Chronic chagasic cardiomyopathy with apparent minimal repercussion and surprising electro-vectorcardiograpic features

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Case report

Male, white, 36-year-old patient; computer technician, from the rural area of Ceará, in the northeast region of Brazil, where he lived for many years in a wattle and daub house, in an area endemic for Chagas disease.

He reports always being asymptomatic. Approximately 3 years ago, on the occasion of being evaluated for a new job, he underwent an ECG that revealed a "minimal issue" according to the physician in his employer company, who requested serology for Chagas disease, which was positive. From then on, he has been regularly taking sotalol 25 mg per day.

He mentions having 5 brothers, with 4 of them being healthy, and only the oldest one with 47 years of age, is a carrier of chagasic heart disease with little repercussion.

Physical examination: weight 75 kg; height 1.75 m; BP 120/60 mmHg, and heart rate of 52 bpm, regularly using beta blockers. Nothing else worth mentioning.

We requested:

- ECG/VCG
- 2D transthoracic Doppler echo.
- Holter
- Cardiac magnetic resonance: normal septum, lateral wall, end diastolic diameter, end systolic diameter, end diastolic volume and end systolic volume, and ejection fraction. Increase in LV myocardial trabeculations. Normal global and segmental biventricular systolic function. Presence of late mesocardial enhancement in the inferolateral-septal-medial segment and subepicardium of the LV apex, with presence of nonischemic fibrotic pattern in these areas.
- Full lab tests: normal.

Questions:

1. What is the electrocardiographic and vectorcardiographic diagnosis?
2. How to explain the aberrant location of ventricular depolarization in a patient with normal left ventricular wall location, size, wall thickness, and left ventricular ejection fraction?
3. How to explain the extreme low voltage of the QRS complexes in the frontal plane?
4. Why is the transition R-wave progression (isodiphasic R/S ratio) not present across the unipolar precordial leads?
5. What is the proper approach and risk stratification?

Português Relato de caso

Paciente masculino branco 36 anos técnico em informática, procedente da zona rural de Ceará no nordeste do Brasil, onde morou por muitos anos em casa de pau a pique e em área endémica para Chagas

Refere que sempre foi assintomático. Há aproximadamente 3 anos por ocasião da admissão a emprego realizou um ECG o qual revelou "um mínimo probleminha" segundo o medico do trabalho que solicitou sorologia para chagas a qual resultou positiva Desde essa data em uso regular de sotalol 25mg por dia.

Refere ter cinco irmãos 4 deles sadios sendo que apenas o maior com 47 anos é portador de cardiopatia chagásica de pouca repercussão.

O exame físico Peso 75kg; altura 1.75m PA 120/60 mm de Hg e frequência cardíaca de 52 bpm em uso regular de betabloqueador. Resto nada digno de nota.

