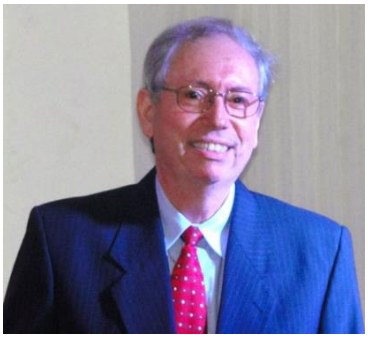
Eighteen years old Caucasian man with progressive familial disabling disease



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Case report

DBS, male, Caucasian, 18 years and 6 months old. The patient had been diagnosed with progressive neurological disease at 8 years of age. He started to walk about age 20 months (delays in waking). Learning disabilities, such as developing speech later than usual and slight mental retardation.

He has a long history of progressive symmetrical weakening of his muscles of inferior members most notably in the proximal musculature of the legs, pelvis, and arms.

By age 9, he required orthotic braces to assist his walking, and by age 17, he was confined to wheelchair ambulation (skeletal deformity).

Family history: He has a sister in good health and a younger brother (age 12) who is confined to a wheelchair with similar problems. No other immediate or distant family members have musculoskeletal difficulties.

He is followed at Hospital Sarah since age 10 years old. (This hospital is a renowned center of neurorehabilitation of neurological diseases with motor and sensory impact).

Physical Examination: he appeared fatigued and short of breath. Minimal scoliosis. Regular tachycardia (heart rate = 110 bpm), respiratory rate = 28 breaths per minute, axillary temperature = 36.7°C, blood pressure = 138/74 mmHg. Normal pupils reactive to light, with intact ocular movements. No dysarthria or facial muscle weakness. Macroglossia.

Jugular venous distention is assessed while the patient is supine with the upper body at a 45° angle from the horizontal plane. The top of the waveform of the internal jugular vein has a height of more than 6 cm from the sternal angle consistent with elevated venous pressure.

Chest: Percussion of the chest suggested pulmonary infiltrates in the lower lung fields bilaterally. Breath sounds were reduced, with significant inspiratory rales heard over both lungs. Lung basal crackles. His cough was very weak, but productive of green sputum.

There was downward and leftward displacement of the apex 2 cm left of the mid clavicular line and in the 6h intercostal space. Apex occupied a diameter >3 cm (apex covered with 2 fingertips).
Heart sounds were normal, with pansystolic murmur +++/5 in apex with axillary irradiation.

Neurological examination: absent deep tendon reflexes in the upper extremities and patella (though the tendon the Achilles reflex remained intact), pain and pseudo hypertrophy in the calves (enlarged and painful).

We requested Electrocardiogram, Chest X-Ray, imaging tests (transthoracic echocardiogram and magnetic resonance imaging), biomarkers blood tests (serum creatine kinase, and serum aldolase), muscle biopsy with immunohistochemical examination and genetic testing for proband and relatives.

Questions

I. Which is the most probable clinical diagnosis?
II. Which is the ECG diagnosis?
III. Why we observe Prominent QRS Anterior Forces (PAF) and deep and narrow Q waves in I and aVL? Justify.

Português

Relato de caso

DBS, masculino, branco, 18 anos e 6 meses. O paciente tinha sido diagnosticado portador de doença neurológica progressiva aos 8 anos de idade.

Começa a caminhar tardiamente aos 20 meses. Dificuldades de aprendizagem, tais como desenvolvimento da fala mais tardia e deficiência intelectual mínima (fronteiriço).

Tem uma longa história de fraqueza muscular simétrica progressiva, principalmente dos músculos dos membros inferiores, na musculatura proximal das pernas, pélvis e braços.

Por volta dos 9 anos, necessitou de cintas ortopédicas para ajudar a sua caminhada, e aos 17 anos ele estava abásico confinado em cadeira de rodas (deformidade esquelética).

Antecedentes familiares: tem uma irmã que goza de boa saúde e um irmão mais novo (12 anos), que está confinado a uma cadeira de rodas com problemas semelhantes. Nenhum outro membro da família imediata ou distantes têm dificuldades musculoesqueléticas.

É acompanhado no Hospital Sarah desde os 10 anos de idade (este hospital é um renomado centro de reabilitação de doenças neurológicas com impacto motor e sensorial).

Exame Físico: Dispneico, escoliose mínima, taquicardia regular (FC = 110 bpm), frequência respiratória = 28 respirações por minuto, temperatura axilar = 36,7° C, pressão arterial = 138/74 mmHg. Pupilas normais reativas à luz, com movimentos oculares intactos. Sem disartria ou fraqueza muscular facial. Macroglossia.

Distensão venosa jugular avaliada enquanto o paciente está em decúbito dorsal, com o tronco a um ângulo de 45° em relação ao plano horizontal. A borda superior da forma de onda da veia jugular interna tem uma altura de mais de 6 cm a partir do ângulo esternal, consistente com a pressão venosa elevada.

Tórax: percussão sugeriu infiltrados pulmonares nos campos pulmonares inferiores bilateralmente. Sons respiratórios hipofonéticos, com estertores inspiratórios significativos ouvidos em ambas as bases pulmonares. Pulmonar basal crepita.

Tosse foi muito fraca, mas produtiva de expectoração esverdeada.

Deslocamento para baixo e para a esquerda dos dois centímetros vértice esquerdo da linha clavicular média e no espaço 6h intercostal. Apex ocupa um diâmetro > 3 cms (apex é coberta com 2 polpas digitálicas).

Bulhas normofonéticas, sopro pansistólico de +++ / 5 com foco no ápice e irradiação axilar esquerda.

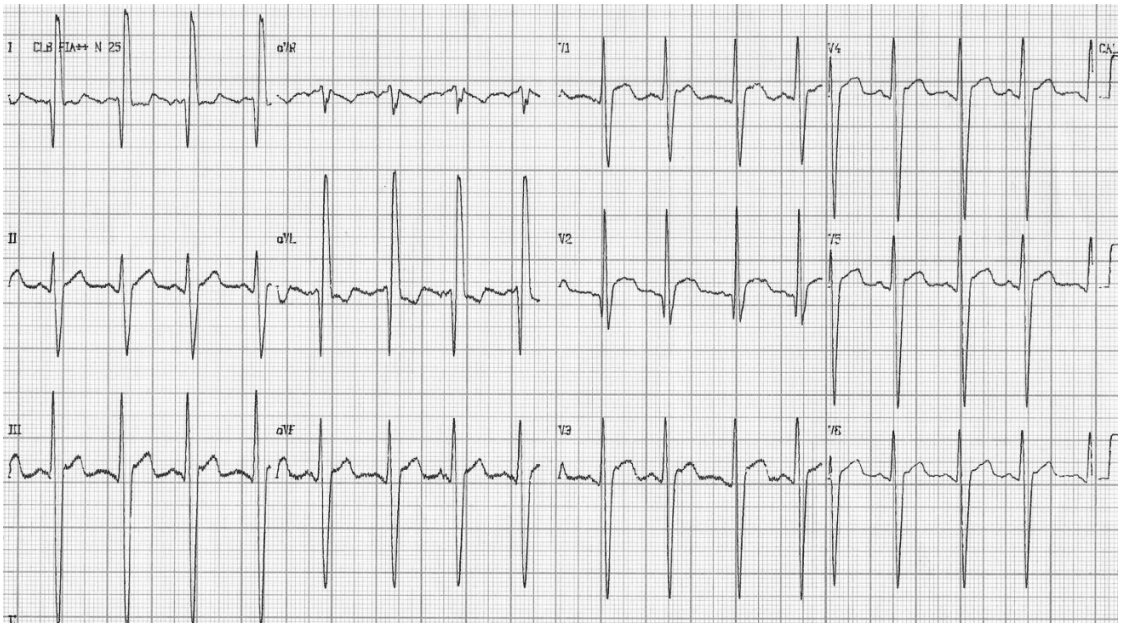
Reflexos neurológicos profundos ausentes nas extremidades superiores e patela (embora o reflexo do tendão de Aquiles permanece intacta), dor e panturrilhas (alargadas e dolorosa).

Solicitamos: Eletrocardiograma, Raio X de tórax, ecocardiograma transtorácico e ressonância magnética (MRI), creatina quinase sérica e aldolase Ssséricas , biópsia muscular com exame de imunohistoquímica e testes genéticos.

Perguntas:

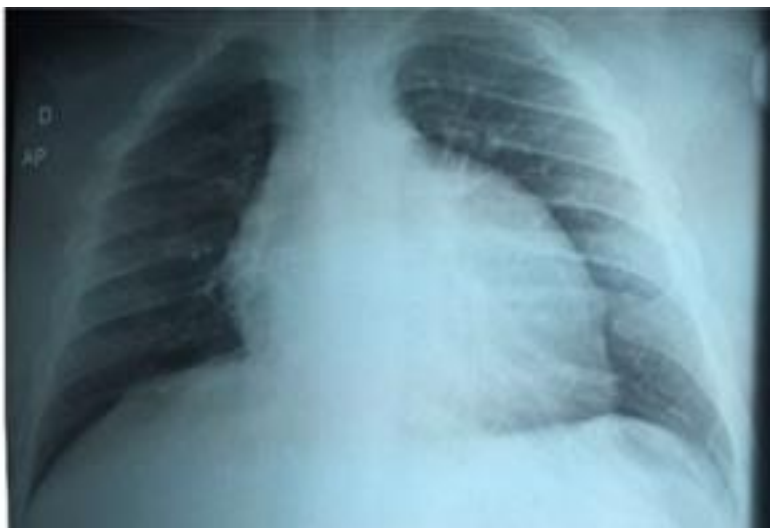
I. Qual é o diagnóstico clínico mais provável?
II. Qual é o diagnóstico ECG?
III. Por que observamos Forças Anterior Proeminentes (PAF) associadas a ondas Q profundas e estreitas em I e aVL no ECG? Justificar.

Electrocardiogram



ECG diagnosis:

AP view of a chest X-ray Posterior-Anterior (PA) projection



Colleagues opinions

Spanish

Hola amigos Mi opinión:

1. Diagnóstico probable de distrofia muscular progresiva heredo-familiar: Steiner o Duchenne (DMD) o Landouzi, las cuales afectan las fibras musculares (miosina) y se asocian con miocardiopatía dilatada e insuficiencia cardiaca congestiva, lo que explica el soplo, por insuficiencia mitral por dilatación del anillo mitral, la ingurgitación yugular por insuficiencia ventricular derecha y la cardiomegalia global Rx por dilatación de ventrículo derecho e izquierdo (biventricular).
2. El ECG muestra taquicardia auricular focal de aurícula izquierda (P negativa en DI) o multifocal (faltaría tira más larga) y por momentos P sinusales con signos de trastornos conducción interauricular.
3. Las ondas Q profundas en I y aVL expresan un bloqueo fascículo anterosuperior izquierdo asociado a fibrosis ínfero-lateral presente en el 90% de la DMD, lo que también explicaría las fuerzas anteriores prominentes (FAP) de V1-V2.

El ecocardiograma revelaría dilatación biventricular, fracción de eyección del ventrículo izquierdo disminuida, hipocinesia ínfero-lateral, insuficiencia mitral, insuficiencia tricúspide e hipertensión en el tronco de la arteria pulmonar.

La RNM demostraría: fibrosis de segmentos inferiores y lateral

La biopsia demostraría el daño de las fibras musculares

Saludos cordiales. Dr. Juan José Sirena Santiago del Estero Argentina

English
Hello friends
My opinion:

1. Probable diagnosis of progressive hereditary-familial muscular dystrophy: Steiner or Duchenne (DMD) or Landouzi, which affect muscle fibers (myosin). These entities are associated with dilated cardiomyopathy(DCM) and congestive heart failure, which explains the dyspnea, for mitral regurgitation secondary to dilation of the mitral ring, jugular ingurgitation consequence of right ventricular failure and overall cardiomegaly
2. The Rx shows by dilation of right and left ventricles (biventricular)
3. The ECG shows atrial tachycardia with focus in left atrium (P negative P wave in I) or multifocal (it is necessary long strip). Sometimes the P is sinus, with signs of atrial conduction disturbance. The deep Q waves in I and aVL express a left anterior fascicular block associated with inferolateral myocardial loss present in 90% of

cases of DMD. Fibrosis would also explain the prominent anterior QRS forces (PAF) inV1-V2

Echocardiography revealed biventricular dilatation, decreased LVEF left ventricular inferolateral hypokinesia, mitral regurgitation, tricuspid insufficiency and hypertension in the pulmonary artery trunk.
The RNM will show: fibrosis in inferior lateral segments
The biopsy will show damage of muscle fibers
Best regards
Juan José Sirena M.D. Santiago del Estero Argentina

This is Duchenne or Becker muscular dystrophy.
Yochai Birnbaum
Professor
Medicine-Cardiology
Baylor College of Medicine
Houston, TX, US

I think he has either Becker or more Likely Duchene muscular Dystrophy as shown by prominent anterior forced likely due to posterior scar no q waves laterally hence more posterior scar.
Melvin M Scheinman
Department of Cardiac Electrophysiology, University of California San Francisco, San Francisco, California, USA. scheinman@medicine.ucsf.edu

Professor of Medicine

Dear Andrés Ricardo, Raimundo and Luiz Carlos,

Allow me to share here my knowledge and experience.

What strikes me most is the small vector, which is where it should not be.

Positive deflection in I and aVL, negative in II and aVF and very positive in aVR.

Could it be the end of a very fractioned P wave? Or could it be the depolarization of the anterior papillary muscle anticipated in relation to the posteromedial (fibrotic), causing posterior valve prolapse and consequently mitral insufficiency?!!!

The second deflection is a deep Q wave in I and aVL leads which is depolarized in the fibrotic cardiac base. This would explain why the R waves are of higher voltage in III than in II in the presence of left anterior fascicular block.

The lower wall is in longitudinal remodeled reciprocation with the cardiac base (either in acute basal and inferior is ischemia or in physiological and pathological basal hypertrophies). aVL is always remodeled with III. This would explain the very high R waves in aVL and deep S waves in II, III and aVF.

The analysis of the limb leads suggests an eccentric hypertrophy of the cardiac base

This basal hypertrophy also explains the Q/R ratio in V2 and someone said that this lead is out of place. I think that in the contrary, it is in the right place. The V2 lead is embryologically, anatomically and circulatory connected to the right area of the basal muscle. Both are embryologically formed at 18 days of gestation by the acardiac bulb, which in the third week forms the outflow tracts of both left and right ventricles in the heart base, formed by the muscular base, the upper third of the left and right septum.

Anatomically, they form the left and right output tract (V2 upper septum and all the base since LI is involved and being expressed in the left area of the ventricular base and aVL expresses the mid and right base and that is why these leads are accompanied by basal hypertrophies).

The first diagonal artery supplies both the right area of the basal muscle and the

upper septum, which explains, as we have described in sudden obstruction of this artery, the ST elevation in V2 and aVL .

Deep S waves in V3 to V6 are due to posteroseptal hypertrophy and the clockwise rotation of the heart on the anterior posterior axis in the presence of the blockage of the left anterior superior fascicle.

Why are the complexes so wide? Because there is severe fibrosis in the ventricles and a down-regulation of connexin 43 which slows the rate of intraventricular conduction.

I think that only the electrocardiogram and magnetic resonance are able to give this kind of information.

It would be interesting to study these cases of Duchenne, to see if those who survive longer are those who do hypertrophies or that directly dilate.

Whether opposing or favorable to this analysis in this discussion, I will answer any question.

