**Miyazaki 2009**). The PCR method rapidly screens for deletions of the dystrophin gene by applying PCR to amplify the DNA in the hot-spot regions and by simultaneously using a number of appropriate primers that flank these hot-spot regions. PCR can be used to detect more than 98% of existing deletions, and it can be performed within 24 hours.

Imaging Studies

Ultrasonography is a relatively noninvasive technique that is used for screening patients with MD; this modality is rapidly replacing **Electromyography (EMG)** in centers that have appropriately trained staff. Even in the early stages of MD, ultrasonography shows increased echogenicity in the affected muscles, with a corresponding reduction in the underlying bone echo. Ultrasonography has the advantage of noninvasiveness, and it is reliable for continued monitoring of the disease course over time. EMG usually demonstrates short-duration, polyphasic, motor-unit action potentials with decreased amplitudes. It should be kept in mind that this finding is common with all myopathic processes and does not specifically identify MDs.

Pulmonary function tests (PFTs), including an analysis of arterial blood gases, and a hematologic workup are necessary as part of the preoperative workup. A pulmonologist may be consulted preoperatively because he or she can be helpful in managing the patient's airway in the postoperative period.

Electrocardiography in cardiomyopathy of Duchenne's muscular dystrophy

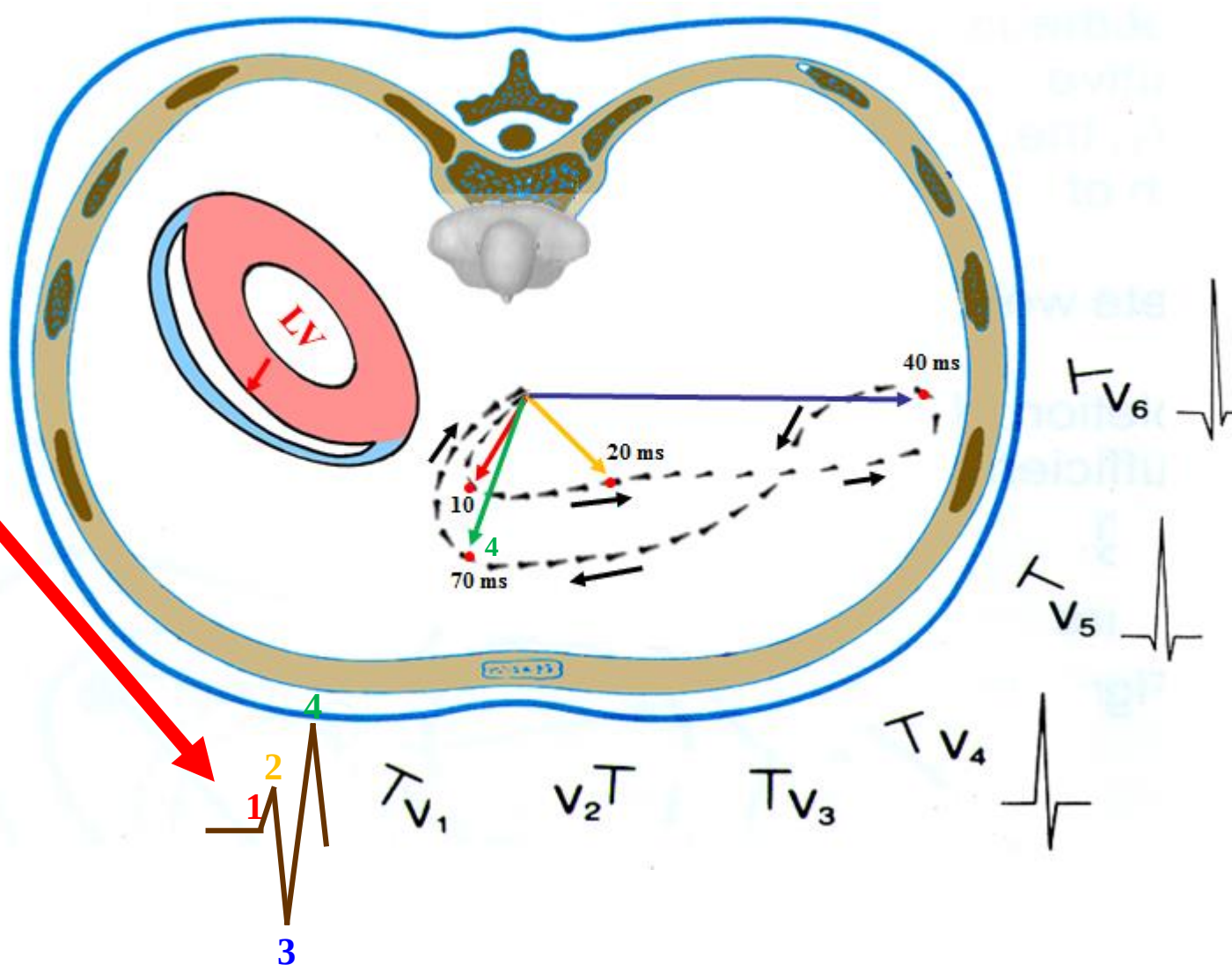
It is abnormal and typical in ≈ 90% of cases.

1. Persistent or labile sinus tachycardia is the most recognized ECG feature. The pathogenesis of this tachycardia is unknown but does not appear related to abnormal autonomic function. It is accompanied minimal physical exertion. Tachycardia was also unpredictable in onset and duration. Because of this lability a single determination of the pulse rate is unreliable for determination of the true incidence.
2. Up to 10% have PR intervals of less than 120ms with an additionally 10% having prolonged PR interval.
3. Tall R waves in V1. Prominent anterior QRS forces (PAF) on VCG horizontal QRS loop are frequent with pseudo infarction lateral pattern (old dorsal). Frequent “bites” on QRS loop are characteristics. It could be a useful parameter for detecting carrier subjects (**Secchi 1982**). Patients with DMD had myocardial fibrosis (mid wall and/or subepicardial) ≈ 70% of patients, and the lateral is the most commonly involved segment in the early stages of cardiomyopathy (**Silva 2007**). This feature is responsible by prominent R wave in V1. Tall RV1, defined as an R/S ratio ≥1, is normal in children and young adults and it is not an infrequent occurrence in emergency department patients. This ECG finding exists as a normal variant in only 1% of patients. Physicians should therefore be familiar with the differential diagnosis for this important QRS configuration. The ECG entities which can present with this finding include RBBB, left ventricular ectopy (ventricular complexes that originate in the LV show RBBB morphology in lead V1), RVH (right axis deviation, and frequent right ventricular strain pattern in the right precordial leads), acute right ventricular dilation, type A Wolff-Parkinson-White syndrome (short PR interval, slurring of the initial portion of the QRS complex (delta wave), QRS prolongation, and positive concordance of the precordial leads and frequent secondary repolarization changes consisting of ST segment and T wave deflection in the opposite direction of the major portion of the QRS complex. Diagnostic confusion may occur when the pre-excitation pattern is subtle. For example, when the QRS duration is only mildly prolonged, or the PR interval is not absolutely short), lateral myocardial infarction (old dorsal), hypertrophic cardiomyopathy (ventricular septal hypertrophy), progressive muscular dystrophy (DMD), myotonic dystrophy, dextroposition or pseudo-dextrocardia (rightward cardiac displacement), misplaced precordial leads (e.g. V1 and V3 reversed), normal variant (**Mattu 2001**) and left septal fascicular block. Abnormal R/S ratio in V1 greater than normal frequently in carriers. Increased amplitude of the R wave in the right precordial leads is the rule in DMD.
4. R/S ratio ≥1: 1 is used as a diagnostic criteria for RVH, not all forms of RVH are associated with this pattern. Prominent R waves in V1 are most likely to be seen in severe right ventricular pressure overload situations such as those that occur in congenital heart disease, eg, severe pulmonary stenosis, Fallot´s tetralogy, and Eisenmenger’s syndrome. They are much less likely to occur when the pressure overload situation begins in adulthood such as that seen in mitral stenosis and chronic pulmonary disease. RVH is diagnosed by the finding of a tall R wave or qR pattern in V1 and a ST-T strain pattern in V1- V2. Other supportive findings are RAE, right axis deviation (>110°), and deep S waves in V5-V6 (R/S ratio ≤1).