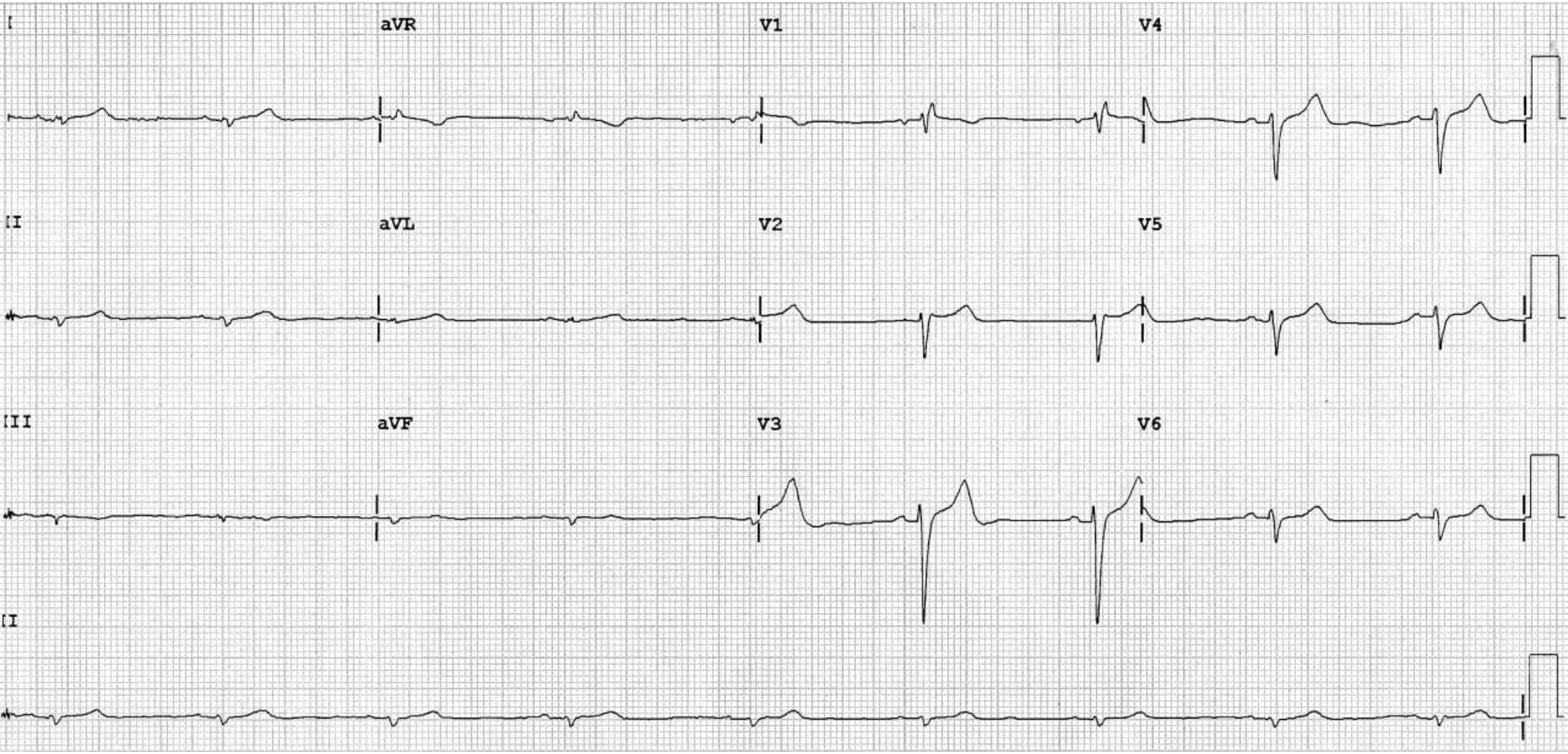
Solicitamos:

- **ECG/VCG**
- **Ecocardiograma transtorácico bidimensional com Doppler**
- **Estudo de Holter de 24 horas**
- **Ressonância magnética do coração** septo, parede lateral, diâmetro diastólico final, diâmetro sistólico final, volume diastólico final e volume sistólico final, e fração de ejeção normais. Aumento da trabeculação miocárdica do VE, função sistólica biventricular global e segmentar normal Presença de realce tardio mesocárdico no segmento ínfero-latero-septal-medial e subepicárdico no apex do VE com presença de padrão fibrótico não isquêmico nessas áreas.
- **Laboratório completo normal**