Kind regards,

Dr. Samuel Sclarovsky (Tel Aviv, Israel)
Emeritus Professor of Tel Aviv University, Israel

ARGENTINA

Spanish: Queridos amigos Andrés Ricardo, Raimundo, Luiz Carlos
Permítame expresarme en este caso, según mi experiencia y conocimiento.
Lo que me llama la atención es el vector pequeño, que se encuentra donde no debe estar. Deflexión positiva en I, aVL, negativa en II y aVF y muy positiva en aVR. ¿Sería la parte terminal de una onda P muy fraccionada? ¿O seria la despolarización del musculo papilar anterior anticipada en relación al póstero-medial (fibrótico), provocando prolapso de la valva posterior y consecuente insuficiencia mitral?!!!
La segunda deflexión es una onda Q profunda en I y aVL que se despolariza en la base cardiaca fibrótica. Esto explicaría el porqué de que las ondas R sean de mayor voltaje en III que en II en presencia de bloqueo fascicular ántero-superior. La pared inferior está en reciprocidad remodelada longitudinal con la base cardiaca (ya sea en isquemias agudas basales e inferiores o en hipertrofias basales fisiológicas y patológicas). Siempre aVL esta remodelada con III. Esto explicaría las R muy altas en aVL y las S profundas en II, III y

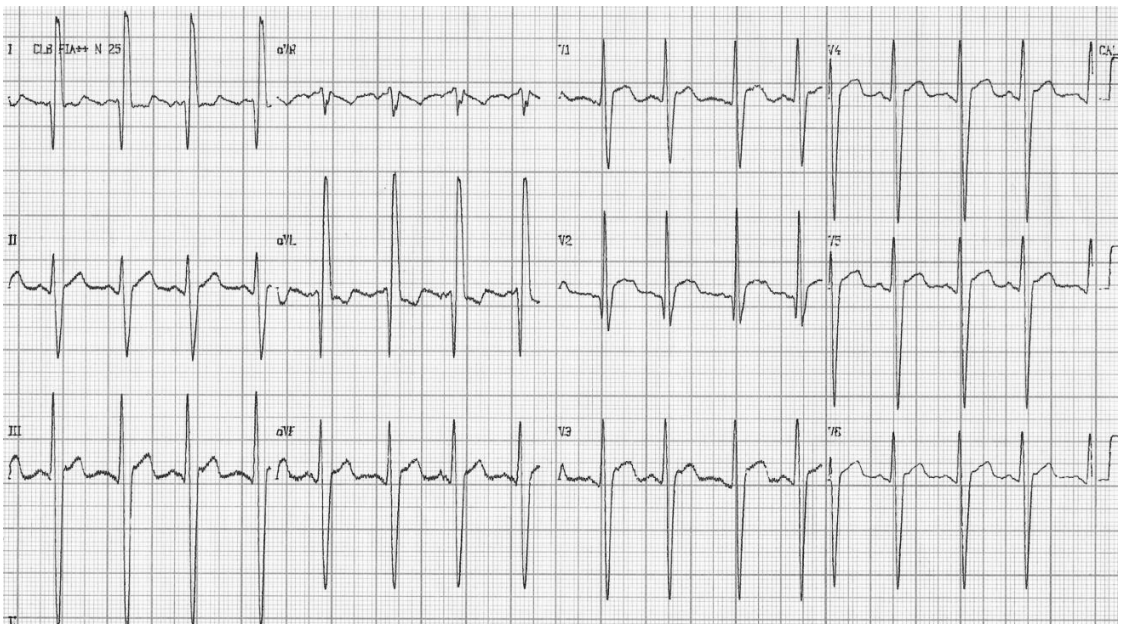
aVF. El análisis de las derivaciones de los miembros sugiere una hipertrofia excéntrica de la base cardiaca. También esta hipertrofia basal explica la relación Q/R en V2, y alguien dijo que esta derivación esta fuera de lugar. Yo pienso contrariamente que está en el lugar apropiado. La derivación V2 está conectada embriológica, anatómica y circulatoriamente con el área derecha del músculo basal. Embriológicamente ambos son formados a los 18 días de gestación por el bulbo cardiaco, el cual a la tercera semana forma los tractos de salida de ambos ventrículos izquierdo y derecho en la base cardíaca, formado por la base muscular, el tercio superior del septo izquierdo y derecho. Anatómicamente forman que es el tracto de salida izquierdo y derecho (V2 septo superior y toda base a ya que I está involucrada (área izquierda de la base ventricular y aVL la base media y derecha y es por esto que estas derivaciones van acompañadas e hipertrofias basales complicadas).
La arteria primera diagonal irriga a ambas e área derecha del musculo basal y al septo alto, lo que explica según hemos descripto en obstrucción súbita de esta arteria, la elevación del ST en V2 y aVL. Las S profundas de V3 a V6 se deben a hipertrofia póstero-septal y a la rotación horaria del corazón sobre el eje anterior posterior en presencia del bloqueo del fascículo antero-superior izquierdo.
¿Porque los complejos son tan anchos? Porque existe fibrosis severa en los ventrículos y baja regulación de la conexina 43 lo que retarda la velocidad de conducción intraventricular. Me parece que apenas el electro y la resonancia magnética son capaces de dar este tipo de información.
Sería interesante estudiar estos casos de Duchenne, para saber si los que sobreviven mayor tiempo son aquellos que hacen hipertrofias o los que se dilatan directamente.
Un fraternal abrazo
La discusión contraria a este análisis o favorable contestare a toda pregunta.
Dr. Samuel Sclarovsky (Tel Aviv, Israel)
Profesor Emérito Universidad de Tel Aviv, Israel

Português
Meu caro Andrés: O caso é muito interessante. Uma possibilidade é Distrofia Muscular Progressiva (idade e perda progressiva de força muscular).A favor desta hipótese, temos as ondas R proeminentes nas precordiais direitas, dado muito comum nesta entidade. A explicação para as R altas em V1 e V2 seria uma necrose posterior, que ocasiona perda das forças posteriores e concomitante o aumento da voltagem da onda R nas precordiais direita.
Outra possibilidade seria cardiomiopatia hipertrófica, que explicaria as ondas Q observadas, em ausência de verdadeiro infarto.
A na primeira hipótese (Distrofia Muscular Progressiva DMP) é a mais provável
Abraços afetuosos do
Hélio Germiniani. Curitiba Brasil

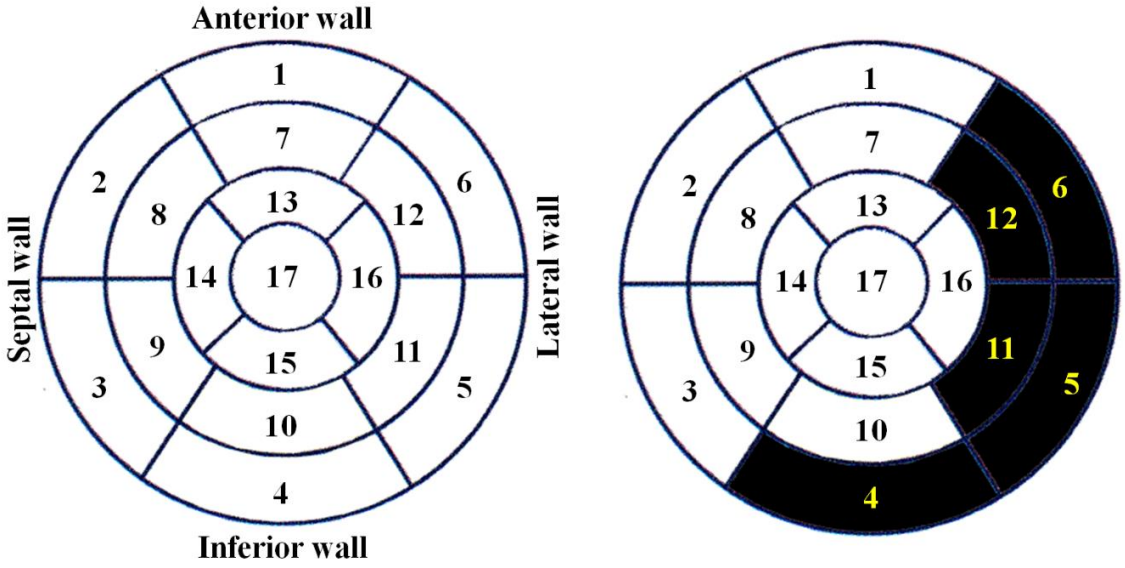
English
Dear Andrés: The case is very interesting. One possibility is Progressive Muscular Dystrophy (age of presentation and progressive loss of muscle strength).The favor of this hypothesis; we have prominent R-waves in the right precordial, as common in this entity. The explanation for the high R in V1 and V2 would be a further necrosis, which causes loss of the posterior forces and consequent increase of the voltage of the R wave in the right precordial leads.
Another possibility would be hypertrophic cardiomyopathy, which would explain the Q waves observed in the absence of truly myocardial infarction.
The first option (Muscular Dystrophy Progressive DMP) is the most likely diagnosis.
Affectionate hugs
Hélio Germiniani. M.D. PhD. Curitiba, Brazil.

Final comments

Hugging my "daughter" Pet “Evita”



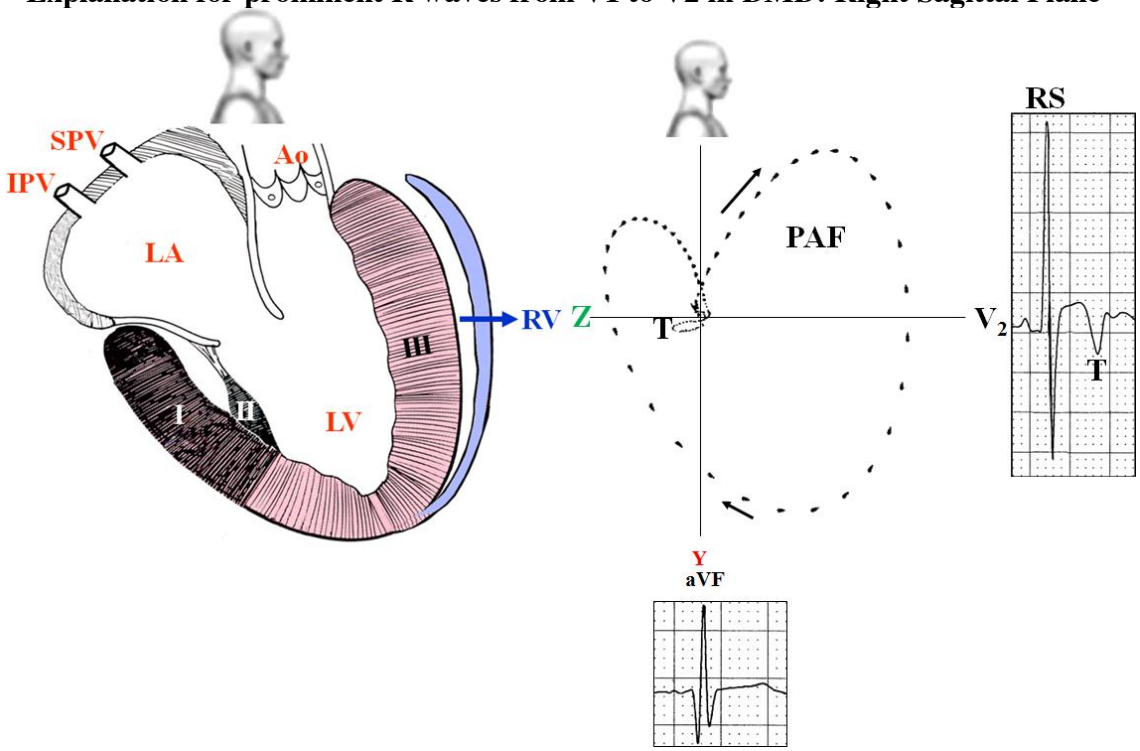
ECG diagnosis: sinus tachycardia (HR 107bpl), short PR interval = 80 ms (see next figure below), extreme left axis deviation (QRS axis –45° LAFB), deep narrow Q waves (Q amplitude ≥2 mm, duration <40ms) in I and aVL, and precordial leads with early transition R-wave because (the transition happens in lead V_1-V_2 it is referred to as an early transition). Selective atrophy and scaring of the **laterobasal region** (old dorsal) and eventually **inferior wall of the LV with posteromedial papillary muscle (PMPM) involvement** are reported and may explain the ECG pattern with abnormal Q-waves and prominent R wave on right precordial leads (Figure xx). Studies at necropsy have shown that the cardiomyopathy of DMD selects the segment 4 (basal inferior, old posterobasal) and lateral LV walls (segments 12, 6, 11 and 5) as initial and primary sites of myocardial dystrophy in the absence of small-vessel CAD in these areas (figure) (**Perloff 1984**) and eventually inferior wall (segments 10 and 15).



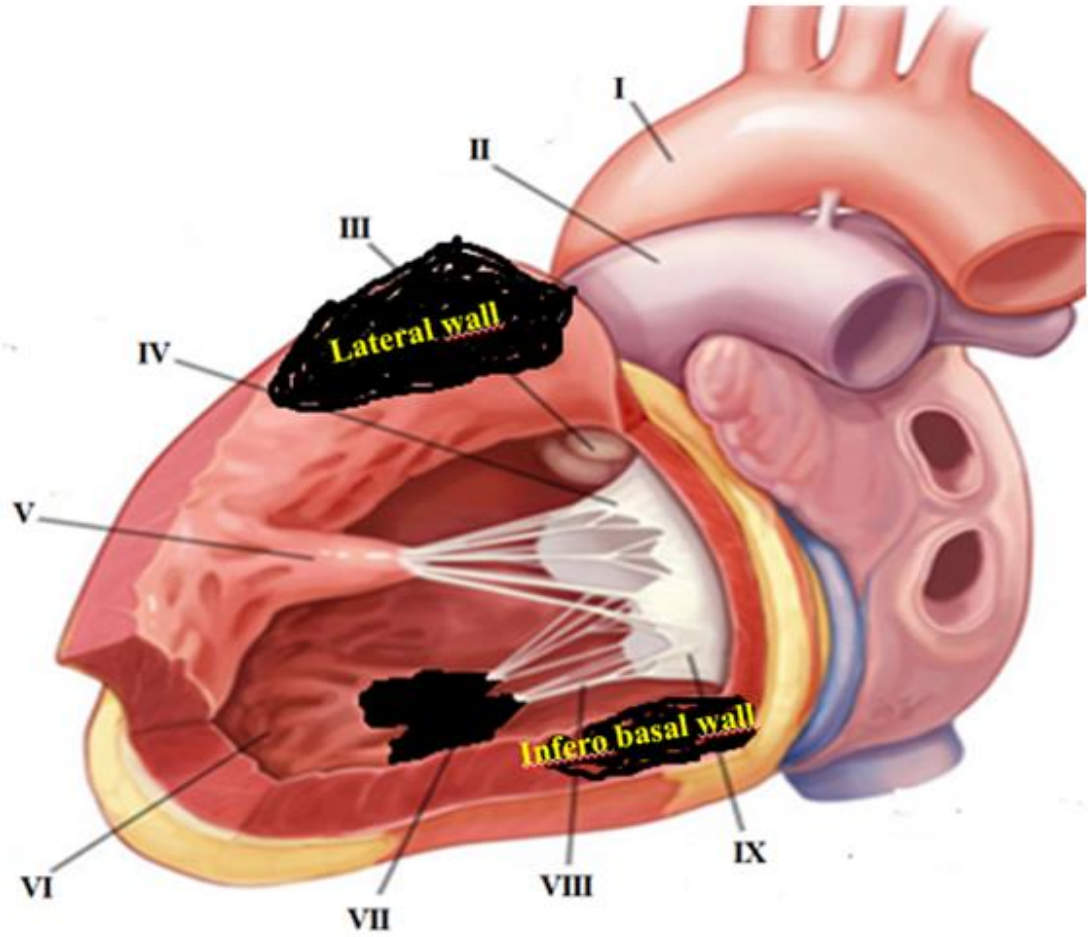
The figure shows cardiac segments initial and primary affected in DMC

The normal amplitudes of R waves in lead V_1 for men between 20-30 years old is 0-5.3 mm (in the present case R-V1 voltage is 13 mm).
The normal amplitudes of R waves in lead V_2 for men between 20-30 years old is 1.1-9.2 mm (in the present case is 19 mm) (**Pérez-Riera 2016**). Consequently, in the present case we have prominent R waves in V_1-V_2. We know that a prominent R wave in V1 is caused by a lateral not posterior MI / fibrosis - based on contrast-enhanced CMR-ECG correlations (**Bayés de Luna 2015**). The presence of prominent the R wave in V1 is due to the lateral MI and not to the involvement of inferobasal segment of inferior wall (old posterior wall) (**Goldwasser 2015**). In cases of Q wave infarctions: ECG criteria for lateral MI are R/S ratio in V1 ≥ 0.5 and R amplitude in V1 >3 mm present very high specificity and lower but very acceptable sensitivity for lateral MI; R waves in V2 or T waves in V1 to V2 do not discriminate between inferior and lateral MI; and R/S amplitude ratio ≥ 1 and R duration ≥40 ms in V1) attain very high specificity but much lower sensitivity (**de Luna 2008**).