5. Triphasic pattern in V_1 in basal inferior myocardial infarction

From a material comprised 106 patients with DMD **(Slucka 1968)**

ECG Data	Cases
Sinus tachycardia	81
Short PR interval	63
Tall R wave in V1	43
Abnormal R/S ratio in V1	79
Polyphasic R wave in V1	13
RSr' complex in V1	24
Tall R wave in V5	33
Deep Q wave in V5-V6	51
Deep Q wave in I	6
Deep Q wave in III	5
Deep Q wave in aVL	4
Altered T wave	4
Left axis deviation	1

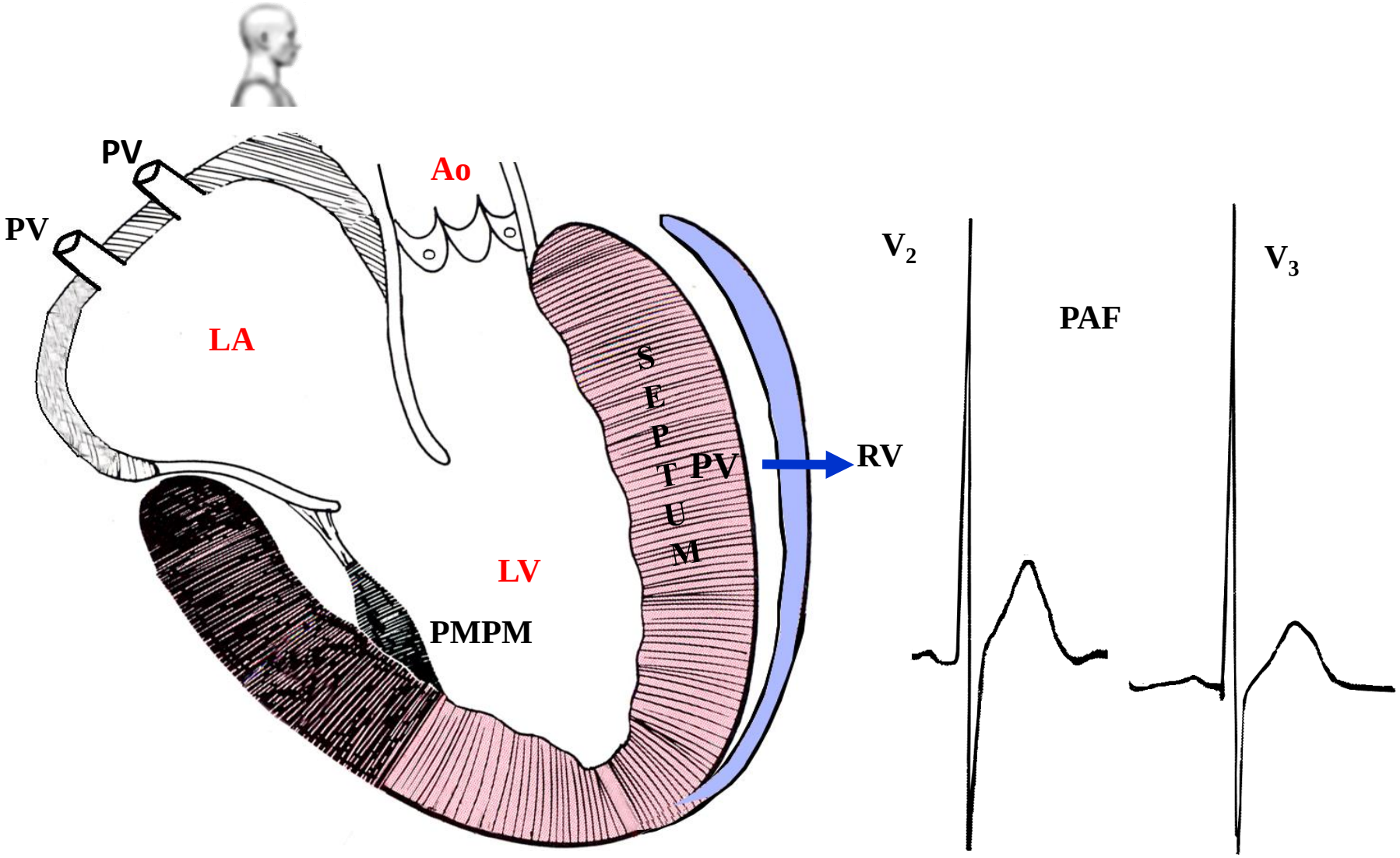


Vectors 1 (septal vector) and vector 2 (vector of the low portion of the septum) of depolarization are not affected and a mild anterior shift of the free wall vector (**vector 3**) is observed and an important one of **vector 4** (basal).

Basal inferior MI affects only middle and final portions of QRS between 40 to 100 ms (the second half of the QRS loop). This abnormal anterior shift of QRS loop in the HP has at least 50% of the area in front of orthogonal X line. Triphasic QRS pattern in right precordial leads simulating IRBBB of the rSr', rSR' or rsR' type in V_3R and V_1 is present in ≈ 36% of the cases.

6. Deep Q waves (amplitude ≥2 mm, duration < 40ms) in left precordial leads and, more rarely in the limb leads.
7. ST segment elevation, without symptoms are described, with the retrospective evaluation of similar cases from personal records. The differential diagnosis between myocardial necrosis and apoptosis is necessary **(Politano 2003).**
8. Inverted T waves. consequence of segmental lateral fibrosis. Autopsy studies have shown that cardiomyopathy of DMD is characterized by fibrosis of the basal inferior and contiguous lateral wall of the left ventricle (**Angermann 1985**).
9. Atrial arrhythmias including atrial fibrillation, and atrial flutter occur as a pre-terminal rhythm.
10. Conduction system disease and tachyarrhythmia's may occur in some individuals. Sudden cardiac death occur in DMD primarily in patients with severe skeletal muscle weakness. SCD is rare in DMD patients with an LVEF >35%. Significant Holter findings are rare in patients with DMD who have an LVEF >35%, and cardiac dysfunction appears to predict significant Holter findings. Holter monitoring is highest yield among DMD patients with cardiac dysfunction (**Villa 2015**). Among patients with DMD or BMD, arrhythmias increase with development of cardiac dysfunction (**Chiang 2016**). Disorders of conduction included abnormal intraatrial or interatrial conduction disturbance with developed paroxysmal atrial fibrillation (**Himmrich 2000**), Mobitz type I block, Mobitz II second-degree AV block, nonconducted atrial premature beats, short PR interval, first-degree AV block, right ventricular conduction delay and rightward axis compatible with left posterior fascicular block.(**Perloff 1984**), bifascicular bundle branch block or a third-degree AV block (**Himmrich 2000**). The role of dystrophic involvement of specialized conduction tissues and of the small vessel coronary arteriopathy remains speculative, but mitral valve prolapse, left atrial size and LV size, function and regional wall motion played no discernible part in the genesis of the rhythm and conduction disturbances. Except for end-stage atrial flutter, these disturbances are not clinically deleterious.

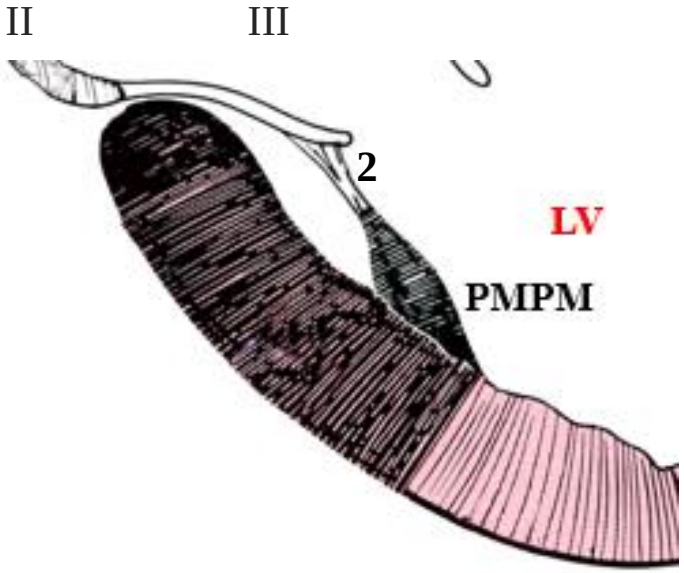
Right sagittal view that shows the inferobasal segment and LV lateral wall involved in DMD

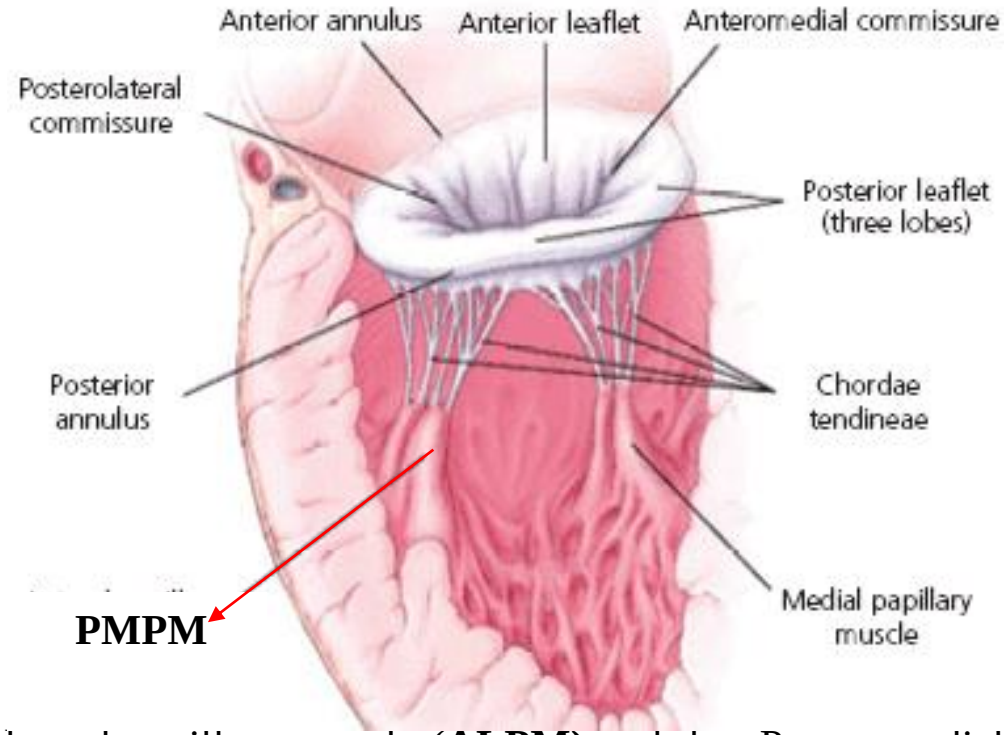


Outline of selective/ segment involvement (myocyte loos) of the inferobasal and basal lateral region of the left ventricle at the beginning of the disease and posteromedial papillary muscle (PMPM). Tall R waves in V1. Abnormal R/S ratio in V1 greater than normal frequently in carriers. Increased amplitude of the R wave in the right precordial leads is the rule: Prominent Anterior QRS forces (PAF).