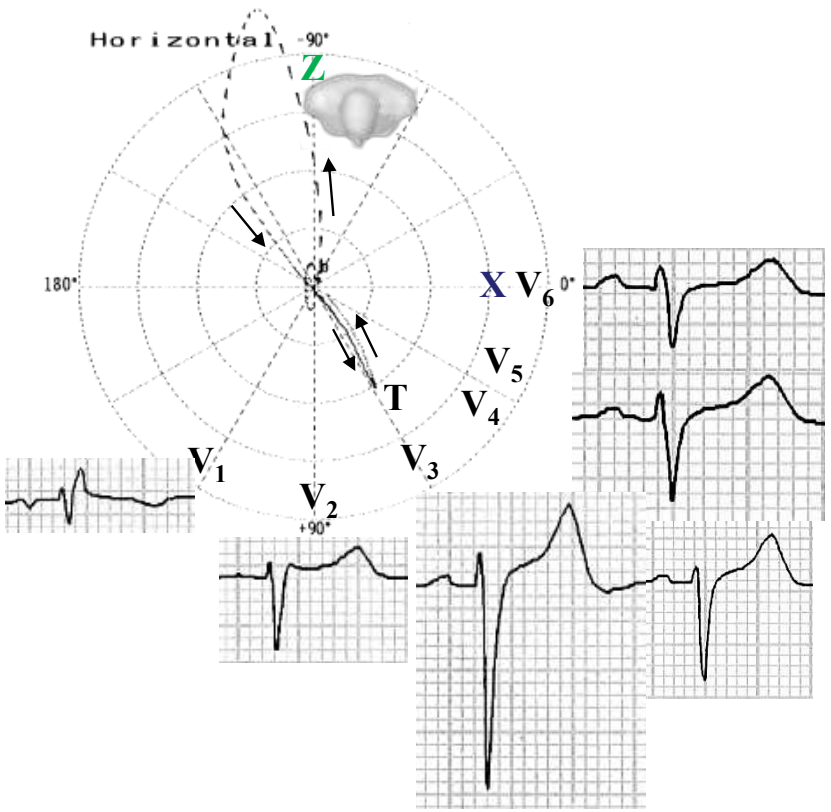
Perguntas:

1. Qual o diagnóstico eletro-vetorcardiográfico?
2. Como explicar a localização aberrante da despolarização ventricular num paciente com localização, tamanho, espessura de paredes e fração de ejeção do ventrículo esquerdo normais?
3. Como explicar a extrema baixa voltagem dos complexos QRS no plano frontal?
4. Por que a zona de transição precordial não está presente de V1-V6?
5. Qual a abordagem adequada e a estratificação de risco?