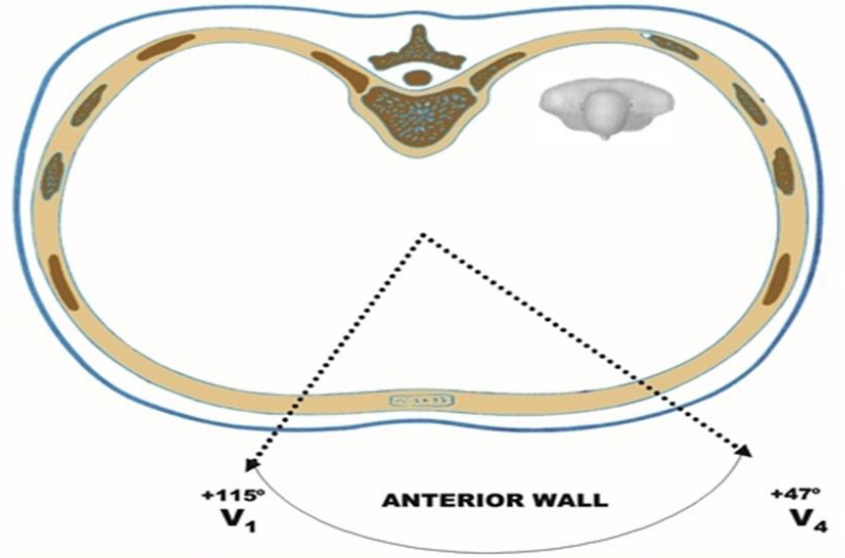
Explanation for prominent R waves from V1 to V2 in DMD: Right Sagittal Plane



I. Inferobasal and lateral selective segmentary loss; II. Posteromedial papillary muscle (PMPM) involvement; III. Interventricular septum; **SPV**. Right superior pulmonary vein; **IPV**. Right inferior pulmonary vein; **LA**. Left atrium; **LV**. Left ventricle; **Ao**. Aortic root; **RV**. Right ventricle; **PAF**. Prominent anterior QRS forces.



I. Aorta
II. Pulmonary trunk
III. Aortic valve
IV. Anterior leaflet of mitral valve
V. Anterolateral papillary muscle
VI. Left ventricle
VII. Posteromedial papillary muscle involvement
VIII. Chordae tendineae
IX. Posterior leaflet of mitral valve
Black color: fibrosis involvement area.

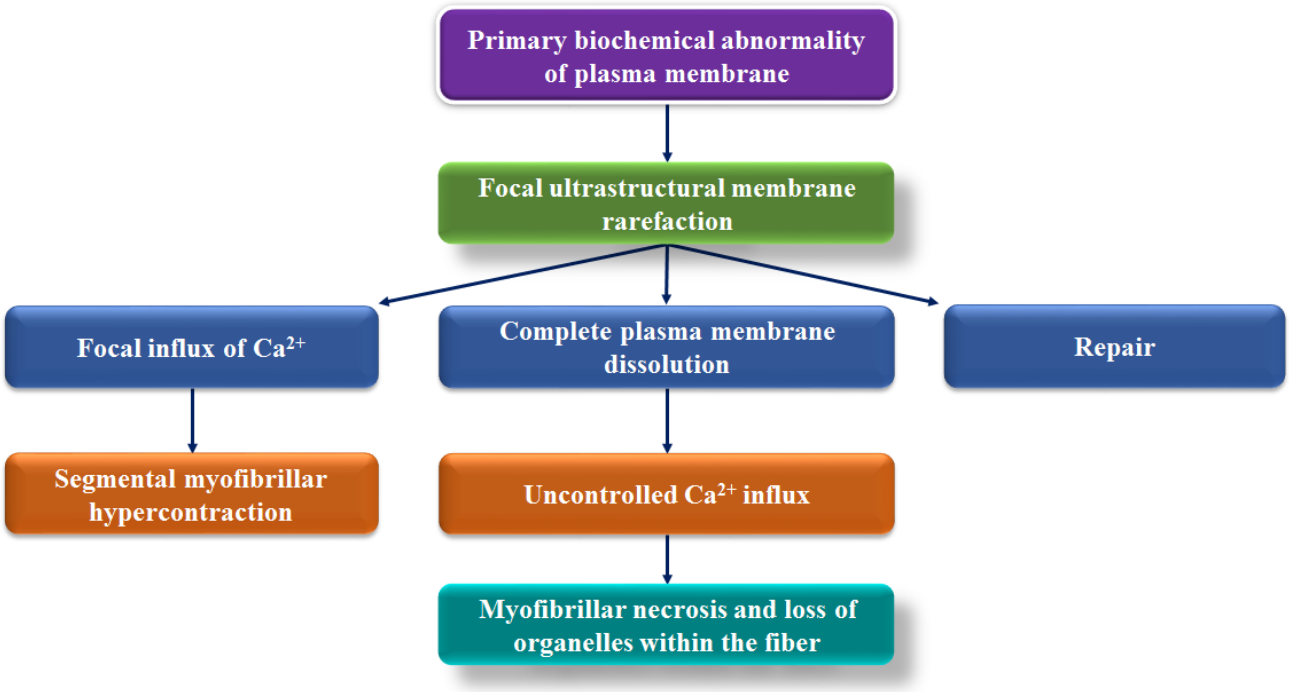


I Lateral	aVR	V1 Septal	V4 Anterior
II Inferior	aVL Lateral	V2 Septal	V5 Lateral
III Inferior	aVF Inferior	V3 Anterior	V6 Lateral

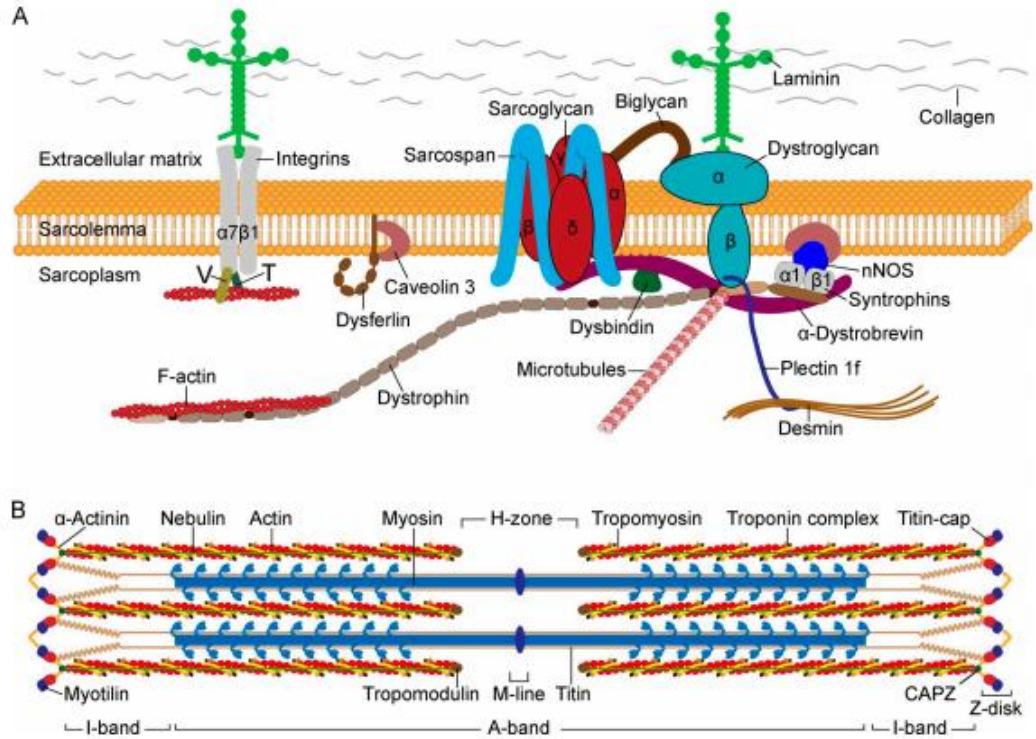
V1 to V4 anteroseptal wall.

Dystrophinopathies may be associated with DCM, characterized by an impairment of LVEF and potentially complicated by clinical HF. Conduction system disease and supraventricular and/ or ventricular arrhythmias may also be present. The prevalence of DCM is extremely high in DMD, intermediate in BMD, and lower in female carriers. Cardiac follow-up is indicated in any patient with a mutation in the dystrophin gene, based on ECG and echo, and must be closer, at least on a yearly basis, in patients with the highest cardiac risk. Systematic cardiac workups allow an earlier diagnosis of cardiac involvement and a prompt treatment. First-line treatments are angiotensin-converting-enzyme inhibitors and other conventional HF treatments (angiotensin II receptor blockers, β-adrenergic blocking agents, aldosterone antagonists and diuretics, anticoagulants which must be systematically initiated at the age of 10 years or earlier in DMD and regarding the identification of cardiac abnormalities in any patient with other dystrophinopathies.
The pathophysiology of muscle cell necrosis in DMD suggests that necrosis of muscle cells is initiated by loss of plasma membrane, followed, after a short interval, by Z disc lysis and mitochondrial changes to constitute the picture of fully developed necrosis. Empty basal

lamina tubes containing collagen indicated that regeneration may fail to occur. The tubes form a basis for collagen deposition. Evidence suggests that small patches of membrane loss can be repaired, though a slice of superficial cytoplasm is lost, and a piece of detached basal lamina results. The markedly hypercontracted fibers seen did not show features of necrosis (**Carpenter 1979**) (figure).



Sarcolemma proteins and sarcomere structure

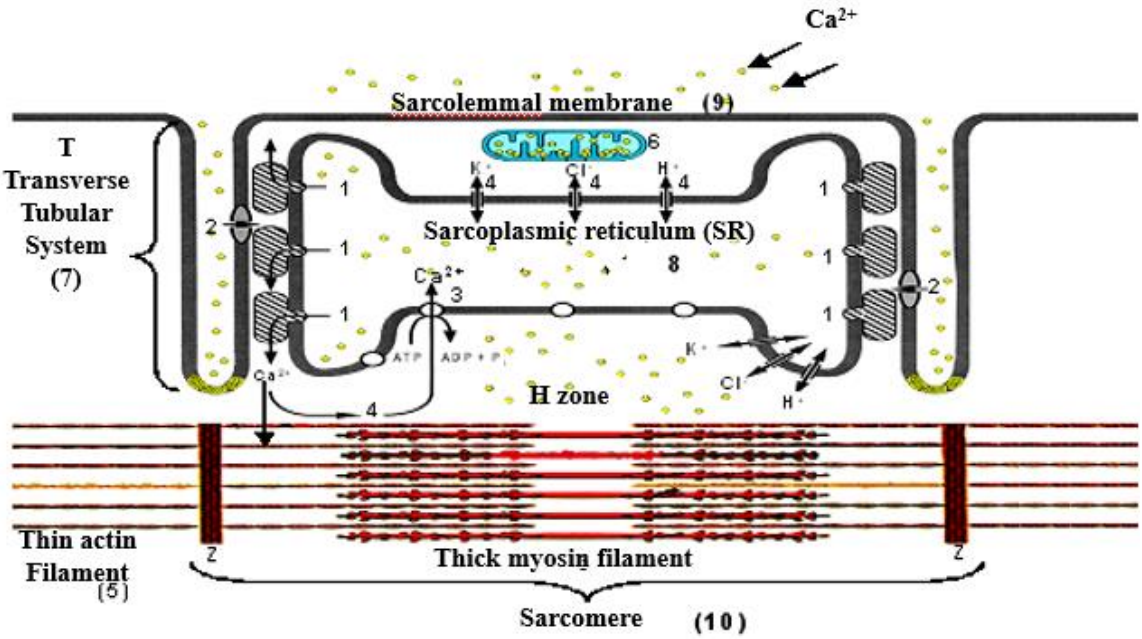


Sarcolemma proteins and sarcomere structure

(A) The dystrophin-associated protein complex (DAPC) is a multimeric protein complex that connects the intracellular cytoskeleton of a myofiber to the extracellular matrix (ECM), which is composed of laminin, collagen, and other proteins. The muscle-specific laminin is composed of α2, β1, and δ1 chains. The α2 subunit directly interacts with glycosylated α-dystroglycan, which in turn interacts with the transmembrane β-dystroglycan. The dystrophin protein has four functional domains including the N-terminal, a long middle rod, cysteine-rich, and C-terminal domains. The central rod domain consists of 24 spectrin-like repeats arranged head-to-tail and interspersed by four flexible hinges. The N-terminal and the spectrin-like repeats bind to F-actin of the cytoskeleton, but not to the α-actin of thin sarcomeric filaments. The cysteine-rich domain binds to β-dystroglycan and the adjacent C-terminal domain binds to α-dystrobrevin and syntrophin. The cytolinker protein plectin binds β-dystroglycan and dystrophin and connects desmin IFs with the DAPC. Microtubules also interact with dystrophin. The four subunits of the sarcoglycan complex interact with each other and with the transmembrane protein sarcospan. The small leucine-rich repeat proteoglycan biglycan in the ECM binds to α- and δ-sarcoglycan andα-dystroglycan. Syntrophins bind to dystrophin, α-dystrobrevin, nNOS, and caveolin-3. The α7β1 integrin dimer binds laminin extracellularly and actin intracellularly via the vinculin (V) and talin (T) proteins.

(B) The basic contractile unit of skeletal/cardiac muscle, the sarcomere, is composed of thin and thick filaments predominantly composed of actin and myosin, respectively. Thin filaments of adjacent sarcomeres are anchored at the Z-disk, which defines the lateral borders of the sarcomere. Myosin has a long, fibrous tail and a globular head, which interacts with actin to produce muscle contraction. Figure

Outline of cellular activation system and the sarcomere



(1) Ca^{2+} release channel, CRC "calcium release channel", receptor or hyperphosphorilated channel by protein kinase (PKA) of intracellular sarcoplasmic reticulum;

(2) Ca^{2+} L-type, slow response upstroke or long-lasting ICa^{2+}-L of membrane surface sarcolemma;

(3) Ca^{2+} uptaker pump or $Ca^{2+} + Mg^{2+}$ +ATPase;

(4) Monovalent ion channels for H^+, Cl^- and K^+;

(5) **Myofilaments:** thin of actin & thick of myosin: both interact during muscular contraction and relaxation;

(6) Mitochondria: provides energy for contraction through ATP. Considered as a true cellular power station;

(7) **T tubular system:** electric signal transmission of the sarcolemma to the interior of the cell, penetrating inside of it through the Z lines;

(8) **Sarcoplasmic reticulum (SR):** cistern that uptakes and releases Ca^{2+} during contractile cycle;

(9) **Sarcolemma membrane:** role in controlling ion gradients; it has channels for ions (action potential); it enables cellular integrity, it has receptors for drugs and hormones;

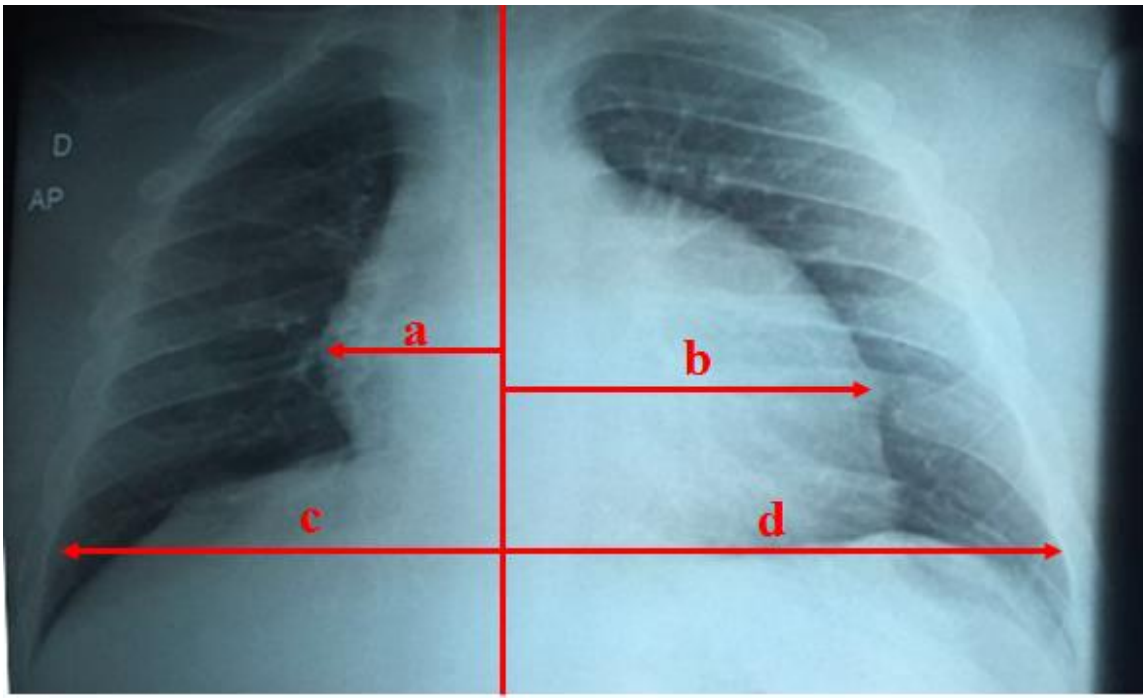
(10) **Sarcomere:** it is the anatomic-functional unit of the muscle or the basic contractile unit of skeletal/cardiac muscle. The distance between two Z lines.