PV: pulmonary vein; LA: left atrium; LV: left ventricle; Ao: Aorta; PAF: Prominent QRS Anterior forces.

Posteromedial muscle blood supply: right coronary artery (RCA) - posterior interventricular artery. The posteromedial muscle affectation/ruptures is more frequently because it only has one source of blood supply (**Fradley 2011**). The pathogenesis of mitral regurgitation in dilated cardiomyopathy is ascribed to several mechanisms. It can develop myocardial infarction in the absence of coronary atherosclerosis and died from acute lung edema following rupture of a papillary muscle of the left ventricle. LV is activated initially in three points middle third of the left septum surface dependent of left septal fascicle, anterosuperior region dependent of the left anterior superior fascicle that ends in anterolateral papillary muscle of mitral valve, and finally the left posterior fascicle that ends in left posteromedial papillary muscle affected frequently in DMD.





The mitral valve apparatus is formed by:

- Subvalvular apparatus: papillary muscles: The anterolateral papillary muscle (**ALPM)** and the Posteromedial Papillary Muscle (**PMPM**) with their supporting left ventricular walls and chordae tendinous (2)
- Mitral annulus (II)
- Mitral valve leaflets (III)

The normal function of the mitral valve depends on its 6 components, which are (1) the left atrial wall, (2) the annulus, (3) the leaflets, (4) the chordae tendineae, (5) the papillary muscles, and (6) the left ventricular wall (see the image below) (**Perloff 1972**).

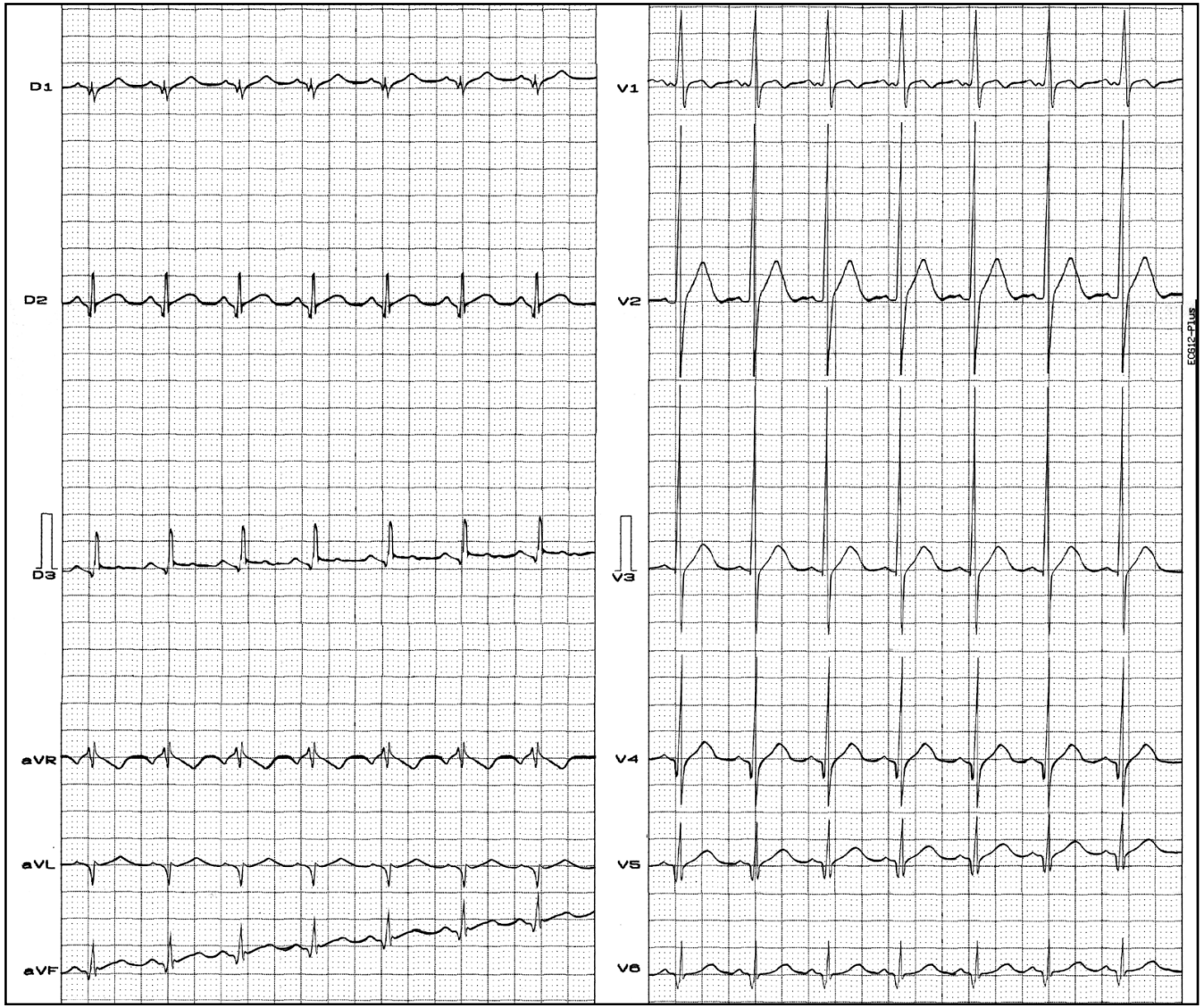
Papillary muscles and left ventricular wall

These 2 structures represent the muscular components of the mitral apparatus. The papillary muscles normally arise from the apex and middle third of the left ventricular wall. The anterolateral papillary muscle is normally larger than the posteromedial papillary muscle and is supplied by the left anterior descending artery or the left circumflex artery. The posteromedial papillary muscle is supplied by the right coronary artery. Extreme fusion of papillary muscle can result into mitral stenosis. On the other hand, rupture of a papillary muscle, usually the complication of acute myocardial infarction, will result in acute mitral regurgitation.

A cardiologist should be consulted preoperatively because cardiac management may be necessary in the postoperative care of dystrophic patients.

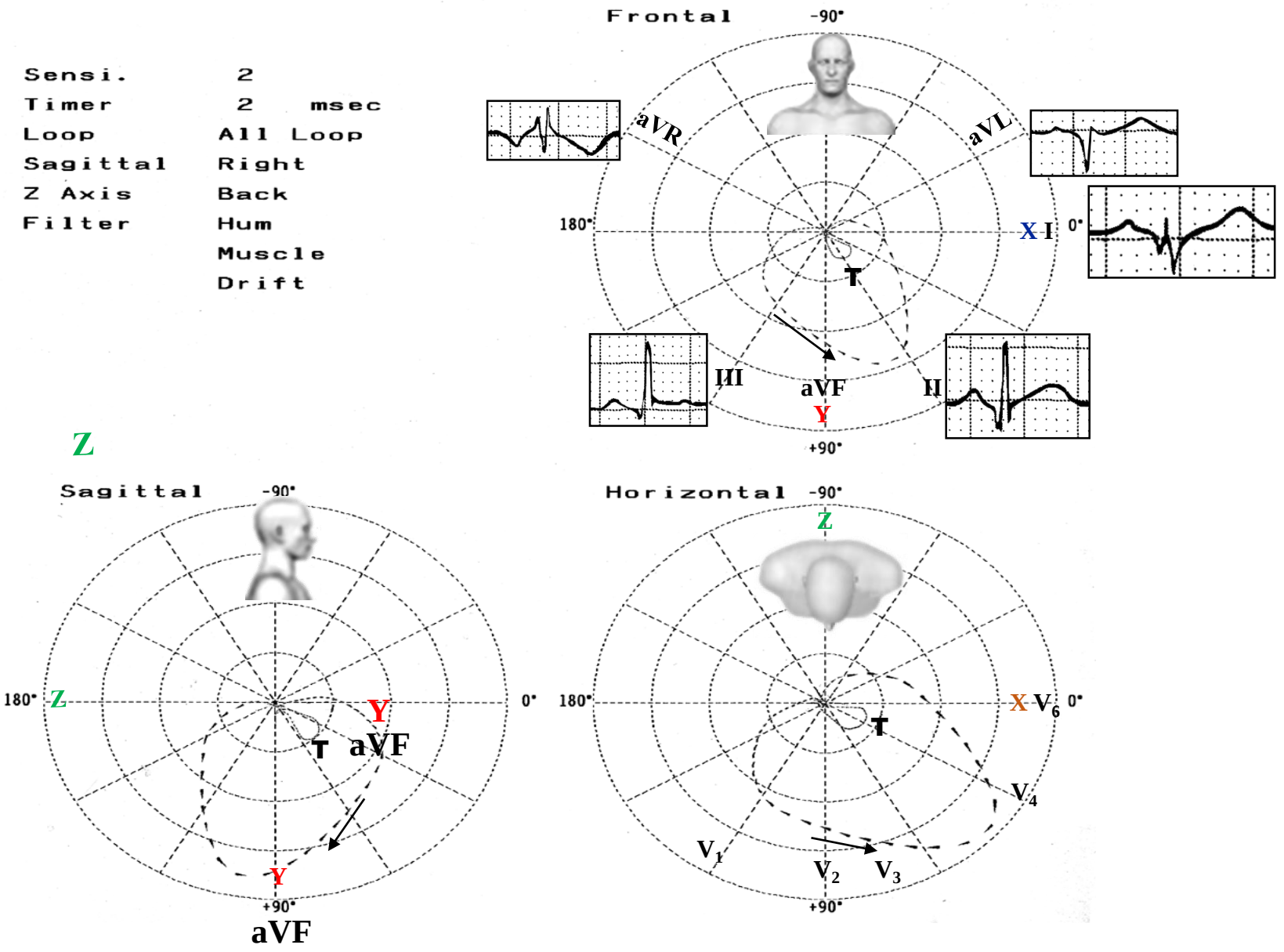
A variety of conditions previously reported to produce "pseudo-infarction" are included in these cases of pseudo myocardial infarction, including myocarditis, hypertrophic cardiomyopathy, and the cardiomyopathy of DMD. Compilation of the ECG data in all patients allowed for the development of criteria for this diagnosis of MI in childhood, and include and prolonged QT interval corrected for heart rate (QTc > 440 ms) (**Towbin 1993**).