ECG



ECG/VCG correlation



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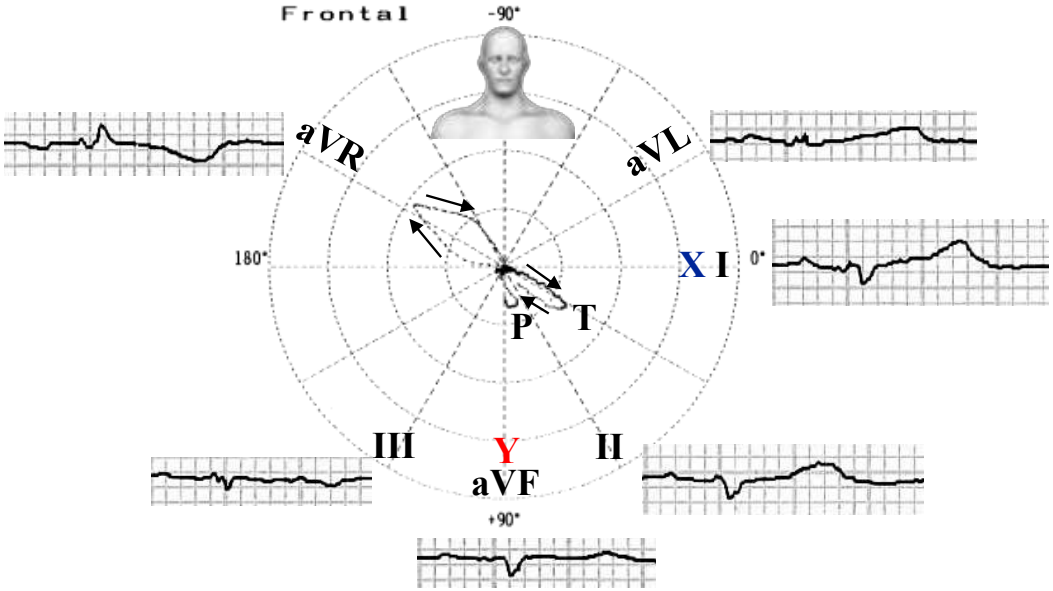
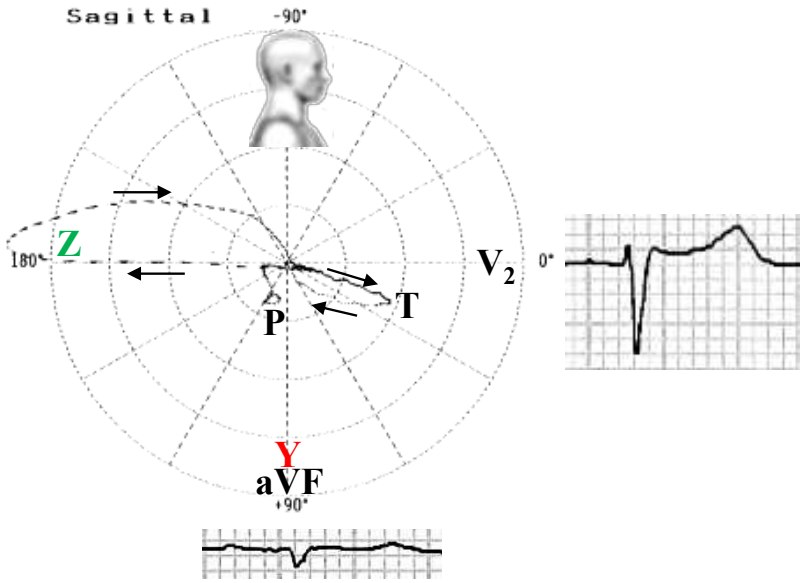