Possible clinical causes for prominent anterior QRS forces (PAF) on ECG/VCG

In the presence of PAF in the anterior wall (tall R waves) in the right and/or middle precordial leads V_1 through V_3 or V_4, the following differential diagnosis should be excluded clinico-electro-vectorcardiographically (**Zema 1990**).

- **Normal subjects:** PAF are observed in only 1% of normal subjects (**Mattu 2001**). There are two main types:
  - Normal variant with marked counterclockwise rotation of the heart around the longitudinal axis of the heart resulting in a shifting of the transition area (R=S) early, i.e. to the right of the precordial lead V_2 (**Yanagisawa 1981; Mori 1992; Paparella 1987**).
  - Athlete's heart (**Ferst 1984**).
- **Misplaced precordial leads as cause of PAF** (**MacKenzie 2004; Mattu 2001**).
- **Ancient strictly posterior, dorsal, high posterobasal MI** (**McManus 2014**). Actual lateral MI (**Bayés de Luna 2006**);
- **Right ventricular hypertrophy (RVH):** vectorcardiographic types A (**Brohet 1990; Suzuki 1978; Hugenholtz 1964**) and B (**Ellison 1972**);
- Diastolic LVH, volumetric or eccentric LVH, secondary to septal hypertrophy (magnitude of increase of 1_{AM} vector) and CCW heart rotation around the longitudinal axis (**Cabrera 1960; Donoso 1955**);
- **Combined ventricular hypertrophy** (**Elliott 1963**);
- **Complete Right Bundle Branch Block**, Kennedy type III, vectorcardiographic type C, Kennedy type I, or Grishman type and Kennedy type II, or Cabrera type (**Baydar 1965; Chen 1980**);
- **Pre-excitation variant of Wolff-Parkinson-White syndrome, with accessory anomalous pathways (Kent fibers), located in a posterior location (Type A):** right posterior, right and left posterior paraseptal and left posterior paraseptal and left posterior pre-excitation (**Chung 1965**);
- **HCM: both obstructive and non-obstructive forms** (**Pérez-Riera 2013**);
- **Progressive muscular dystrophy of childhood, Duchenne's cardiomyopathy, DMD, X-linked muscular dystrophy, pseudo-hypertrophic muscular dystrophy, childhood muscular dystrophy** (**Secchi 1982; Yotsukura 1999**);
- **Endomyocardial fibrosis** (**Tobias 1992**);
- **Cardiac dextroposition:** Example: left pneumonectomy (**Pérez Riera 2011**).
- **Left Septal Fascicular Block:** There are several papers in literature that prove in a conclusive and incontestable way, that the left branch of the His bundle, in most instances (≈85% of the cases) splits into three fascicles of variable morphological pattern, and not into two: left anterior fascicle (LAF), left posterior fascicle (LPF), and left septal fascicle (LSF). The above mentioned manuscripts have anatomical, histological, anatomo-pathological, electrocardiographic, and vectocardiographic, body surface potential mapping or ECG potential mapping and electrophysiological foundation.
- A combination of the above.

AP view of a chest X-ray Posterior-Anterior (PA) projection



Augmented Heart Size: global cardiomegaly
Cardiac Transverse Diameter (CTD) = a + b < 15.5 cm (males) and < 15.0cm (females). Cardio-Thoracic Ratio (CTR) = (a + b) / (c + d) (normal value ≤ 0.5). In this case, it is > 0.5: cardiomegaly. The cardiothoracic ratio (CTR) is increased globally. The **CTR** aids in the detection of enlargement of the cardiac silhouette, which is most commonly from cardiomegaly but can be due to other processes such as pericardial effusion. The CTR is measured on a PA chest X-ray, and is the ratio of maximal horizontal cardiac diameter to maximal horizontal thoracic diameter (inner edge of ribs/edge of pleura). A normal measurement should be <0.5.

Transthoracic Echocardiography April 4, 2016
End-diastolic LV diameter 52cm.; End systolic LV diameter 43cm; LV septal diastolic thickness = 8mm; LV diastolic posterior wall thickness = 6mm; Aortic Roth 28mm; Left atrium diameter= 37mm; LV ejection fraction= 36%; LV mass 145g; Shortening Percent cavities 17%; Volume end-diastolic 130ml; LV Systolic Volume= 83ml; Ratio mass/ volume 0.97ml / g and mild mitral regurgitation

Conclusions: Moderate LV dilation and discrete of the left atrium; discrete mitral reflux; diffuse and moderate hypocontractility of the LV; moderate systolic and diastolic dysfunction of the LV; LVEF 36% (Teichotz) LVEF 38% (Simpson); right ventricular systolic dysfunction (S = 7 cm/s) and tricuspid annular plane systolic excursion (TAPSE) = 12mm.

Muscle biopsy examination of quadriceps femoral

Used techniques: ATP 9.4, estearase, Gomori, HE, Periodic acid–Schiff (PAS), Succinic dehydrogenase (SDH), Sudan

Microscopy	
Representativity	Satisfactory
Presence of technical artifacts	Discrete
General structure	Amended
Variations of the fibers diameter	Moderate
Atrophy of the fibers	Moderate
Atrophy pattern	Angled and rounded
Distribution of atrophic fibers	Diffuse
Selective atrophy of the fibers	Absent
Fiber hypertrophies	Discrete
"Splitting" of the fibers	Discrete
Predominance of the fibers	Absent
Fiber grouping	Absent
Inflammatory reaction	Discrete
Distribution of the inflammatory reaction	Focal
Fiber necrosis	Focal
Phagocytosis of the necrotic fibers	Focal
Fiber regenerations	Focal
Conjunctive proliferation	Discrete
Distribution of the conjunctive proliferation	Endomysial and perimysial
Nuclear centralization	Mild up to 30%
Nuclear abnormalities	Absent
Structural changes in the fibers	Fibers "moth eaten"
Intramysial deposits	Glycides
Vascular changes	Absent
Nerve changes	Absent
Muscular spindles	Not disclosed

Conclusion: Muscular changes with myopathic pattern, commonly seen in cases of Duchenne/Becker.

Immunohistochemical examination

Antigen	Result	Intensity	Distribution
Dystrophin	Negative		
Spectrin	Positive	Strong	Diffuse

Conclusion: The immunohistochemical findings are consistent with Duchenne progressive myopathy linked to chromosome X.

Progressive Duchenne Muscular Dystrophy (DMD)

Background

Muscular dystrophy (MD) is a collective group of inherited non-inflammatory 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.

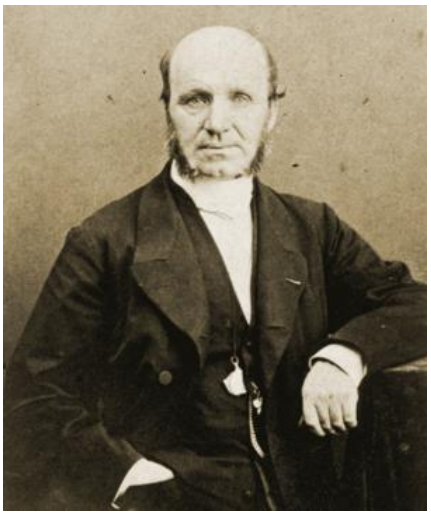
The first historical account of MD was reported by Conte and Gioja et al in 1836 (**Conte 1836**). They described two brothers with progressive weakness starting at age 10 years. These boys later developed generalized weakness and hypertrophy of multiple muscle groups, which are now known to be characteristic of the milder Becker Muscular Dystrophy (BMD). At the time, however, many thought that Conte and Gioja described tuberculosis; thus, they did not achieve recognition for their discovery.

Meryon et al (**Meryon 1852**) 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 comprehensive monograph on MD and even went on to suggest a sarcolemma defect to be at the root of the disorder. He further suspected that the disorder is genetically transmitted through females and affects only males.

Duchenne gave a comprehensive account of 13 patients with the disease, which he called "paralysie musculaire pseudo-hypertrophique" (**Duchenne 1868**). Because he was already held in 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 MD, Duchenne MD, now bears his name DMD. DMD is an X-linked recessive disorder, caused by the absence of dystrophin, which affects 1 of 3.500 male births (**Finsterer 2003**). Guillaume-Benjamin-Amand Duchenne (de Boulogne-sur-Mer Pas-de-Calais, France) was a French neurologist (born Sept. 17, 1806, Boulogne sur-Mer, Fr.—died Sept. 15, 1875, Paris), 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 Brief historical trajectory: Guillaume-Benjamin-Amand Duchenne was born in Boulogne-sur-Mer (Pas-de-Calais, France). He studied medicine in Paris and became a physician in 1831. He practiced general medicine in his native town for about 11 years and then returned to Paris to initiate pioneering studies on electrical stimulation of muscles. Duchenne used electricity not only as a therapeutic agent, as it was commonly the case earlier in the 19th century, but chiefly as a physiological investigation tool to study the anatomy of the living body. Without formal appointment he visited hospital wards across Paris searching for rare cases of neuromuscular disorders. He built a portable electrical device that he used to functionally map all bodily muscles and to study their coordinating action in health and disease. He gave accurate descriptions of many neuromuscular disorders, including pseudohypertrophic muscular dystrophy to which his name is still attached DMD. He also invented a needle system (Duchenne's histological harpoon) for percutaneous sampling of muscular tissue without anesthesia, a forerunner of today's biopsy. Duchenne summarized his work in two major treatises entitled De l'électrisation localisée (1855) and Physiologie des mouvements (1867). Duchenne's iconographic work stands at the crossroads of three major discoveries of the 19th century: electricity, physiology and photography.

In an absorbing monograph entitled Mécanisme de la physionomie humaine, Duchenne de Boulogne proposed that each emotion has its own specific facial muscle. Employing the most recent and exciting technical inventions of the mid nineteenth century, Duchenne used faradism to stimulate the facial muscles and photography to record their actions. Using electrical stimulation, he virtually dissected by this novel method the sheets of facial musculature into a number of emotional entities. By masking the stimulated area, he proved that no reflex activity occurs elsewhere in the face--an illusion hitherto accepted almost universally. Classical sculpture which purported to show a specific emotion was resculpted by Duchenne de Boulogne to show the proper use of the specific facial muscles for that emotion. The concept of emotional expression as a basis for muscle classification in the face is shown to be stimulatingly original, although not entirely valid as a scientific basis for physiological research. But the great individualist
This is best exemplified by his investigation of the mechanisms of human physiognomy in which he used localized faradic stimulation to reproduce various forms of human facial expression. The album that complements his book on this issue is considered a true incunabulum of photography. Duchenne de Boulogne, a shy but hard-working, acute and ingenious observer, became one of most original clinicians of the 19th century. He died in Paris in 1875 (**Parent 2005**).



Guillaume-Benjamin-Amand Duchenne
September 17, 1806 in Boulogne-sur-Mer – September 15, 1875 in Paris

The heart in human dystrophinopathies

Dystrophin is a protein located on the inner side of skeletal and cardiac muscle cells. This protein links cytoskeleton to the extra cellular matrix. The lack of dystrophin leads to progressive fiber degeneration. The consequence is a progressive muscle wasting and weakness of variable distribution. Clinical manifestations of DMD are visible before the age of 6 years and are characterized by progressive loss of strength. By the age of 12, most patients are confined to wheelchair. Cardiac involvement is present in about 90% of the patients and 20% of patients die from cardiac complications.
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 MD, 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) (**Yanagisawa 2008**).

Minor variations notwithstanding, all types of MD 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 and imbalance, all of which can further compromise function and longevity. 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 MDs tend to develop worsening contractures and rapidly progressive scoliosis. On average, for each 10° of thoracic scoliosis curvature, the forced vital capacity (FVC) decreases by 4% (**Hoffman1987**). In a patient with an already-weakened cardiopulmonary system, this decrease in FVC could rapidly become fatal.

The goal of orthopedic management is, therefore, to preserve or prolong patients' ambulatory status for as long as possible. This goal can be achieved with soft-tissue releases for contractures. If the patient develops significant scoliosis, which generally occurs after they stop walking, early stabilization of the spine should be considered.

Etiology

Classification of types of muscular dystrophy

The etiology of MD is an abnormality in the genetic code for specific muscle proteins (**Bushby 2000**). 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:

I. Sex-linked MDs – Duchenne (DMD), Becker (BMD), Emery Dreifuss Duchenne (DMD) and Becker (BMD) muscular dystrophies are X-linked recessive disorders associated with both skeletal myopathy and progressive cardiomyopathy in males. Although BMD patients present milder skeletal muscle involvement, they have been shown to present more advanced cardiomyopathy than DMD. Female DMD/BMD carriers are usually free of skeletal muscle symptoms but they may also develop cardiomyopathy. Cardiac involvement is a frequent finding in female carriers of DMD, but rarely observed in carriers of BMD. Both, DMDc and BMDc with cardiac involvement demonstrate the same myocardial fibrosis pattern as their male counterparts with overt disease. Interestingly, in contrast to what is seen in male patients with DMD and BMD, female carriers of

DMD present with a more advanced cardiomyopathy than carriers of BMD (**Florian 2016**).

II. Autosomal dominant MDs - Facioscapulohumeral, distal, ocular, oculopharyngeal
III. Autosomal recessive MD – Limb-girdle form.

Genetic defects and dystrophin

In the X-linked forms of MD, such as the DMD and BMD, 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 BMD.

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**).