Name: SA ; **Date:** 06/15/2001; **Age:** 13 y/o; **Sex:** M; **Race:** Caucasian; **Weight:** 48 Kg; **Height:** 1.50 m; **Biotype:** Normal

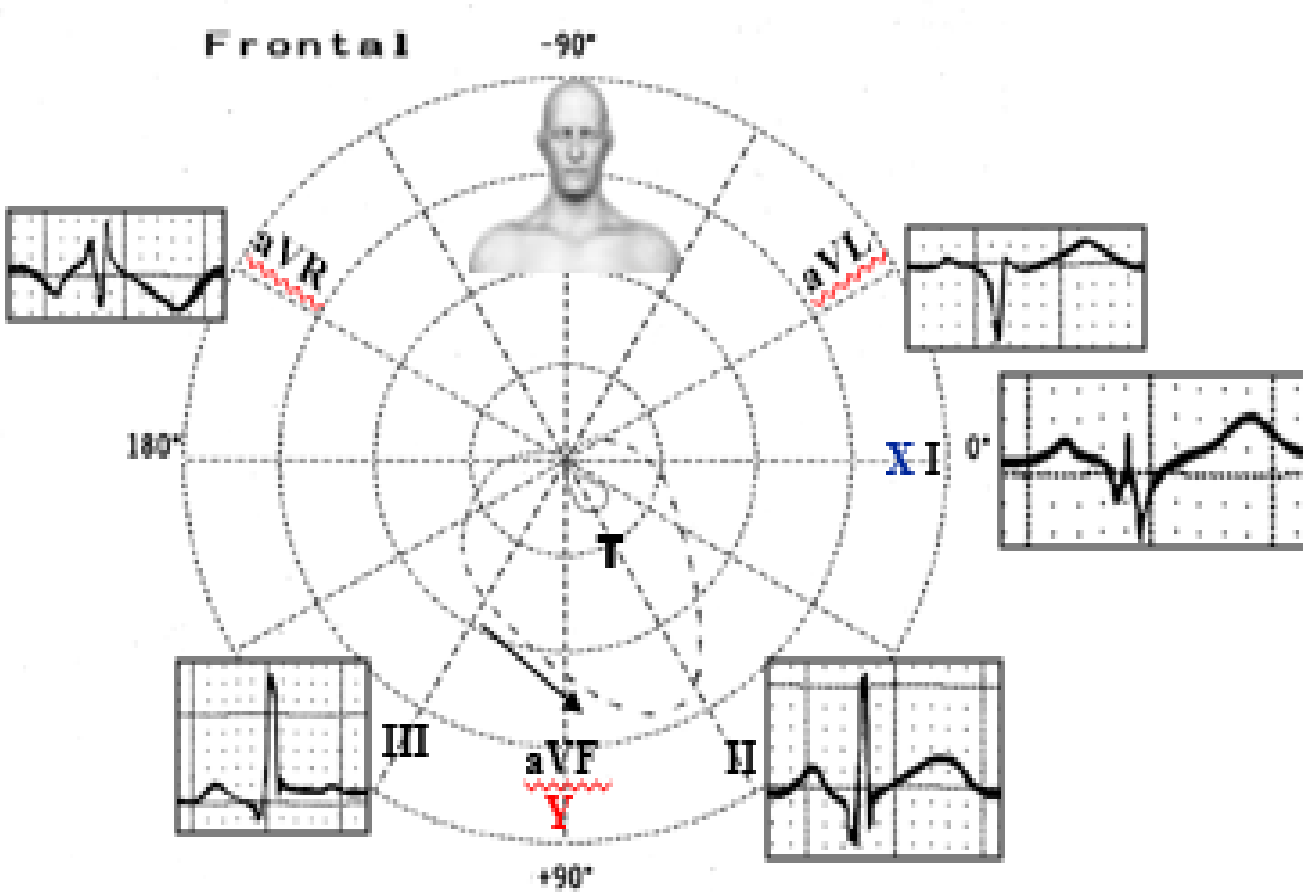


Clinical diagnosis: Duchenne Muscular Dystrophy (DMD).
ECG diagnosis: sinus tachycardia, short PR interval, PAF, deep and broad Q wave in lateral wall and hinted in the inferior one.
In this age range, average voltage of R wave in V_1 is 6 mm.
Conclusion: lateroinferior electrically inactive area. PAF (old inferodorsal) .

VCG



ECG/VCG correlation of the same patient, which shows in the horizontal plane, anterior shift of the loop, predominantly located in the left anterior quadrant. Note prominent QRS anterior forces in the HP: QRS loop located predominantly in left anterior quadrant.