Genes associated with muscular dystrophies

Disease	Inheritance	Gene	Protein	References
DMD, BMD	XR	DMD	Dystrophin	**Monaco 1986; Burghes 1987**
Emery-Dreifuss muscular dystrophy	XR AD/AR	EMD FHL1 LMNA	Emerin Four and a half LIM domain 1	**Bione 1994** **Guenau 2009** **Bonne 1999**
LGMD1A	AD	MYOT	Myotilin	**Hauser 2000**
LGMD1B	AD	LMNA	Lamin A/C	**Muchir 2000**
LGMD1C	AD	CAVE3	Caveolin 3	**Minetti 1998**
LGMD1D	AD	DES	Desmin	**Greenberg 2012**
LGMD1E	AD	CNAJB6	Dnaj(Hsp40) homolog, subfamily B, member 6	**Sarparanta 2012**
LGMD2B,	AR	DYSF	Dysferlin	**Bashir 1998**

Mioshi myopathy, distal anterior compartment myopathy		CAPN3		**Liu 1998**
LGMD2C	AR	SGCG	Gamma Sarcogycan	**Noguchi 1995**
LGMD2D	AR	SGCA	Alfa Sarcogycan	**Roberds 1994**
LGMD2E	AR	SGCB	β-Sarcoglican	**Bonnemann 1995; Lim 1995**
LGMD2F	AR	SGCD	δ-SGCD	**Nigro 1996**
LGMD2G	AR	TCAP	Tintin cap	**Moreira 2000**
LGMD2H	AR	TRIM 32	Tripartito motil containin 32	**Frosk 2002**
LGMD2J	AR	TIN	Titin	**Udd 1993**
Tibial MD	AD			**Udd 1993**
LGMD2L	AR	ANO	Anoctamin 5	**Bolduc 2010**
LGMD2Q	AR	PLEC	Plectin	**Gundesli 2010**
MDDGA1,MDDGC1(LGMD2K)	AR	POMT1	Protein-o-mannosyltrasferase1	**Beltrán-Valero de Bernabé 2002**
MDDGA2,MDDGC2(LGMD2N)	AR	POMT2	Protein-o-mannosyltrasferase2	**van Reeuwijk 2005**
MDDGA3,MDDGC3 (LGMD2O)	AR	POMGNT1	Protein o-linked manosse beta 1, 2 N acetylgucosaminyltransferase	
MDDGA4,MDDGC4(LGMD2M)	AR	FKTN	Fukutin	**Kobayashi 1998**
MDDGA5, MDDGC5(LGMD2I)	AR	FKRP	Fukutin related protein	**Brockington 2001**
MDDGA6	AR	LARGE	Likeglycosyltranferase	**Longman 2003**
MDDGA7	AR	ISPD	Isopenoid synthase domain containing	**Roscioli 2012 Willer 2012**
MDDGA-B	AR	GTDC2	Glycosiyltransferase-like domain containing 2	**Manzini 2012**
MDDGA	AR	B3GNT1	UDP-GlcNAc beta Gol beta 1,3 N acetylglucosaminytransferase 1	**Buysse 2013**
MDDGC9(LGMD)	AR	DAG1	Dystroglycan	**Hara 2011**
DM1	AD	DMPK	CTG in 3'UTR	**Mahadevan**

				1992
DM2	AD	CNBP	CTC in intron 1	Liquiori 2001
FSHD1	AD	DUX4	Double homebox 4,	
FSHD2	AD		Double homebox4, structural maintenance of chromosomes flexile hinge domain containing 1	Lemmers 2012

AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive; LGMD, limbgirdle muscular dystrophy(LGMD1), autosomal dominant; LGMD2, autosomal recessive; MDDG, muscular dystrophydystroglycanopathy; DM, myotonic dystrophy; FSHD, fascioscapulohumeral muscular dystrophy, exp, expansion. *Alternative or previous nomenclature is provided in parentheses.

Epidemiology

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 (**Dubowitz 1995; Emery 1993**). One third of cases occurs as a result of spontaneous new mutations (**Emery 1991**). BMD 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 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 than in other groups (**Pratt 1986**). Distal MD tends to occur in Sweden.

Prognosis

Despite modern advances in gene therapy and molecular biology, DMD 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.

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 DMD 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 (**Dubowitz 1995; Prosser 1969; Leibowitz 1981; Pane 2012**). In addition to mental deficits, another milestone delay is the

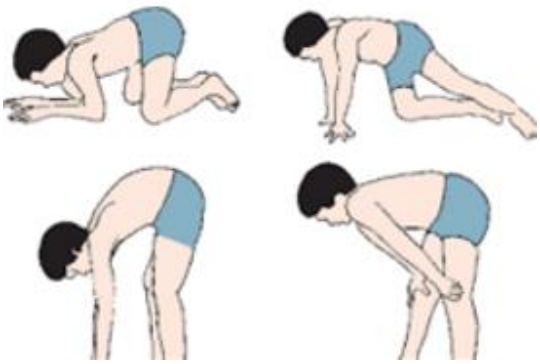
patient's age at ambulation. Children with DMD usually do not begin to walk until about age 18 months or later. In the Dubowitz study (**Dubowitz 1995**), 74% of children with DMD manifested the disease by age 4 years. By age 5 years, awareness increases as the disease is manifested in all affected children when they experience difficulty with school-related activities (eg, getting to the bus, climbing stairs, reciprocal motions during activities).

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. 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 (Figure).

Gower sign



Although the Gower sign is a classic physical examination finding in DMD, it is by no means pathognomonic; other types of MD and disorders with proximal weakness may also cause this sign.

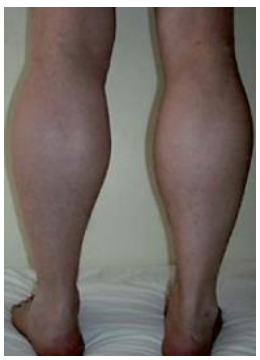
While still ambulatory, the child may have minimal deformities, including iliopsoas or tendo Achillis tightness. Mild scoliosis may be present if the child has an asymmetrical stance. Upper-extremity involvement rarely occurs in the beginning, although proximal arm muscle weakness may be evident on manual 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 BMD, the milder form of MD.

In Emery's work (**Emery 1993**), 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; Dubowitz 1995; Shapiro 1993; Sussman 1984; Weimann 1983**). However, some reports showed that respiratory function after spinal fusion did not significantly differ (**Almenrader 2006; Kinali 2006; Birnkrant 2006; Miller 1988-1991**). The investigators concluded that respiratory failure resulted from muscle weakness and not the mechanical bellows of the chest cage, as was previously assumed.

DMD is a terminal disease in which death usually occurs by the third decade of life (mostly from cardiopulmonary compromise) (**Dubowitz 1995**). 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), macroglossia (30%), and pseudohypertrophy of the calf (60%). Figure below.



Pseudohypertrophy of the calves

Cardiopulmonary involvement is present from the beginning of the disease stages, but the findings are not so clinically obvious. ECG tracings show sinus tachycardia, short PR interval, right ventricular strain, tall R waves in anterior wall, deep narrow Q waves, and inverted T waves (**Thrush 2009**).

BMD is similar to DMD, but because patients have some measure of functioning dystrophin, the manifestations of BMD occur later and are more mild. Patients tend to live past the fourth or fifth decades.

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 atrioventricular (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 midlife.

None of the autosomal dominant conditions significantly affect longevity.

Complications

Complications of MD usually include 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 no ambulatory status

Laboratory Studies

A creatine phosphokinase (CPK) determination is the most specific test for MDs. 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 3 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 DMD, with less elevation noted in BMD.

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.

Electrocardiography /Arrhythmias

ECG pattern associated with Duchenne's dystrophy results from multifocal degenerative changes involving myocardium, predominantly the basal inferior region (old dorsal), lateral wall of the left ventricle and the posteromedial papillary muscle of mitral valve.

varying degrees of myofibrillar loss, alterations in mitochondria and sarcoplasmic reticulum, depletion of glycogen particles, a paucity of lipid or lipofuscin granules, the absence of viruslike particles and the preservation of nuclear morphology and the transverse tubular system. In recent years, ultrastructural evidence of myofibrillar loss has been found in association with diverse forms of myocardial damage. The selective myofibrillar loss in DMD, involved both thick and thin filaments. In areas of minimal involvement, the absolute number of myofilaments is decreased, producing a diffuse pattern. In more severely affected areas, there was complete disappearance of both thick and thin filaments, lending a "moth-eaten" appearance to the myofiber.

- The most frequent ECG findings in cases of DMD is sinus tachycardia present in ≈ 60% of cases. It may be attributed to cardiac autonomic nervous impairment (**Lanza 2001; Yanagisawa 2008; Kirchmann 2005**).
- Deprivation of circadian rhythm (present in ≈ 30% of cases).
- Reduced heart rate variability (observed in ≈ 50% of cases).
- Short PR/PQ interval observed in ≈ 43% of patients. The most common findings are short PR interval and RVH (37%) (**Thrush2009**). Truly Wolff–Parkinson–White syndrome has been reported exceptionally in both DMD (**Fayssoil 2013**) and BMD (**Romfh 2010**).
- Tall R waves is present in 45% of patients with RS ≥1 in lead V1 as well as deep S waves in leads V5 and V6. A distinctive ECG pattern, consisting of tall R waves over V1 with R/S ratio exceeding 1 and deep but narrow Q waves over left leads I, aVL, V5, and V6, has been consistently reported in 80-90% of patients with DMC patients. Although these ECG abnormalities may closely simulate a myocardial infarction pattern, there are certain differences. In patients with DMC the Q waves are deep and narrow, unlike the broad Q waves (≥40ms) of patients with MI. In addition, the VCG studies do not reflect abnormal initial forces, but do point toward a diffuse myocardial involvement."," Histologic observations (**Frankel 1976**) further substantiate the hypothesis that generalized cardiomyopathy forms an integral part of DMC. These investigators have shown that in patients with this disorder, the histologic evidence of degenerative changes initially begin at the basal-inferior (old posterobasal segment) of the LV, subsequently spread to involve the lateral LV free wall and posteromedial papillary muscle mitral valve, finally, manifest as diffuse transmural fibrosis, and varying degrees of involvement of the interventricular septum, and free wall of the right ventricular wall, with only minimal changes in the right or left atrium. Furthermore, these ultrastructural changes show a broad spectrum that extends from areas with only a

minimal loss of actin and myosin filaments to others that show extensive changes characterized by total myofibrillar loss and replacement by collagen fibrils. Several investigators have suggested that such changes in cellular structure of the myocardium can produce a loss of epimyocardial forces and result in an anterior shift of the QRS forces that may manifest as tall R waves over right precordial leads (**Perloff 1967**). Since the dystrophic changes in skeletal and cardiac muscle in patients with DMD are progressive, it is possible that during early stages of the disease the dystrophic changes of the myocardium are minimal and produce little alteration in the epimyocardial forces. This would explain the normal ECGs sometimes observed. Progression of the disease, on the other hand, may be associated with increasing myofibrillar loss, which could produce significant alterations in epimyocardial forces. A predilection of these dystrophic changes for the LV, especially the basalinferior area (**Ronan JA 1972**) would explain a progressive anterior shift of QRS forces, producing taller R waves with an abnormal R/S ratio over the right precordial leads, the most common ECG abnormalities in patients with DMD. Replacement of normal cardiac tissue by fibrosis, with lateral extension of scarring, may explain the presence of Q waves in these patients, as suggested by Perloff (**Perloff 1967**). In addition, dystrophic changes may involve the conduction system as well (**Sanyal 1977**), and thus provide a basis for the left axis deviation and short P-R interval in some patients. Finally, papillary muscle involvement may produce papillary muscle dysfunction, mitral regurgitation and left atrial enlargement. Thus, ultrastructural observations support the contention that the classical ECG profile in patients with DMD results from multifocal degenerative changes of the cardiac muscle, predominantly in the LV. Furthermore, these degenerative changes of the heart, at both the cellular and subcellular levels, are identical to those seen in skeletal muscle.

- Abnormal deep and narrow Q-waves in lateral leads I, aVL, V5–V6, or in II, II and aVF. The Q waves are deep but narrow, (amplitude ≥2 mm, duration <40ms). Atrophy and scaring of the lateral-basal region (ancient dorsal) and the adjacent lateral wall of the left ventricle are reported and may explain the ECG pattern with abnormal Q-waves and prominent R wave on right precordial leads.
- Complete RBBB (**Sanyal 1978; Frankel 1976**).
- Right axis deviation.
- RVH (37%) (**Thrush2009**).
- Inverted T waves.
- Prolonged QT interval.
- Increased QT dispersion (**Finsterer 2003**).
- Electrical changes were therefore found in both patients and carriers with equal significance: in the first group the main appearances were of pseudo-infarction pattern principally involving the lateral wall (old posterior wall). Atrial premature contractions.
- Supra-ventricular arrhythmias.
- Ventricular premature contractions (PVCs). It has been reported at least 2 asymptomatic PVCs in 33% of young DMD patients (age from 12 to 24 years) (**Lanza 2001**).
- Conduction abnormalities: abnormal intraatrial or interatrial conduction, Mobitz type I AV block, non-conducted atrial premature beats, short PR interval, right ventricular conduction delay and left posterior fascicular block (**Perloff 1984; Nigro 1990**). 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

left ventricular 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 were not clinically deleterious. Arrhythmias are attributed to progressive fibrosis of the cardiac conduction system and impairment in the cardiac autonomous nervous system. Patients with LVEF <35% have more arrhythmias including non-sustained atrial tachycardia, frequent PVCs, ventricular couplets/triplets, and NS-VT compared to the other groups. LVEF <35% is the only predictor of clinically significant Holter finding (**Vila 2015**). Analysis of Holters from patients with DMD demonstrated that arrhythmias increased with decreasing LVEF regardless of age, but that age is also a significant predictor of arrhythmia development. Among patients with DMD or BMD, arrhythmias increase with development of cardiac dysfunction (**Chiang 2016**). The factors associated with mortality are increased age, advanced grade of myocardial delayed enhancement (MDE), higher LV end-systolic volume, lower LVEF, use of β-blockers, and VT. Myocardial fibrosis detected by CMR is an independent predictor of adverse cardiac remodeling, ventricular arrhythmias, and death in DMD. Cardiac MRI using MDE can be applied as a screening tool to detect patients at risk for ventricular arrhythmias, more advanced disease, adverse LV remodeling, and death (**Menon 2014**).

- Because of the defect in dystrophin protein on membranes of Purkinje fibers, fatty and fibrous tissue replacement of the involved segment may rarely result in complete AV block (**Bies1992**). Electrophysiologic studies revealed conduction disturbances at His and infra His level in patients with various types of muscular dystrophy and in follow up permanent pacemaker's implantation is indicated because of AV block (**Himmrich 2000**). Because of symptomatic AV complete block development in the background of trifascicular block, a dual chamber permanent pacemaker implantation is the choice approach. ACC/AHA Association guidelines for cardiac pacing and anti-arrhythmic devices suggest permanent pacemaker implantation as class I indication in patients with muscular dystrophies (**Gregoratos 1998**). DMD, BMD, and limb-girdle types 2C-2F and 2I are muscular dystrophies in which the development of a dilated cardiomyopathy DCM development of the DCM. Patients are considered for pacemakers or implantable cardioverter-defibrillators (IDCs) on the basis of guidelines used for non-ischemic cardiomyopathies.

Arhythmia management in DMD/BMD

Cardiac arrhythmias are highly prevalent in DMD and BMD. The earliest changes that are seen frequently involve sinus tachycardia and PVCs. As high as 33% of DMD patients age 12 to 24 years had at least two asymptomatic PVCs with 58% having had at least one PVC (**Chenard 1993**) and 17% experienced sinus tachycardia (age range of 5 to 22.5 years) (**Kirchmann 2005**). Arrhythmias, once identified, can be treated with medical therapy or device implantation. Because the frequency with which arrhythmias occur in DMD and BMD patients is unknown, preventative ICD placement is a difficult decision. In patients with more advanced stages of disease, this can be complicated by kyphoscoliosis and muscle wasting. If surgery is not an option, external portable home defibrillators are an alternative to be discussed with patients and caregivers.

Monitoring HF in DMD is difficult because the typical symptoms of reduced exercise tolerance are difficult to discern in the non-ambulatory patient. In wheelchair bound DMD patients, symptoms referable to HF may include increased fatigue, difficulty sleeping,

difficulty with concentration and subtler variants of poor performance. Noninvasive measures of HF have not been shown to be reliable indicators of HF. Plasma ANP and BNP levels are not sensitive markers for the early detection of cardiac systolic dysfunction in DMD patients. Although, an increase in ANP and BNP along with a decrease in deceleration time of early diastolic filling and systolic dysfunction are associated with poor prognosis (**Mori 2004**). It is important to monitor DMD and BMD patients for cardiomyopathy because early diagnosis and treatment of DCM has been demonstrated to lead to LV remodeling in DMD and BMD patients when drug therapy was administered after the first abnormal echocardiogram (**Jefferies 2005**). In order to achieve early diagnosis and treatment, recommendations are for DMD patients to undergo echocardiography every 2 years up to the age of 10 and annually thereafter (**Bushby 2003**). Recommendations for BMD patients vary widely from annual echocardiograms starting in the second decade of life and routinely every 2 years thereafter in the absence of echocardiographic findings (**Kirchmann 2005**) to every five years. In addition, 24-hour Holter monitor should be considered annually in DMD patients over the age of 8 and especially if LV dysfunction is present (Table below). Therapies for DCM can be applied to individuals with dystrophin mutations including angiotensin converting enzyme (ACE) inhibitors and β-adrenergic blockade. Both of these agents have been associated with improved outcome in both ischemic and non-ischemic forms of DCM. One study of 69 patients with DMD or BMD were studied for the presence of DCM. Of these, approximately half had abnormal LV function and size at the time of entry into the study. Those with evidence of cardiomyopathy were initiated on ACE inhibitors and/or β-adrenergic blockade. The majority of these patients showed improvement or normalization of LV function and size consistent with cardiac remodeling that has been reported after myocardial infarction (**Jefferies 2005**). ACE inhibitors can also be used for prevention of LV dysfunction. Through cardiac remodeling, these agents may actually prevent LV dysfunction and halt or limit cardiomyopathy progression. One study of 80 DMD patients from 10 centers examined whether cardiomyopathy could be inhibited. Twenty patients were excluded from the study and BNP along with a decrease in deceleration time of early diastolic filling and systolic dysfunction are associated with poor prognosis. It is important to monitor DMD and BMD patients for cardiomyopathy because early diagnosis and treatment of DCM has been demonstrated to lead to LV remodeling in DMD and BMD patients when drug therapy was administered after the first abnormal echocardiogram. In order to achieve early diagnosis and treatment, recommendations are for DMD patients to undergo echocardiography every 2 years up to the age of 10 and annually thereafter. Recommendations for BMD patients vary widely from annual echocardiograms starting in the second decade of life and routinely every 2 years thereafter in the absence of echocardiographic findings to every five years. In addition, 24-hour Holter monitor should be considered annually in DMD patients over the age of 8 and especially if LV dysfunction is present (Table below). Therapies for DCM can be applied to individuals with dystrophin mutations including ACE inhibitors and β-adrenergic blockade. Both of these agents have been associated with improved outcome in both ischemic and nonischemic forms of DCM. In a study, 69 patients with DMD or BMD were studied for the presence of DCM. Of these, approximately half had abnormal LV function and size at the time of entry into the study. Those with evidence of DCM were initiated on ACE inhibitors and/or β-adrenergic blockade. The majority of these patients showed improvement or normalization of LV function and size consistent with cardiac remodeling that has been reported after MI. ACE

inhibitors can also be used for prevention of LV dysfunction. Through cardiac remodeling, these agents may actually prevent LV dysfunction and halt or limit DCM progression. One study of 80 DMD patients from 10 centers examined whether DCM could be inhibited (**Duboc 2005**). Twenty patients were excluded from the study that reduced LV function is a good predictor of cardiovascular events. The prudent course of action, consistent with routine management of isolated DCM, is to offer treatment. Given the relative rarity of DMD, it is not clear that large enough clinical trials can be carried out to provide definite evidence dictating management strategy. This uncertainty has led to considerable debate regarding the appropriate management of these patients (**Bourke 2006**).

Table - Cardiomyopathy/arrhythmia screening, medication and device recommendations in pediatric neuromuscular disease

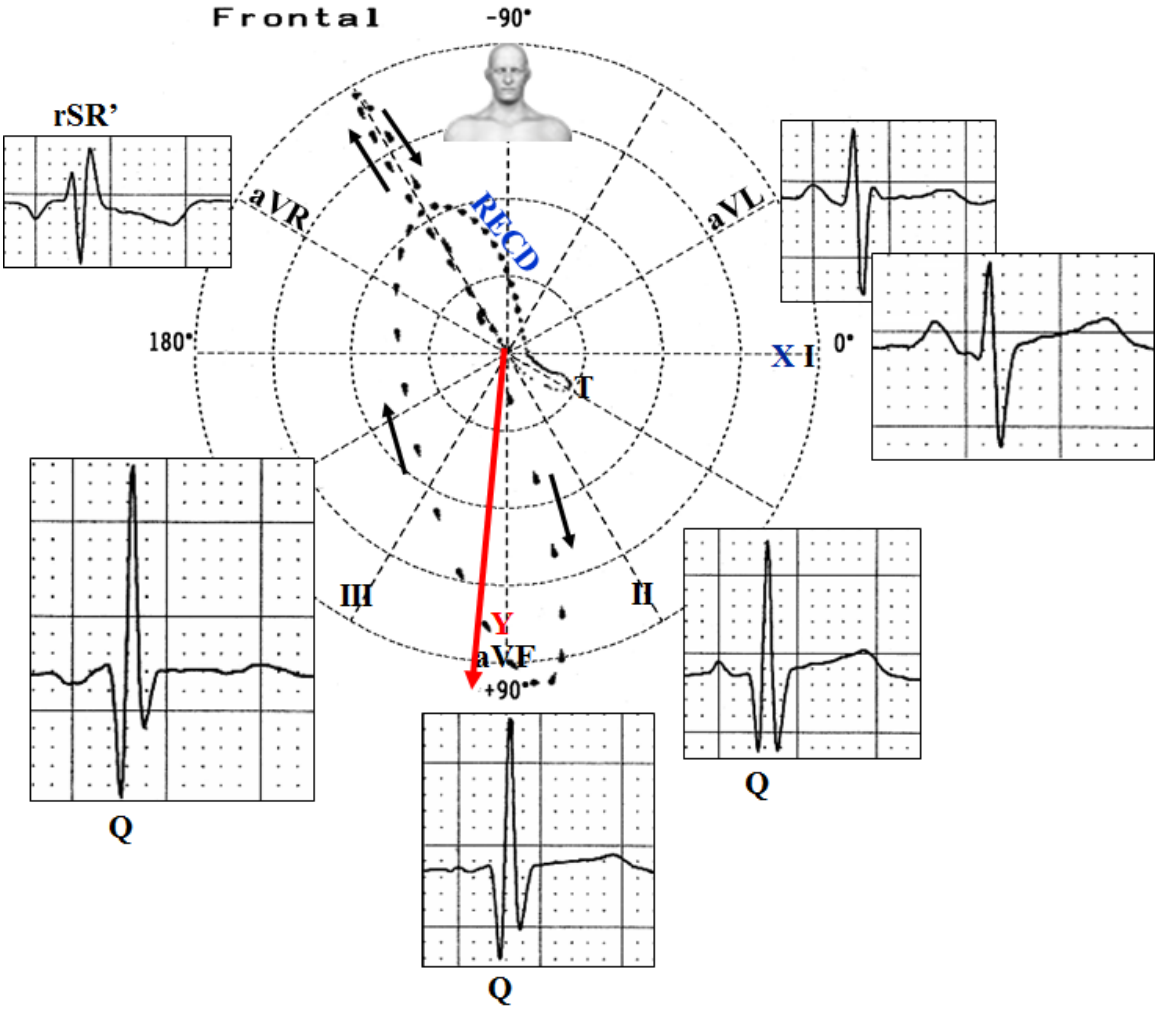
	Echocardiogram	Holter monitoring	Medication/device
	Initial screen and frequency with negative finding	Initial screen and frequency with negative finding	Age and /or circumstance for consideration
DMD	Initial: age 6 yr	Initial: age 6 yr	ACE inhibitor B-adrenergic blockade.
BMD	Frequency: 1-2 yrs Initial: age 10yr Frequency 1-2 yrs	Frequency: 1-2 yrs Initial: age 10yr Frequency 1-2 yrs	Age 8-10yr or with decrease in LVEF ACE inhibitor B- adrenergic blockade with decrease in LVEF
DMD carrier female	Initial: age 20-30 yr Frequency 5 yrs	Initial: age 20-30 yr Frequency 5 yrs	As needed with decrease in LVEF.
Lamin A/C	Initial: age 10yr Frequency 2-3 yrs	Initial: age 10yr Frequency 2-3 yrs	ICD primary prevention. Consider ACE inhibitors and β-adrenergic blockade*.
Myotonic dystrophy (Classical form)	Initial: age 10-20 yr Frequency 2-3 yrs	Initial: age 10-20 yr Frequency 2-3 yrs	Pacemaker as needed. Consider ACE inhibitors and β-adrenergic blockade*.

ACE: angiotensin converting enzyme; BMD: Becker muscular dystrophy; DMD: Duchenne muscular dystrophy; ICD: implantable cardiac defibrillator. * Medication recommendation are based on experience: studies have not been performed to support this recommendation.

Vectorcardiographic features

VCG displays a clear tendency to get worse with age. Vectorcardiographic features well agree with the post-mortem findings of a progressive but scattered myocardial fibrosis with elective localization in inferobasal (old dorsal) and lateral free wall of left ventricle. (**Zeppilli 1979**), VCG criteria of lateral myocardial infarction are fulfilled in 70% of cases (**Secchi 1982**) (Figure).

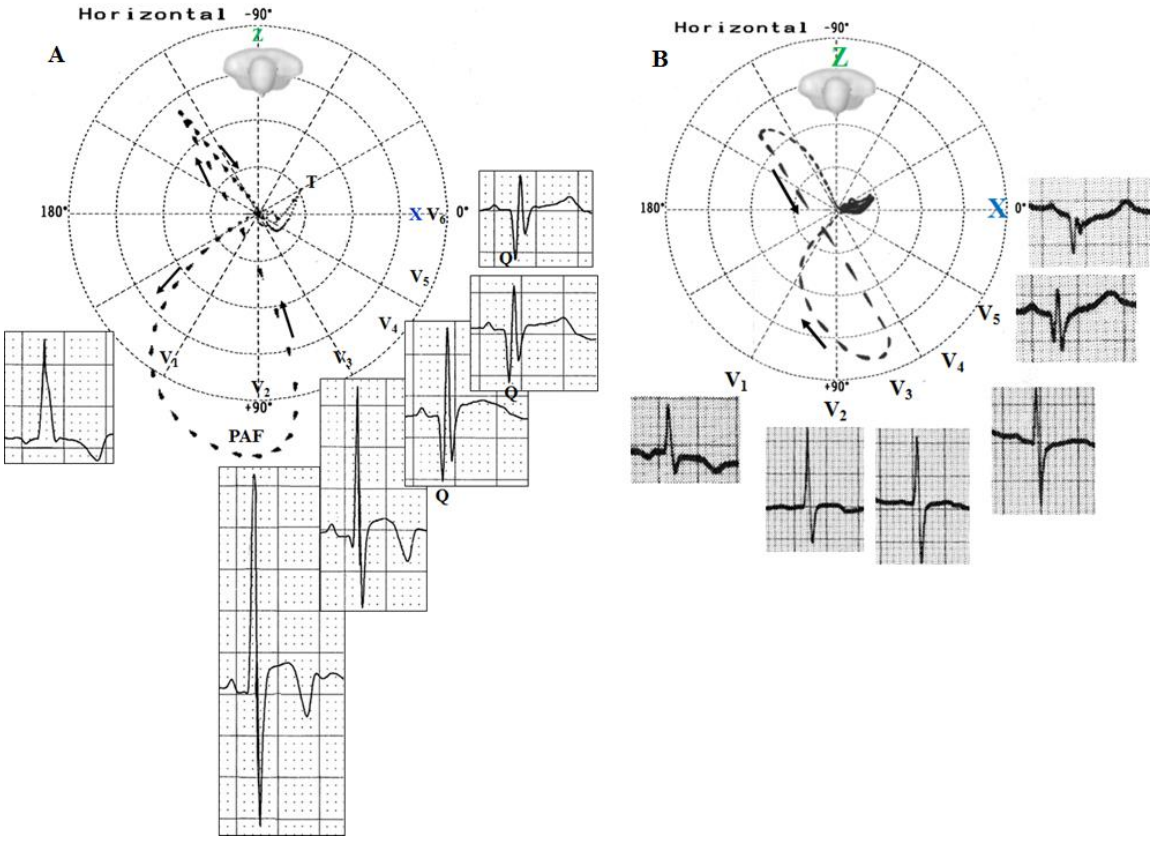
ECG/VCG correlation in the frontal plane in a patient with DMD



Deep narrow Q waves in inferior leads. QRS axis +95°. rSR' in aVR: RECD on right ventricular outflow tract (RVOT).

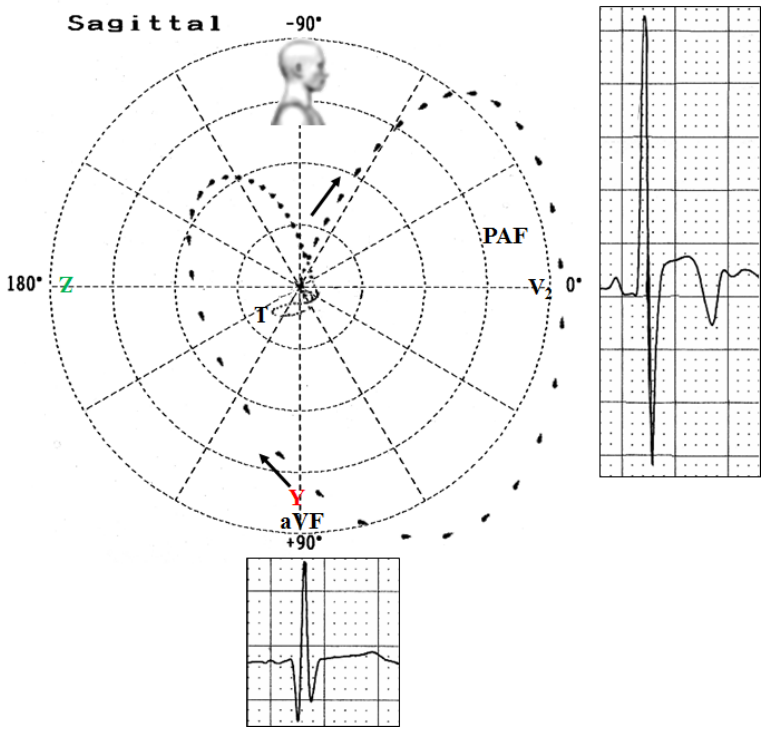
ECG/VCG correlation in the horizontal plane