Frontal
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aVR
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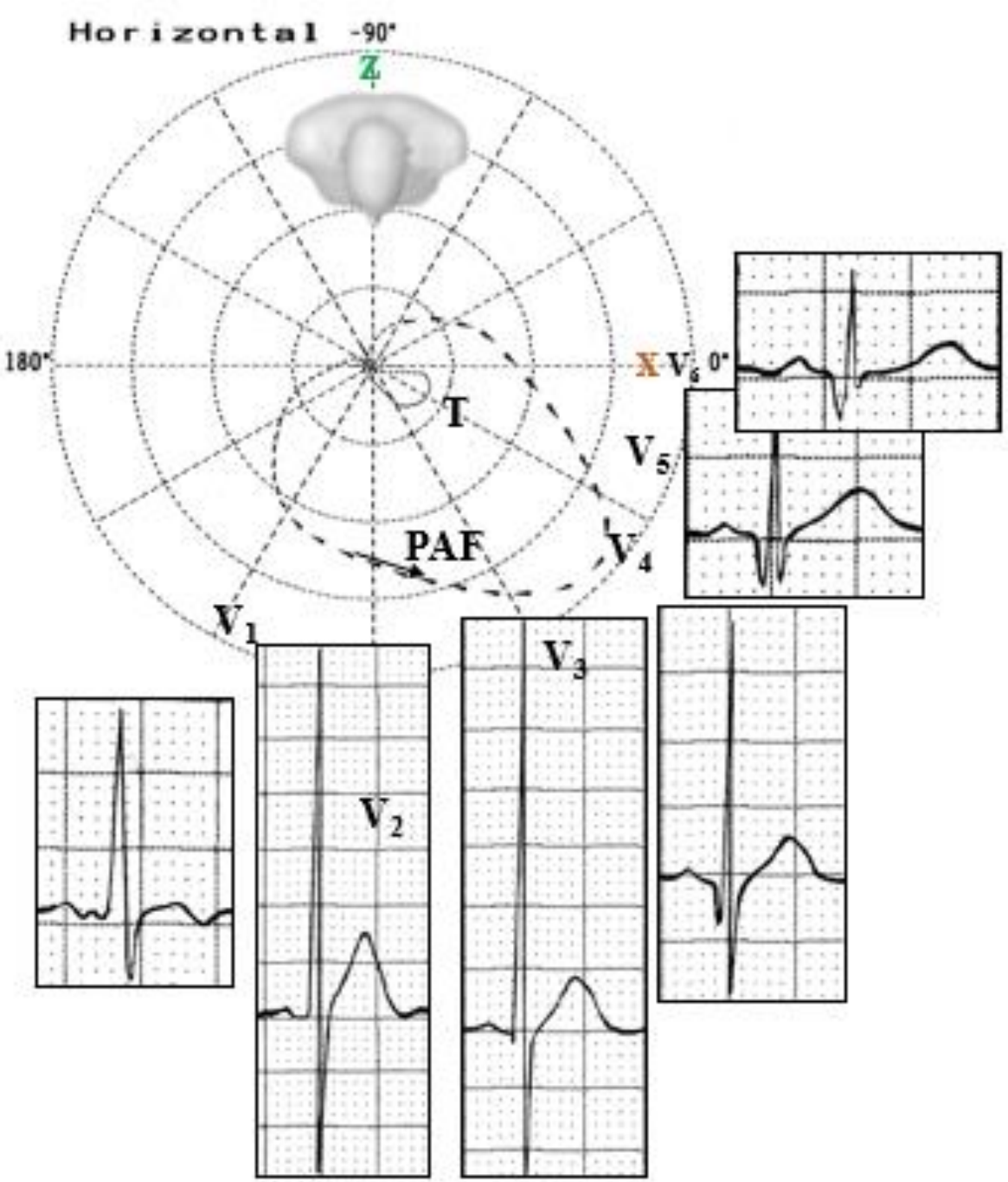
Horizontal
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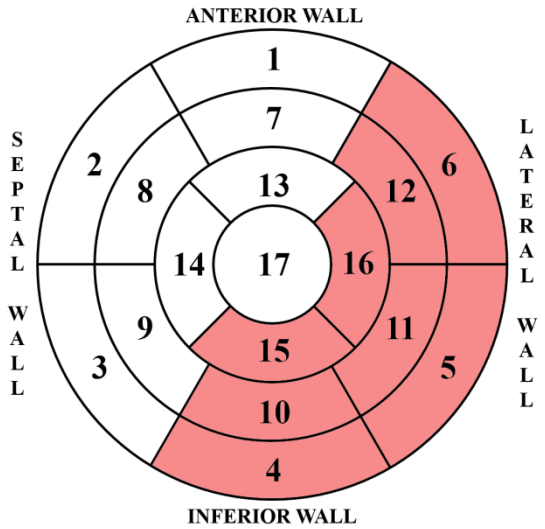
ANTERIOR WALL
SEPTAL WALL
LATERAL WALL
INFERIOR WALL
1
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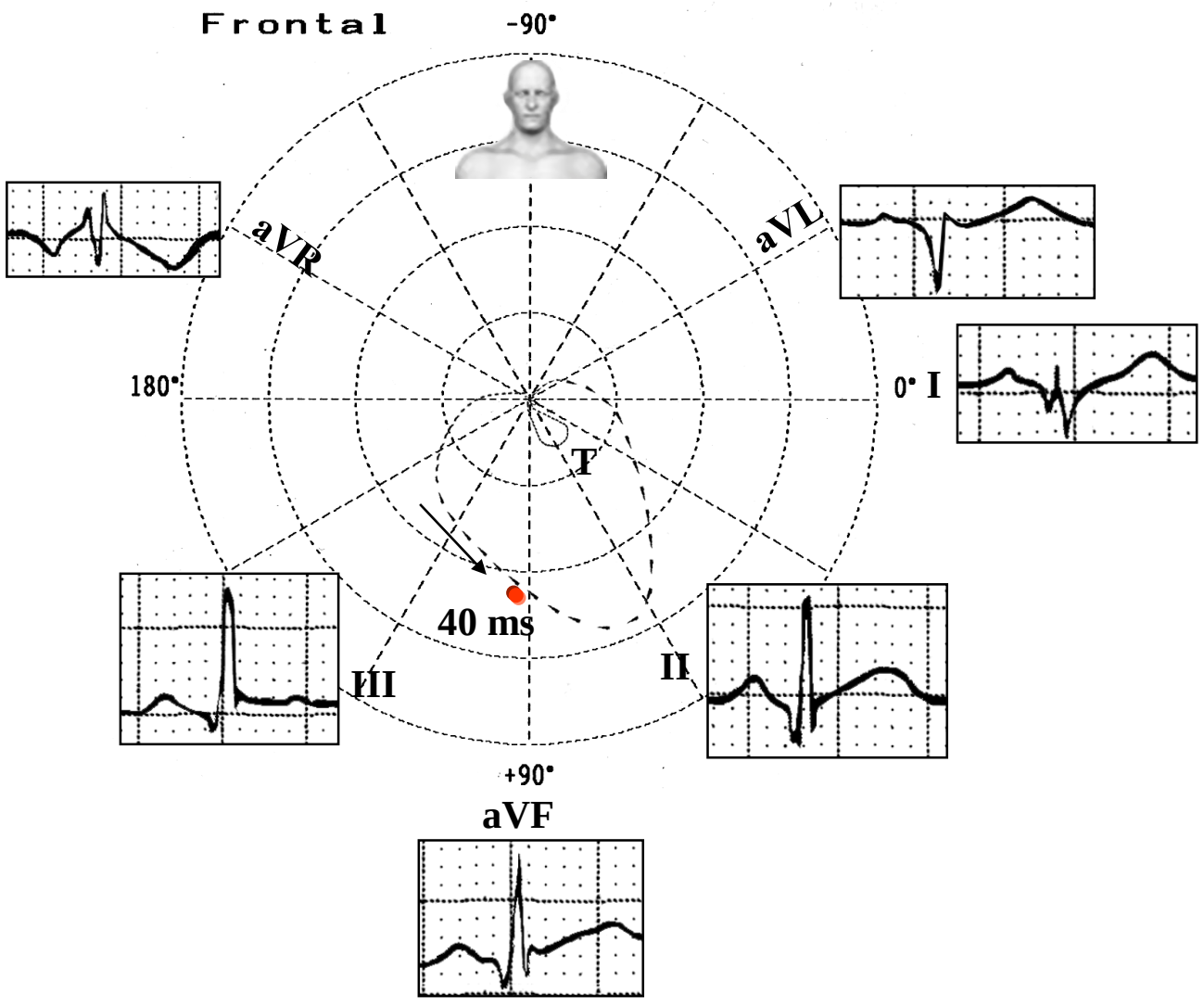
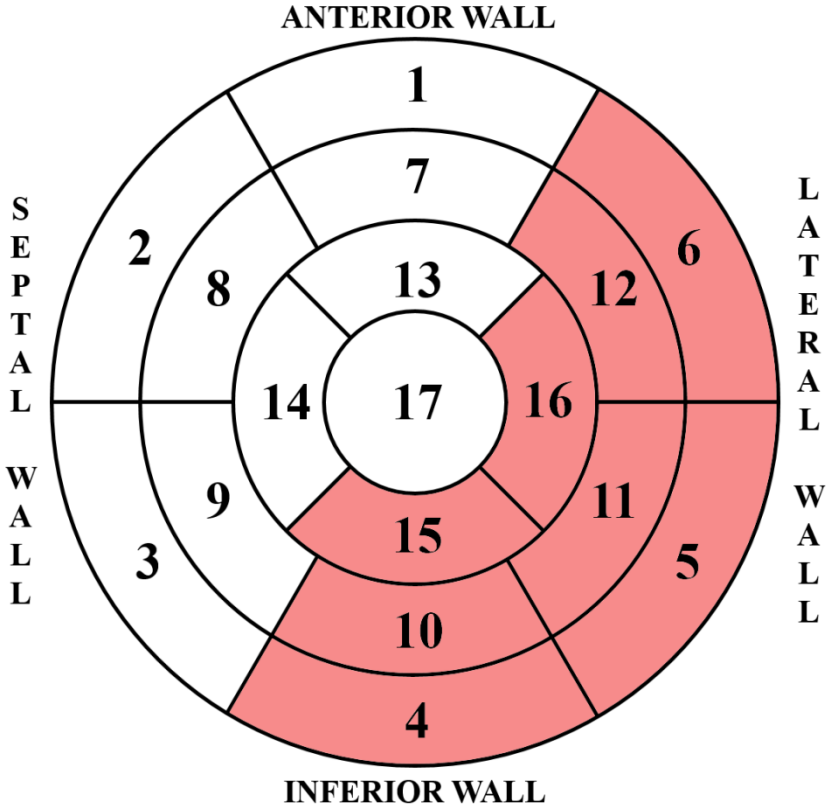
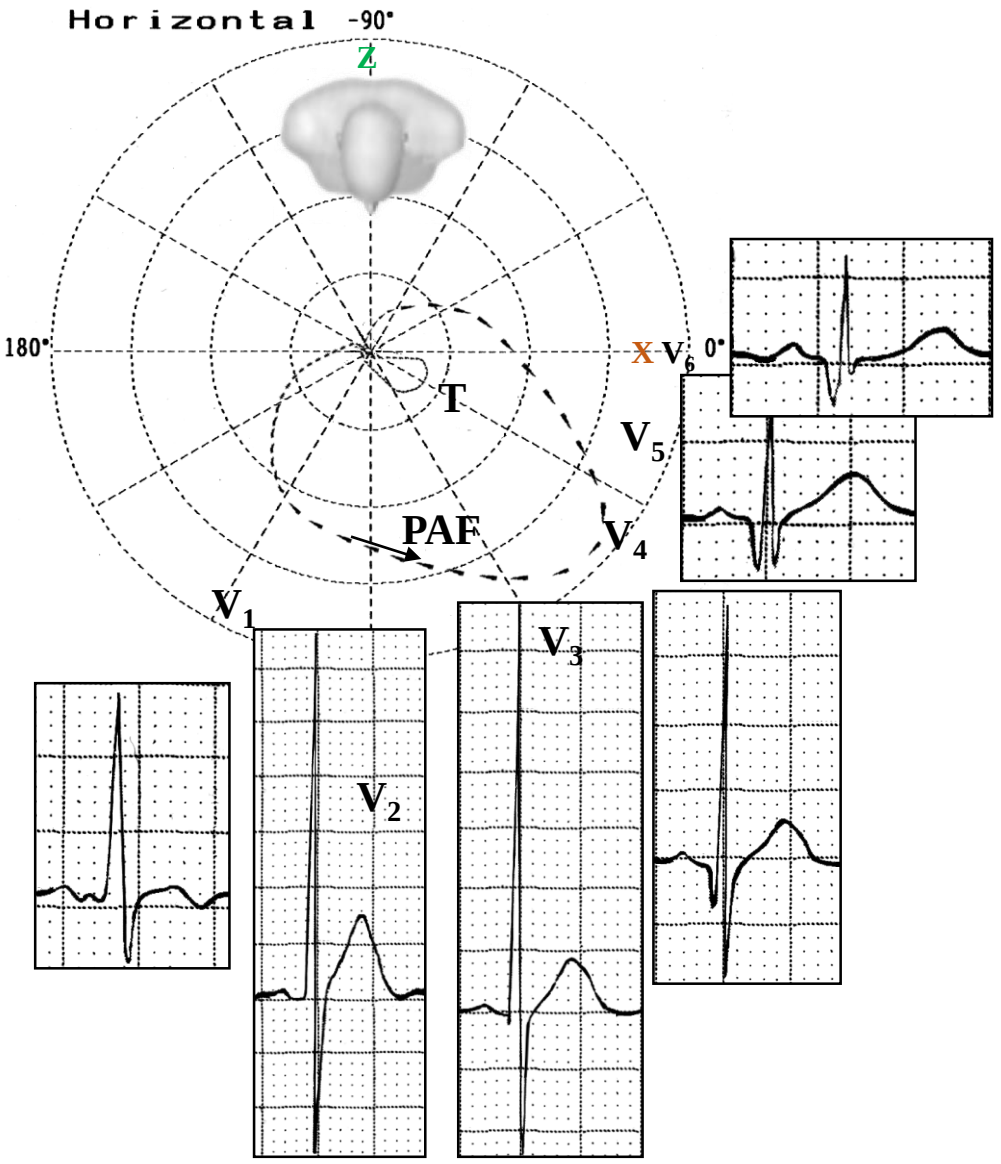
ECG/VCG correlation in the frontal plane