In a patient with DMD **In a patient with truly lateral MI**



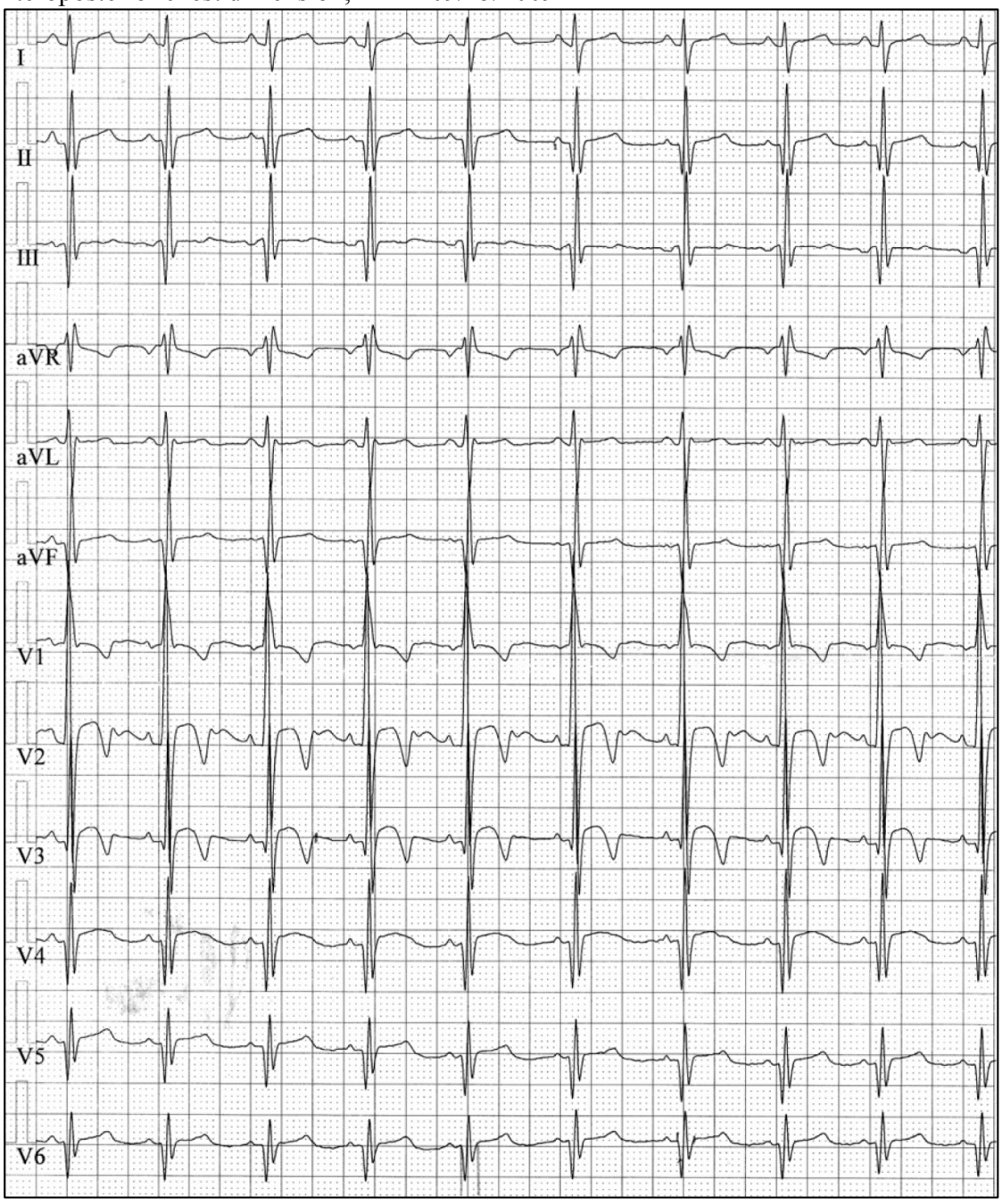
A) ECG/VCG correlation in the Horizontal Plane in a patient with DMD;
B) ECG/VCG correlation in the Horizontal Plane in a patient with truly lateral myocardial infarction. Note prominent R wave in V_1 or V_1-V_2 and deep Q wave in left leads.

ECG/VCG correlation in the right sagittal plane in a patient with DMD



ECG/VCG correlation in the Right Sagittal Plane in a patient with DMD. Note prominent QRS anterior forces (PAF) and deep Q wave in aVF.

Name: LAP; **Gender:** Male; **Age:** 10 y.o.; **Ethnic Group:** Caucasian; **Weight:** 20 Kg; **Height:** 1,20 m; **Biotype:** Severe thorax deformity (Scoliosis) and reduction in the anteroposterior chest dimension; **Date:** 09/25/2009



Clinical diagnosis: DMD.

ECG diagnosis: QRS axis +95°; deep narrow Q waves in inferior, lateral leads (I, aVL, V4-V6); rSR' in aVR: RECD on right ventricular outflow tract (RVOT); prominent R wave in V_1 or V_1-V_2.

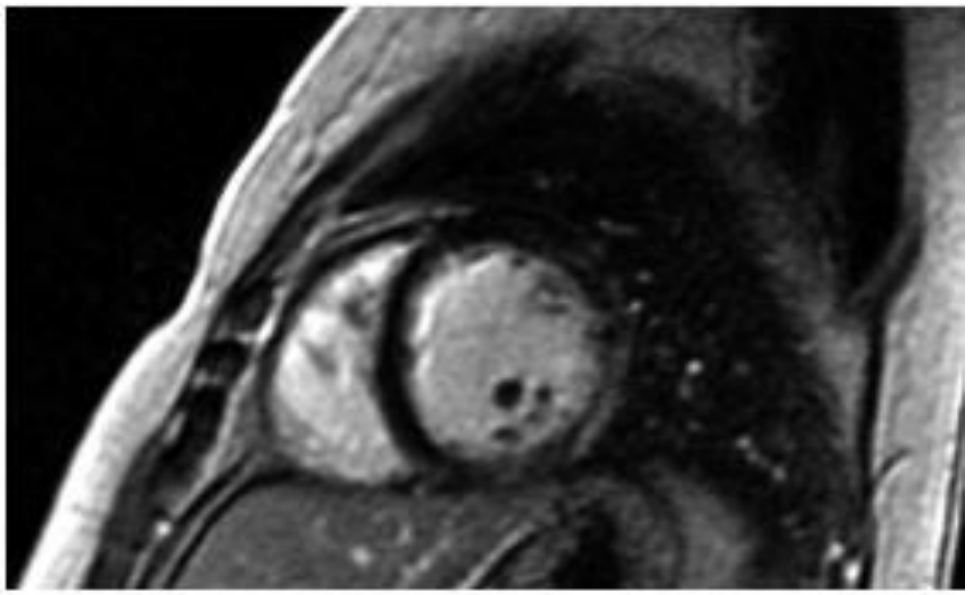
Imaging Studies

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

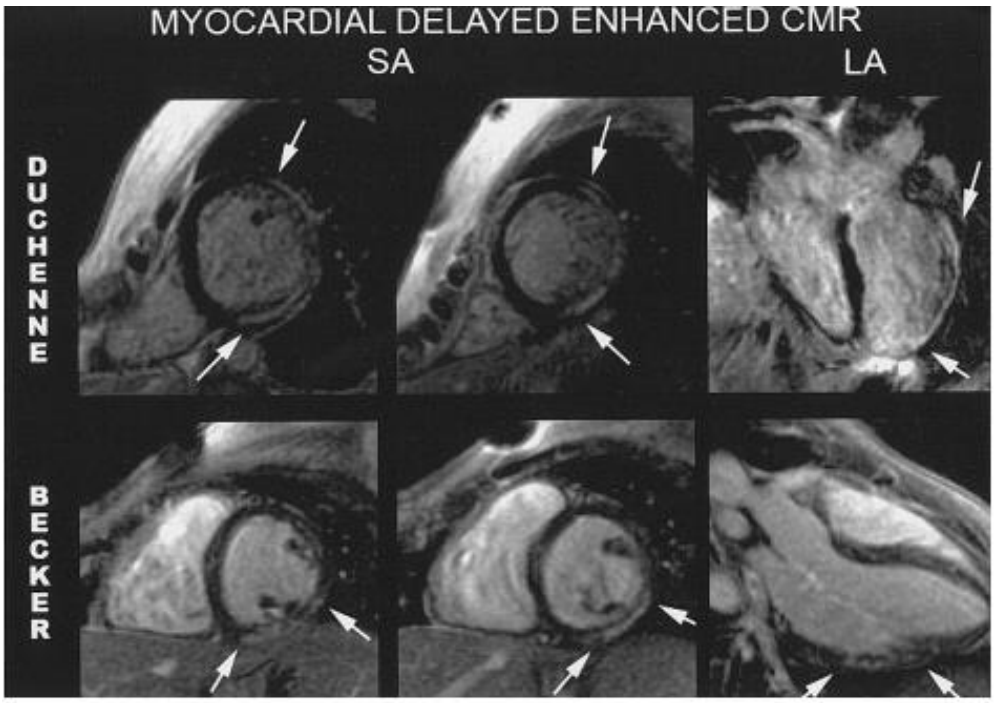
Cardiovascular Magnetic Resonance

Cardiovascular magnetic resonance (CMR) is a reliable a noninvasive, non-radiating method for assessing global and regional cardiac function, allowing also for the detection of myocardial fibrosis The method has been proved the most robust tool for detection of early myocardial fibrosis in DMD, BMD and female carriers, using late gadolinium enhancement (LGE). The pathology of cardiomyopathy in dystrophinopathies includes the presence of subepicardial fibrosis in the inferolateral wall and posteromedial papillary muscle (**Mavrogeni 2010**). The application of CMR in DMD/BMD and female carriers, in addition to the standard monitoring is of great value because:

- Early start of heart failure treatment may delay the progression of LV dysfunction (**Raman 2015**);
- Myocardial fibrosis, assessed by LGE, may be observed, even if the echocardiographic evaluation remains normal (**Silva 2007**) and can potentially be used as an early sensitive index to start cardioprotective treatment (**Bushby 1991**);
- It can be also applied as a screening tool to detect patients at high risk for ventricular arrhythmias, more advanced disease, adverse LV remodeling and death (**Menon 2014**). An impaired LV systolic function (LVEF ≤ 45%) and a "transmural" pattern of myocardial fibrosis independently predicts the occurrence of adverse cardiac events in DMD/BMD patients. Even in DMD/BMD patients with relatively preserved LVEF (> 45%), the simple and visually assessable parameter "transmural LGE" is of additive prognostic value;
- In mutation carriers, CMR revealed a pattern of fibrosis similar to that observed in DMD (**Fayssoil 2013**), but without any correlation with genotype-phenotype (**Giglio 2014**); even in the absence of overt muscular disease; and (**Bradley 1978**) new CMR techniques, such as postcontrast myocardial T1 mapping, have been used in DMD to detect diffuse myocardial fibrosis. It was documented that postcontrast T1 obtained from the Look-Locker sequences (T1LL) ratio is abnormally shortened in DMD compared with controls, even in DMD patients with otherwise normal CMR study. It is assumed that the application of more aggressive therapy for DMD with shorter T1LL may improve morbidity and mortality in DMD cardiomyopathy (**Turkbey 2012**).



Fibrosis of the left ventricle in a mother Duchenne muscular dystrophy carrier, presented as late gadolinium enhancement in the lateral wall of left ventricular.

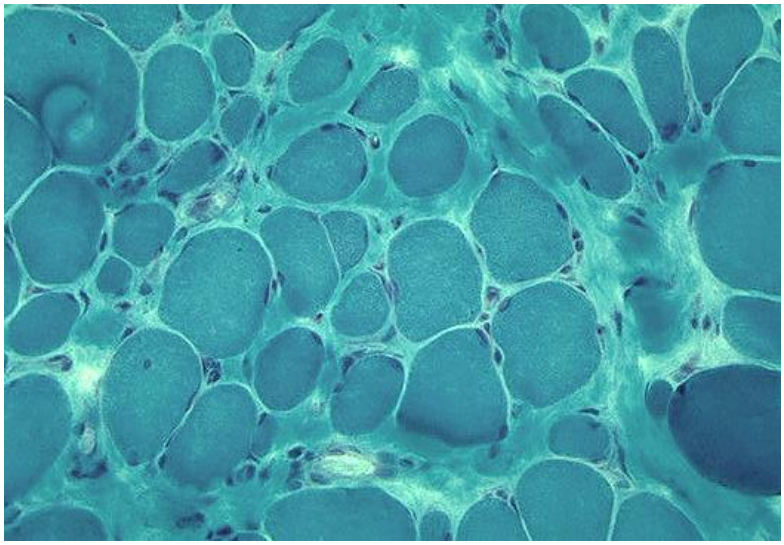


Myocardial Fibrosis in DMD and BMD by CMR Adjacent short-axis (SA) and long-axis (LA) views of 2 patients. top: Duchenne, bottom: Becker by CMR using myocardial delayed enhancement technique. Between arrows are regions of myocardial delayed enhancement indicating myocardial fibrosis.

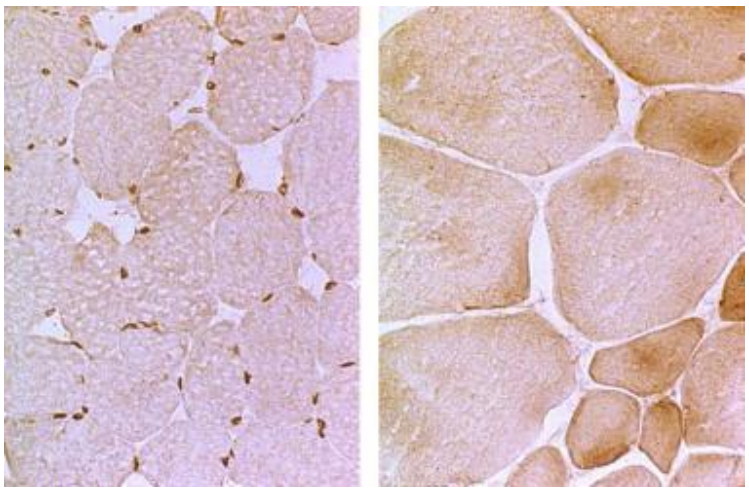
Pulmonary function test (PFTs), including an analysis of arterial blood gases, and a hematologic workup are necessary as part of the preoperative workup. A pulmonologist may be consulted preoperatively because he or she can be helpful in managing the patient's airway in the postoperative period.
EMG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

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 Findings
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.



This modified Gomori's trichrome stain in DMD demonstrates the endomysial fibrosis which is so prominent early in the disease.



Left: 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.

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 to 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.

Pharmacological Therapy

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.

Mendell et al (**Mendell 1989**) performed a randomized, double-blind, multicenter study of 103 male patients with DMD 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 (**Mendell 1989**), 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, has been the new therapeutic drug of choice (**McAdam 2012; Lebel 2013**). 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.

Growth curves for ambulatory males treated with corticosteroids showed significantly shorter stature, heavier weight, and greater BMI compared with ambulatory, steroid-naïve males with DMD and general-population US males. Adjusted linear mixed-effects models for ambulatory males treated with corticosteroids showed that earlier initiation, daily dosing, longer duration, and greater dosages predicted shorter stature with prednisone. Longer duration and greater dosages predicted shorter stature for deflazacort. Daily prednisone dosing predicted lighter weight, but longer duration, and greater dosages predicted heavier weight. Early initiation, less than daily dosing, longer duration, and greater doses predicted greater BMIs. Deflazacort predicted shorter stature, but lighter weight, compared with prednisone (**Lamb 2016**). In children with DMD, prednisone should be offered for improving strength (Level B) and pulmonary function (Level B). Prednisone may be offered for improving timed motor function (Level C), reducing the need for scoliosis surgery (Level C), and delaying cardiomyopathy onset by 18 years of age (Level C). Deflazacort may be offered for improving strength and timed motor function and delaying age at loss of ambulation by 1.4-2.5 years (Level C). Deflazacort may be offered for improving pulmonary function, reducing the need for scoliosis surgery, delaying cardiomyopathy onset, and increasing survival at 5-15 years of follow-up (Level C for each). Deflazacort and prednisone may be equivalent in improving motor function (Level C). Prednisone may be associated with greater weight gain in the first years of treatment than deflazacort (Level C).

Deflazacort may be associated with a greater risk of cataracts than prednisone (Level C). The preferred dosing regimen of prednisone is 0.75 mg/kg/d (Level B). Over 12 months, prednisone 10 mg/kg/weekend is equally effective (Level B), with no long-term data available. Prednisone 0.75 mg/kg/d is associated with significant risk of weight gain, hirsutism, and cushingoid appearance (Level B) (**Gloss 2016**).

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 necrotic 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.

Other drugs

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% (**Casey 1996; Tarnopolsky 2000**). 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 (**Tarnopolsky 1997**). Several other human clinical trials of creatine supplementation have been conducted since that time with similar results (**Chung 2007; Klopstock 2000; Louis 2003**).

A meta-analysis of all randomized clinical trials using creatine monohydrate supplementation in neuromuscular disorders versus placebo was performed (**Kley 2011**). It found that short- and intermediate-term treatment with 0.03-0.04 g/kg/d of creatine monohydrate supplementation resulted in modest but significant increase 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.