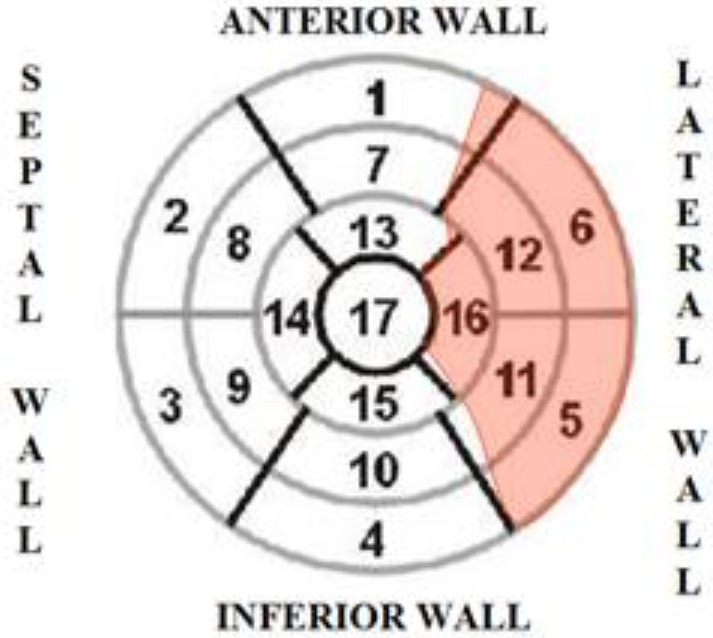




ECG/VCG correlation of the FP Pseudo inferior MI: fibrosis infererolateral. See next slide in the HP..

ECG/VCG correlation in the horizontal plane





ECG/VCG correlation shows in the horizontal plane, anterior shift of the QRS-loop, predominantly located in the left anterior quadrant. Prominent anterior QRS forces from V1 to V4 present in 90% of cases. Consequence of laterobasal initial selective LV fibrosis. **PAF**: Prominent Anterior QRS forces. It is caused by lateral fibrosis(ancient dorsal). Deep and broad Q waves in V5-V6. Its express lateral wall fibrosis(red).

Cardiovascular Magnetic Resonance with Late Gadolinium Enhancement (LGE) in Duchenne cardiomyopathy

CMR has been proven to be the gold standard for precise evaluation of global and regional cardiac function (**Castillo 2003**)**.** Furthermore late gadolinium enhancement (LGE) is suitable for non-invasive assessment of myocardial fibrosis in ischemic and nonischemic cardiomyopathies (**McCrohon 2003**)**.** Cardiac changes in DMD patients and carriers have been most commonly demonstrated to occur in the inferolateral basal LV wall, both pathologically (**Frankel 1967**), electrocardiographically (**Goldberg 1982**), and by cardiac magnetic resonance imaging (CMR) (**Silva 2007**; **Puchalski 2009**). LGE patterns were found mainly in the posterior segments, by CMR (**Silva 2007; Pucalski 2009**).

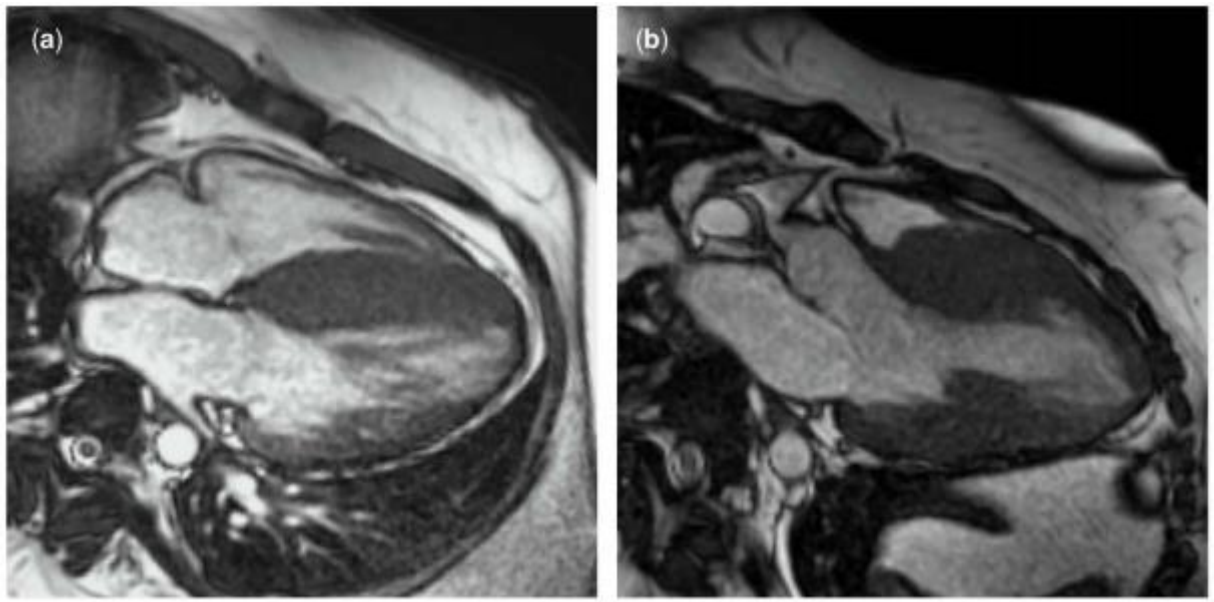
Recently, Olivieri et al (**Olivieri 2006**) compare the ability of native T1 and extracellular volume (ECV) measurements to differentiate risk of myocardial disease in DMD and controls. The design and evaluation of early prophylactic therapies to prevent DMD cardiomyopathy require quantitative measures of LV remodeling to detect early, subclinical myocardial changes and monitor effectiveness (**Hagenbuch 2010**). However, current measures of LV remodeling, such as ECG (**Corrado 2002**), echocardiography evaluation including diastolic indices and myocardial strain imaging (**McNally 2015**), and serum biomarkers (**de Lemos 2009**), are limited. CMR offers additional diagnostic benefits in the assessment of myocardial changes present in cardiomyopathy. CMR using LGE imaging is able to show areas of edema and fibrosis (**Hor 2013**), however, the extent of disease can be underestimated in conditions where the myocardium is affected globally, such as DMD cardiomyopathy (**Florian 2014**).

T1-mapping by CMR is an emerging technique, which offers the ability to quantify myocardial fibrosis. Widely used protocols for T1-mapping in the heart are based on either inversion or saturation recovery using imaging sequences such as Modified Look-Locker (MOLLI) and Saturation recovery single shot acquisition (SASHA), respectively. Baseline normal values of T1 are different for different methods (**Moon 2013**), and there is current debate on the pros and cons for each technique (**Kellman 2014**).

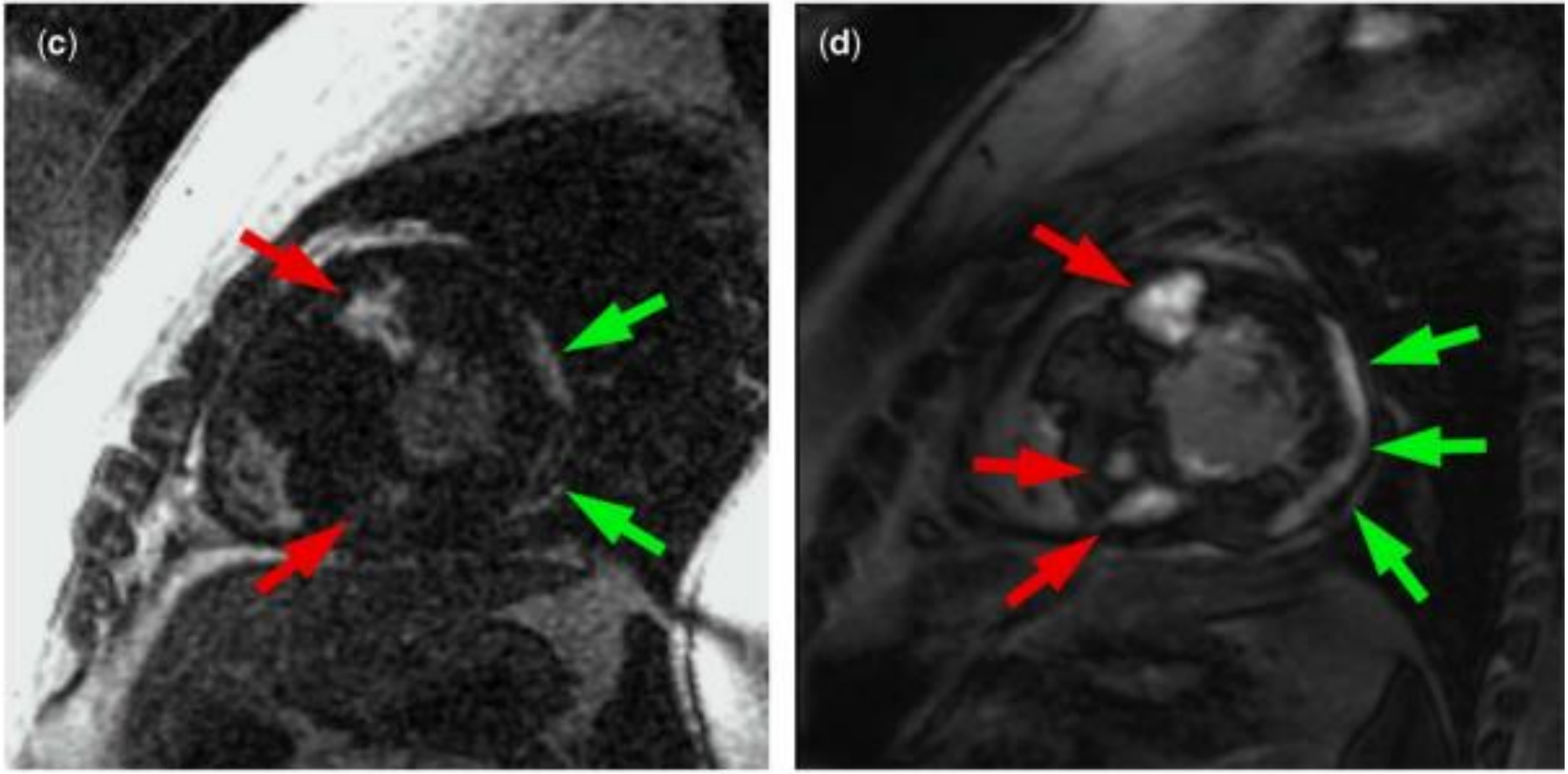
Pre- and post-contrast T1 can be measured and combined for the assessment of extracellular volume (ECV) for detection and quantification of diffuse myocardial fibrosis (**Kellman 2012**). However, with new concerns regarding gadolinium accumulation in the brain (**Malayeri 2016**), pre-contrast, or”native” T1 measurements have been studied and shown to provide useful clinical data without contrast administration (**Puntmann 2013**). The ability to detect and follow subclinical myocardial fibrosis using noninvasive imaging may be a powerful tool to monitor response to early prophylactic myocardial therapies. Olivieri et al aim to compare native T1 and extracellular volume (ECV) measurements in DMD and controls, and evaluate their ability to stratify myocardial disease. This study was the first to demonstrate the novel utility of native T1 measures to stratify DMD patients by extent of myocardial disease. ECV measures, while increased in DMD compared to control, could not distinguish disease severity within the DMD cohort. Native T1 imaging provides a novel imaging biomarker for monitoring myocardial changes related to early

subclinical disease in DMD and possibly other cardiomyopathies. This study used CMR to demonstrate significant differences in the native T1and ECV measurements in the myocardium of DMD subjects compared to age-matched controls. Most importantly, this is the first study to demonstrate that native T1 measurements in LGE-negative myocardium are proportional to the degree of cardiovascular disease in the DMD cohort using regression analyses. Thus, native T1 values can be measured with CMR and used to assess myocardial changes, including fibrosis and inflammation, and disease state among myocardial segments that all appear “normal on LGE”, making this a viable, quantitative measure of subclinical disease without the use of contrast that could be used to monitor early cardiac therapies.

This case was diagnosed initially as HCM. The co-occurrence of two disorders, DMD and HCM of this patient exhibits the typical skeletal muscle phenotype of DMD, but the cardiac phenotype is atypical, because absence of prominent R wave in V1. The asymmetric ventricular septal hypertrophy, hyperdynamic LV systolic function, and septal mid-myocardial late gadolinium enhancement are characteristic of HCM, whereas the sub-epicardial LV lateral free wall late gadolinium enhancement is consistent with the DMD cardiac phenotype. Tandon et al (**Tandon 2015**) postulate that the cytoskeletal pathways mediated by dystrophin and the sarcomeric pathways mediated by myosin binding protein C (cardiac) and troponin T type 2 (cardiac) are both deranged, resulting in a cardiac phenotype with characteristics of both DMD and HCM. However, the downstream interaction of these two pathways has abrogated the typical DMD expected in patients his age, exemplified by the lack of significant LV systolic dysfunction and the presence of myocardial hypertrophy. Although there has been a report of cardiac hypertrophy in a patient with Becker MD, this is the second report of a patient with co-occurring DMD and HCM.



Four-chamber (a) and three-chamber (b) bright blood CMRI showing asymmetric septal hypertrophy.

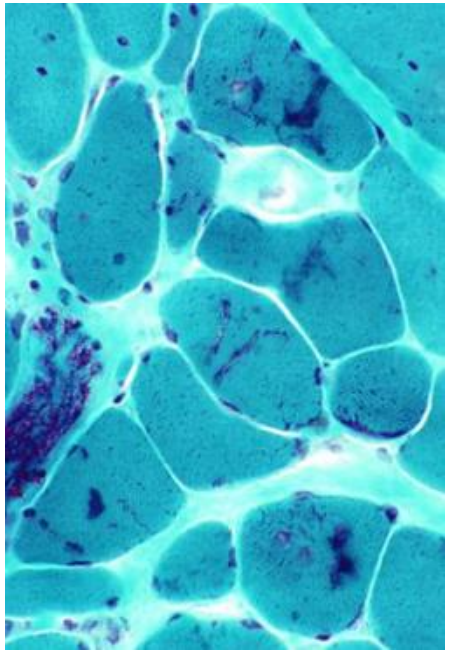


(c): Short-axis post-contrast imaging showing diffuse sub-epicardial left ventricular free wall late gadolinium enhancement (green arrows) and multiple focal septal areas of mid-myocardial late gadolinium enhancement (red arrows). (d): Short-axis post-contrast imaging at age 27 showing progression of sub-epicardial left ventricular free wall enhancement (green arrows) and progression in terms of both number and thickness of focal areas of mid-myocardial septal enhancement (red arrows).