These effects were reliably seen in patients with dystrophinopathies and type II myotonic myopathy (**Kley 2011**). No consistent changes were noted in patients with type I myotonic dystrophy, and none were noted in those with metabolic myopathies. Although there were no serious side effects noted in most patients, high-dose creatine treatment can impair ADL and increase muscle pain in glycogen storage disease type V (McArdle disease).

PTC124 (PTC Therapeutics, Inc, South Plainfield, NJ) is an oxadiazole compound that, when taken orally, can override nonsense stop translation signals induced by the dystrophin gene mutation; the protein produced is thus the full-length protein (**Hamed 2006; Welch 2007**). PTC124 clinical trials for patients with DMD and cystic fibrosis. The selectivity of PTC124 for premature termination codons, its well characterized activity profile, oral bioavailability and pharmacological properties indicate that this drug may have broad clinical potential for the treatment of a large group of genetic disorders with limited or no therapeutic options.

An open-label, phase 2, dose-escalation study evaluated the safety and efficacy of intravenously administered AVI-4658 phosphorodiamidate morpholino oligomer (PMO) in patients with DMD (**Cirak 2011**). Using data from 19 ambulant patients aged 5-15 years with amenable deletions in DMD, the investigators noted that AVI-4658 was well tolerated with no serious drug-related adverse events; AVI-4658 induced exon 51 skipping in all cohorts and new dystrophin protein expression in a significant dose-dependent, but variable, manner in boys (dose 2 mg/kg) onwards.

Although the early clinical results of AVI-4658 are biochemically promising for dystrophin production without significant adverse effects, functional ambulatory changes have not been as consistently correlated. These results suggest that AVI-4658 may be a potential disease-modifying drug for DMD (**Cirak 2011**).

Gene therapy

Another novel method of treatment under intense investigation is somatic gene therapy, wherein healthy immature myoblasts are introduced into the diseased muscles, which then fuse and stimulate production of enough dystrophin to reverse the degeneration that occurs in the affected muscles (**Ragot 1993**).

However, although somatic gene therapy has been achieved successfully in the X-linked muscular dystrophic mouse (murine MDX) model with the fusion of the donor and host muscle cells, which expressed some dystrophin, the benefit may not translate into human males (**Ragot 1993**). The mice cannot demonstrate muscle strength, and the laboratory-raised mice were not able to mount a rejection response that may occur in humans. Other investigations have been conducted on the canine MDX model, which more closely approximates the human condition (**Wang 2007; Howell 1998**).

Human trials of gene therapy began in 1990. The first was an uncontrolled trial of 8 patients who were injected with myoblasts from family donors (**Griggs 1990**). Strength testing and staining for dystrophin was performed after several months. Early results demonstrated no improvement in patients' muscle strength or dystrophin staining. Later studies showed an increase in the expression of dystrophin proteins. However, the clinical results remain unchanged. These preliminary results, although disappointing, do not dampen the promise of gene therapy. Most supporters believe that these failures were merely the result of a lack of expertise, as with once-novel techniques such as organ transplantation.

Other molecular approaches to therapy include recombinant versions of the dystrophin gene using viral or non-viral vectors and antisense oligonucleotides (**Rando 2007; Wells 2006**). In the viral vector therapeutic approach, adenosine-associated virus leads the way. In non-viral gene therapy, plasmid-mediated gene delivery, antisense-mediated exon skipping, and oligonucleotide-mediated gene editing has moved from successful trials in the lab to the clinic. In approximately 10-20% of the preclinical cases (**Wells 2006**), it is possible to chemically persuade the translational machinery to read through a premature stop codon, as noted with the dystrophin mutation, and lead to production of a more functional full-length protein.

In spinal muscular atrophy (SMA), the molecular genetic basis is the loss of function of the survival motor neuron gene *SMN1*. The *SMN2* gene, a near identical copy, has been detected as a possible target for therapy. Drugs such as valproic acid (**Gurpur 2009**), phenylbutyrate, sodium butyrate, M344 (a benzamide and histone deacetylase [HDAC] inhibitor), and suberoylanilide hydroxamic acid (SAHA) can stimulate *SMN2* and elevate levels of the protein. In phase II clinical trials and individual experimental curative approaches, patients show promising results. Phase III control drug trials are pending.

Surgical Therapy

The orthopedic problems in children with MD are as follows: Progressive weakness with loss of ambulatory status, Soft-tissue contractures and Spinal deformities

The role of the orthopedic surgeon is to correct the deformities and to help maintain the dystrophic child's ambulatory status for as long as possible, usually 1 to 3.5 years (**Brooke 1989; Heckmatt 1985**). The modalities available to obtain these goals have been well outlined by Drennan (**Drennan 1990**) and include the following: Functional testing, physical therapy, use of orthoses, fracture management, soft-tissue, bone, spinal surgeries, use of a wheelchair when indicated, genetic and/or psychological testing.

Non-operative measures

Functional testing, as its name implies, refers to frequent evaluation of the involved muscle's range of motion and strength. This modality provides therapists with goals for patients' individualized therapy programs. Regular therapy sessions are necessary because the therapist also works with patients for gait training and transfer techniques. The use of all adaptive equipment is considered necessary by the orthopedist to maintain the patient's ambulatory status.

Drennan also recommends that a home program be taught to dystrophic patients, with stretching exercises for the lower extremities performed twice a day on a firm surface to minimize contractures (**Drennan 1990**). Occasionally, serial casting may be necessary to manage significant flexion contractures at the knee or equinus contracture at the ankle. The goal for patients with MD is continued mobility despite the use of a cast to prevent rapid loss of strength and bone mineral density. Even with initial loss of muscle strength for weightbearing, flexible soft-tissue and rigid ankle-foot orthosis (AFO) or ischial supportive knee-ankle-foot orthosis (KAFO) can help the patient maintain standing balance for additional months to years.

Operative approaches to contractures and deformities

Significant upper-extremity contractures rarely occur in patients with MD. Occasionally, tightness of the long flexors may become problematic with hand function in operating an automatic wheelchair, but historically this has been treated with a nighttime orthosis.

In patients with MD, lower-extremity contractures start with equinus deformities. Initially, the contractures are supple and can occur in children as young as 6 years. Patients may be treated with various types of procedures to lengthen the tendo Achillis, including Vulpius tendon lengthening (which avoids overlengthening the already weakened muscle), percutaneous Hoke-Miller triple cut (which limits the incision and, thus, the postoperative immobilization), Warren-White lengthening, or standard z-lengthening.

Occasionally, when an associated varus deformity is present as a result of overpull of the unaffected tibialis posterior muscle, a posterior tibial tendon transfer through the interosseous membrane or a split-posterior tibial tendon transfer may also be indicated. In cases of severe contractures at the foot and ankle, posterior tibial lengthening or tenotomy may be necessary to achieve a plantigrade position.

Hip and knee contractures develop later in MD. Once patients become wheelchair-bound, hip and knee flexion contractures are more rapidly progressive. The abduction contracture was initially thought to be useful in obtaining stability with a wider base gait, but it also makes it difficult for patients to fit in standard wheelchairs or to be comfortable in bed. Various tenotomies are available, including the Yount (resection of the iliotibial band [ITB] distally at the knee) (**Yount 1926**) modified Souter-Strathclyde (resection of the ITB proximally), and complete resection of the ITB from the hip to the knee.

Transfer of the iliopsoas has also been tried with limited success; this is no longer a procedure of choice in patients with MDs. Posterior capsulotomy of the knee can allow for maintenance of flexible extremities for bracing, although this is not routinely performed. KAFOs with locked knees may extend the ambulatory status of weakened patients by 1 to 3 years (**Heckmatt 1985; Shapiro 1993**). The locked knees, however, are not well tolerated, as they cause children to feel as if they are going to fall. This is a worse condition than buckling because of weakness at the quadriceps. Postoperatively, all patients are given some type of orthosis.

The surgical approaches to contractures in dystrophic patients, especially those with DMD, can be summarized into the following three broad categories: ambulatory, rehabilitative and palliative. Within the ambulatory group, the approach can be aggressive, so that all contractures are addressed at the start, before patients lose ambulatory status or within the first month of their losing ambulatory status. The rehabilitative approach indicates that surgery is used only to correct deformities that may limit physical therapy and orthosis wear. The palliative approach, as its name implies, is used to treat only problems of immediate concern for the patient's comfort, such as difficulty with shoe wearing, ulcerations, and problematic positioning in wheelchairs. Early aggressive surgical releases can prolong the patient's ambulatory status as long as 3.5 years (**Brooke 1989; Heckmatt 1985**).

Scoliosis is another common problem in patients with muscular dystrophy. It is more common in DMD than in other forms, with an incidence of 75-90% (**Brooke 1989; Heckmatt 1985; Thompson 2000**). The scoliosis develops early and tends to be rapidly progressive, especially when patients become non-ambulatory. The curve is usually thoracolumbar or lumbar with associated pelvic obliquity, thoracic kyphosis, and lumbar hyperlordosis. The abnormal sagittal alignment may cause problems with seating systems, even modified systems, and the rapid progression of the scoliosis requires frequent wheelchair adjustments. Braces are not effective in progressive paralytic or neuromuscular curves, and surgery is often indicated (**Suk 2014**).

Advances in pulmonary care and cardiac drugs may negate the absolute need for scoliosis surgery in DMD, allowing patients to live into adulthood. A 10-year retrospective study showed that 44 of 123 non-ambulatory patients aged 17 or older were managed satisfactorily without surgery (**Kinali 2006**). Although this is only a single report, it gives much hope for many dystrophic patients with scoliosis.

The technique of choice for scoliosis when the curve measures 20° or more in patients who are non-ambulatory is a posterior spinal fusion from T2 to the sacrum. The indication for earlier operative stabilization of the spine in these patients is due to the rapidly deteriorating cardiopulmonary function (**Miller 1988**). The FVC is at its maximum in children younger than 10 years. After this point, the FVC rapidly declines, and anesthetic complications rise dramatically in those patients with an FVC < 30%.

Spinal fusion is extended to the pelvis, with complete obliteration of the facet joints to ensure arthrodesis. The instrumentation used has often consisted of a Luque rod with segmental sublaminar wires to the L5 level, with bone arthrodesis extending into the sacrum. Currently, however, this method is being employed less frequently; most spine surgeons are now using pedicle screws with extension of the instrumentation to the pelvis (**Brooks 2015; Jain 2015**).

Occasionally, instrumentation and fusion are extended only to L5 because of the diffuse osteopenia in the sacrum, early surgery and low magnitude curves, or because of the possible complications of instrument failure. The literature has cited a high incidence of failure and revision with fusion short of the sacrum; therefore, spinal fusions in patients with MD are extended to the pelvis, especially if done after the curve magnitude is over 30º (**Gaine 2004; Sengupta 2002; Mubarak 1993**).

Preoperative considerations

Before any operative is undertaken, the patient's overall status of any patient must be considered; this is of particular importance in patients with muscle weakness, such as those with MD. For example, posterior spinal fusion to the pelvis straightens the scoliosis and allows better upright sitting balance. However, in patients with low vital capacity (<30%), the risks of pulmonary complications are much higher, and these risks may tip the scale in favor of not operating on the scoliosis.

Other examples include equinus contractures in patients who are very weak; tendon lengthening itself is necessarily a weakening procedure on the involved muscle. If the patient has to maintain a rigid equinus foot position for stability of gait and the tendon is lengthened by surgery, the patient will not be able to ambulate.

Preoperatively, patients should undergo a detailed cardiac assessment, a pulmonary evaluation with pulmonary function tests (including arterial blood gas analysis), and a hematologic workup. Because of potential cardiomyopathy, intraoperative monitoring is an essential component of administering anesthetics.

Dilated cardiomyopathy in DMD is characterized by replacement of the myocardium with connective tissue. Myocardial fibrosis in DMD can be best documented by application of cardiac MRI and administration of gadolinium to assess the amount of late gadolinium enhancement (LGE). Assessment of LGE in DMD is important since the amount of LGE strongly correlates with LV systolic dysfunction (**Tandon 2015**).

Intraoperative blood loss is usually substantial in patients with MD as a result of their muscle dysfunction, which causes ineffective vessel constriction. Another potential complication of anesthesia is malignant hyperthermia, which is more common in patients with muscle diseases than in patients with other disease entities; this risk is diminished with the use of nitrous oxide, intravenous narcotics, sedatives, and non-depolarizing muscle relaxants.

After scoliosis surgery, patients may need additional pulmonary support and an extended stay in the intensive care unit (ICU). Preoperative tracheostomy is usually not any more effective in early mobilization of dystrophic patients; if necessary, this procedure is performed only after the patient's condition has been stabilized and after a mold has been obtained for a hard brace with chest and abdominal cutouts.

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Addendum

Dear colleagues; with great pride and satisfaction we announce the release of a new book on electrocardiography entitled **"Electrocardiogram in emergency and urgency medicine"** by Manole publisher in Brazil.

The content and meaning of the book is very clear expressed in it and the preface was written no less than the Professor Dr. Pedro Brugada.

Preface

Prof. Dr. Pedro Brugada Chairman, Cardiovascular Division, UZ Brussel-VUB, Brussels, Belgium.

In many languages the word Medicine relates to the art of healing. Just take the Dutch word for it: Geneeskunde – Genees from healing and Kunde from to be able to do it or to have the capacity to heal or be blessed with the art of healing. This artistic aspect of Medicine is usually forgotten. Doctors are seen as a sort of biological machine with programmed knowledge that reacts to certain stimuli, being the complaints of the patients or the results of multitude of tests. Nothing more wrong than this thought. Dealing with biological phenomena is far from solving a mathematical problem or the newspaper sudoku.

By definition, solving a diagnosis involves more than intelligence, more than knowledge, even more than detective intuition, it involves a very special part of our brains that makes "pattern recognition" possible. And not only "pattern recognition", but instant pattern recognition. You may think, what is that? Well, that is what this book is offering to physicians, nurses and allied professionals that have to deal with rapid (almost instant) diagnoses in the emergency room. It is the art of imprinting an electrocardiographic image in your brain that you will recognize forever any time you come across it. This is a most welcome book that was long needed.

Enjoy it!

Raimundo Barbosa-Barros& Andrés Ricardo Pérez-Riera

Português

Prezados colegas; com enorme orgulho e satisfação anunciamos o lançamento de um novo livro de Eletrocardiografia intitulado “Eletrocardiograma na medicina de urgência e emergência” pela editora Manole do Brasil.

O conteúdo e sentido do livro está muito claro expressado no seu prefácio escrito nada menos de que pelo Professor Dr Pedro Brugada:

Prefácio

Em muitos idiomas, a palavra medicina refere-se à arte da cura. A título de ilustração, na palavra geneeskunde, o equivalente à medicina no idioma holandês, genees significa cura, e Kunde, ter a capacidade de curar ou ser abençoado com a arte da cura. Esse aspecto artístico da medicina geralmente é esquecido. Os médicos são vistos como uma espécie de máquina programada de conhecimento biológico que reage a certos estímulos, como as queixas dos pacientes ou os resultados de múltiplos testes. Nada mais errado que esse pensamento. Desvendar fenômenos biológicos não é o mesmo que resolver um problema de matemática ou um desafio de sudoku. Por definição, encontrar o diagnóstico envolve mais que inteligência, que conhecimento e até mais que a intuição de um detetive. É uma parte muito especial do nosso cérebro que faz com que "o reconhecimento dos padrões" seja possível. Mais que isso, não apenas o "reconhecimento dos padrões", mas o "reconhecimento instantâneo dos padrões". Você pode estar pensando: o que é isso? Bem, isso é exatamente o que este livro está oferecendo a médicos, enfermeiros e outros profissionais que têm que lidar com o diagnóstico rápido (quase instantâneo) nas salas de emergência. Trata-se de um estudo sobre a arte de gravar uma imagem eletrocardiográfica no cérebro e reconhecê-la cada vez que você deparar com ela. Um livro mais do que bem-vindo e sempre necessário.

Raimundo Barbosa-Barros& Andrés Ricardo Pérez-Riera