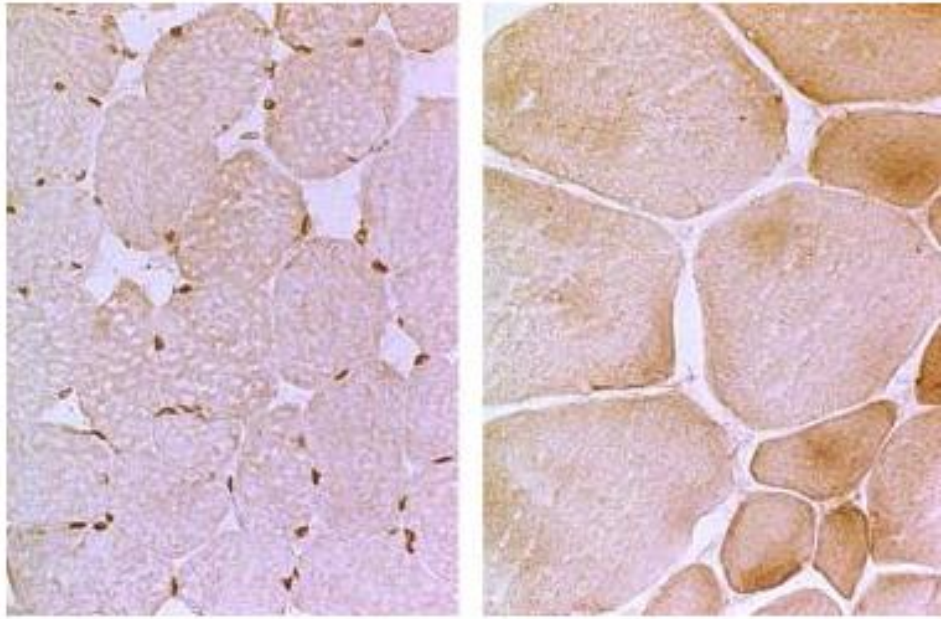
Biopsy: Until the advent of molecular biology techniques, muscle biopsy was the definitive test for diagnosing and confirming muscular disease. Histologic changes depend on the stage of disease and the muscle selected. The optimal site for biopsy is the vastus lateralis, accessed via a small lateral thigh incision.

Histologic specimens from muscle biopsy samples obtained early in the muscular dystrophy disease show only variations in muscle fiber sizes with focal areas of degenerating or regenerating fibers. In later stages of MD, the changes are more obvious, with marked variations in muscle fiber sizes, degeneration, and regeneration. Rounded opaque fibers, internal nuclei, splitting of fibers, and a proliferation of connective and adipose tissues are also present. As the disease progresses, fewer and fewer regenerative fibers are seen. In the end phase, the muscle is mostly replaced by adipose tissue, with residual islets of muscle fibers in a sea of fat.

Histochemical staining with the standard adenosine triphosphatase (ATPase) reaction shows a predominance of type I muscle fibers, with loss of clear-cut distinction into the various fiber types. Electron microscopy demonstrates nonspecific degeneration of the fibers, and immunocytochemical techniques show a persistence of fetal and slow myosin in many of these fibers.



Gomori trichrome–stained section in patient with myofibrillar myopathy. Note the abnormal accumulations of blue-red material in several muscle fibers.



The photomicrograph is a muscle biopsy with normal emerin immunostaining. Right: The micrograph is from a patient with X-linked Emery-Dreifuss muscular dystrophy. Note the absence of nuclear staining as well as the hypertrophied and atrophied muscle fibers.

Prognosis

Despite modern advances in gene therapy and molecular biology, MD remains incurable. With proper care and attention, patients have a better quality of life than they would otherwise, but most still die by the time they are age 30 years, usually as a result of cardiopulmonary failure.

Approach Considerations

The indications for any operative intervention in patients with muscular dystrophy (MD) include making a diagnosis by means of muscle biopsy or prolonging the patient's function and/or ability to ambulate by specific procedures. Other indicated procedures include tendo Achillis and iliopsoas tenotomies for ease of fit into braces, tibialis posterior tendon transfers or tenotomies for more rigid equinovarus deformities of the foot, and segmental spinal stabilization for rapidly developing scoliosis. In patients with muscular dystrophy, some relative contraindications for surgery include obesity, rapidly progressive muscle weakness, poor cardiopulmonary status, and a patient's lack of motivation for participating in postoperative rehabilitation programs. The ability of advancing technology and molecular biology with fetal blood detection of affected fetuses as early as the first trimester opens the door to many ethical issues. One such issue is whether pregnancy termination should be available as an option when a muscle disease is detected that may be fatal in the third decade of life. Detection of myocardial fibrosis and LV dysfunction in DMD is the corner stone for further therapeutic studies. Little is known about the ability of CMR to evaluate progression of myocardial fibrosis. Myocardial fibrosis seems to occur prior to global LV dysfunction in DMD diseased males and carrier females. CMR could be used to evaluate progression of myocardial fibrosis and LV function and may thus serve as an important diagnostic tool in the evaluation of therapeutic options in DMD (**Walcher 2011**).

Steroids: Since Duchenne's time, multiple drug regimens have been tried in treatment of the muscle weakness. Of all the drugs that have come and gone, the only one with some proven benefit is prednisone. The beneficial effects were initially thought to be mediated through the suppression of cytotoxic T-cell expression from the necrotic muscles. In the early 1970s, Drachman et al (**Drachman 1974**) treated 14 boys who had DMD with

steroids and noted some benefits; however, because this was an uncontrolled study, the steroid therapeutic approach did not become a widely accepted treatment protocol. In 1989, Mendell et al [34] performed a randomized, double-blind, multicenter study of 103 male patients with Duchenne MD who ranged from age 5-15 years. Over a period of 6 months, the patients were given prednisone at a dosage of 1.5 mg/kg/day, prednisone at a dosage of 0.75 mg/kg/day, or placebo. The researchers, who followed the expected course outlined by natural history, noted definite improvement in muscle strength in the steroid-treated boys at 1, 2, and 3 months compared with the control subjects receiving placebo. The benefit of the dose-dependent steroid in this study, [34] however, was short-lived. The children's gained strength leveled off after the third month, and then they again began to lose strength. In addition, the adverse effects of the higher-dose steroids, such as rapid weight gain, myopathy, osteoporosis, and growth retardation, offset the beneficial effects of temporary minimal increases in strength. As a result, deflazacort, an oxazoline derivative of prednisolone, is a newer therapeutic drug of choice. [35, 36] Deflazacort reportedly has more bone-sparing and carbohydrate-sparing properties with less weight-gain effects and improves strength and function. Because of the limited side effects and the beneficial properties of muscle sparing and delayed scoliosis progression, deflazacort is being used despite patients' permanent wheelchair status. Clinical investigations are exploring the possibility of limited courses of steroid bursts (which have shown lasting benefits <18 months) and other immunosuppressive drugs, such as azathioprine and cyclosporine. Although the glucocorticoid drugs delay the cytotoxic damage of MD to the necrosing muscle cells, these drugs cannot and do not make, or stimulate the synthesis of, the dystrophin and DAG proteins that are deficient, which is the root cause of the disease

Others agents: Cardiomyopathy is a leading cause of mortality among DMD patients and lacks effective therapies. Phosphodiesterase type 5 is implicated in dystrophic pathology, and the phosphodiesterase type 5 inhibitor tadalafil has recently been studied in a clinical trial for Duchenne muscular dystrophy. Prophylactic use of tadalafil delays the onset of dystrophic cardiomyopathy, which is likely attributed to modulation of

TRPC6 levels and permeability and inhibition of protease content and activity. Consequently, phosphodiesterase type 5 inhibition is a candidate therapy for slowing the development of cardiomyopathy in DMD patients (**Hammers 2016**).

Carvedilol therapy appears to be safe for patients with DCM secondary to MD and produces a modest improvement in systolic and diastolic function but statistically significant improvement in CMR-derived LVEF. Carvedilol also is associated with significant improvements in both the mean rate of pressure rise (dP/dt) during isovolumetric contraction and the myocardial performance index. A trend toward improved shortening fraction, E/E' ratio, and isovolumetric relaxation time also was observed. Runs of NS-VT exceeding 140 bpm) before carvedilol administration. VT exceeding 140 bpm was not observed after carvedilol therapy. Carvedilol is well tolerated, and no serious adverse events are identified (**Rhodes 2008**). In 2-year, follow-up, randomized clinical trial of patients with DMD or Becker MD whose LVEF was preserved and myocardial fibrosis was present as determined on CMR, ACE inhibitor therapy was associated with significantly slower progression of myocardial fibrosis. The presence of myocardial fibrosis was associated with worse patient prognosis (**Silva 2016**). Another potential therapy is creatine monohydrate supplementation. Creatine is a natural compound occurring in meats and is also endogenously produced by the liver and kidneys. Creatine supplementation has been shown to enhance athletic performance of healthy individuals in up to 10%. Studies looking at creatine use in neuromuscular disorders have been popularized since late 1997, with the publication of the first human study by Tarnopolksy et al showing an increase in high-intensity power output with use. Several other human clinical trials of creatine supplementation have been conducted since that time with similar results. A meta-analysis of all randomized clinical trials using creatine monohydrate supplementation in neuromuscular disorders versus placebo was performed. It found that short- and intermediate-term treatment with 0.03-0.04 g/kg/day of creatine monohydrate supplementation resulted in modest but significant increases in mean maximum voluntary contraction of 9.2 N higher than placebo. There is also an increase in fat free muscle mass. Globally, 44% of patients felt better in the creatine treated group, compared with 10% in the placebo group.

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