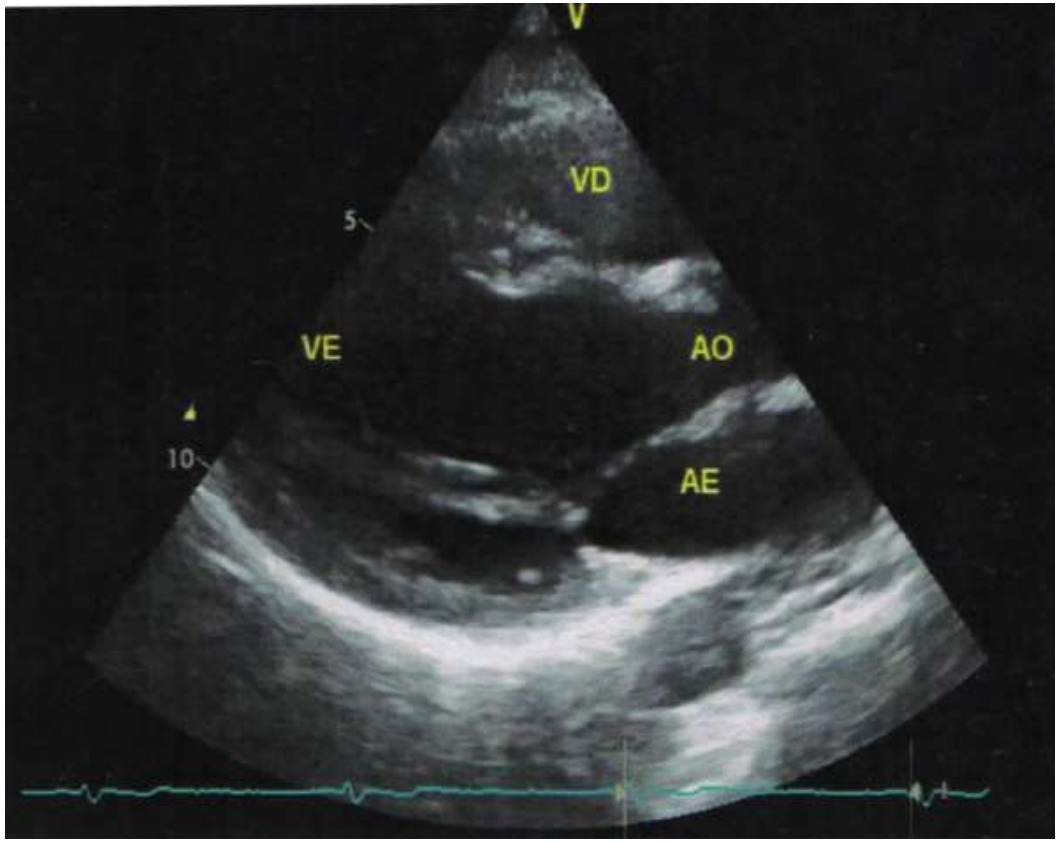
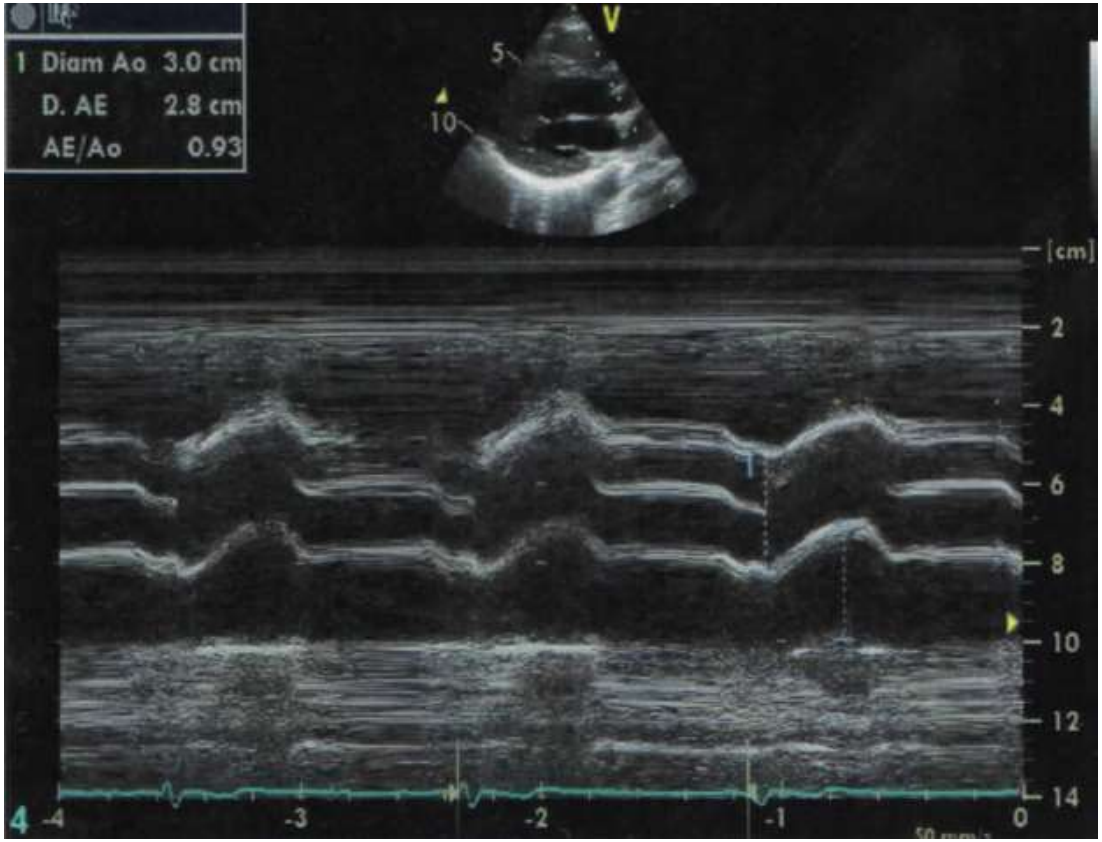
Timer: 2 msec
Sagittal: Right
Z axis: Front
Filter: Hum
Muscle
Drift





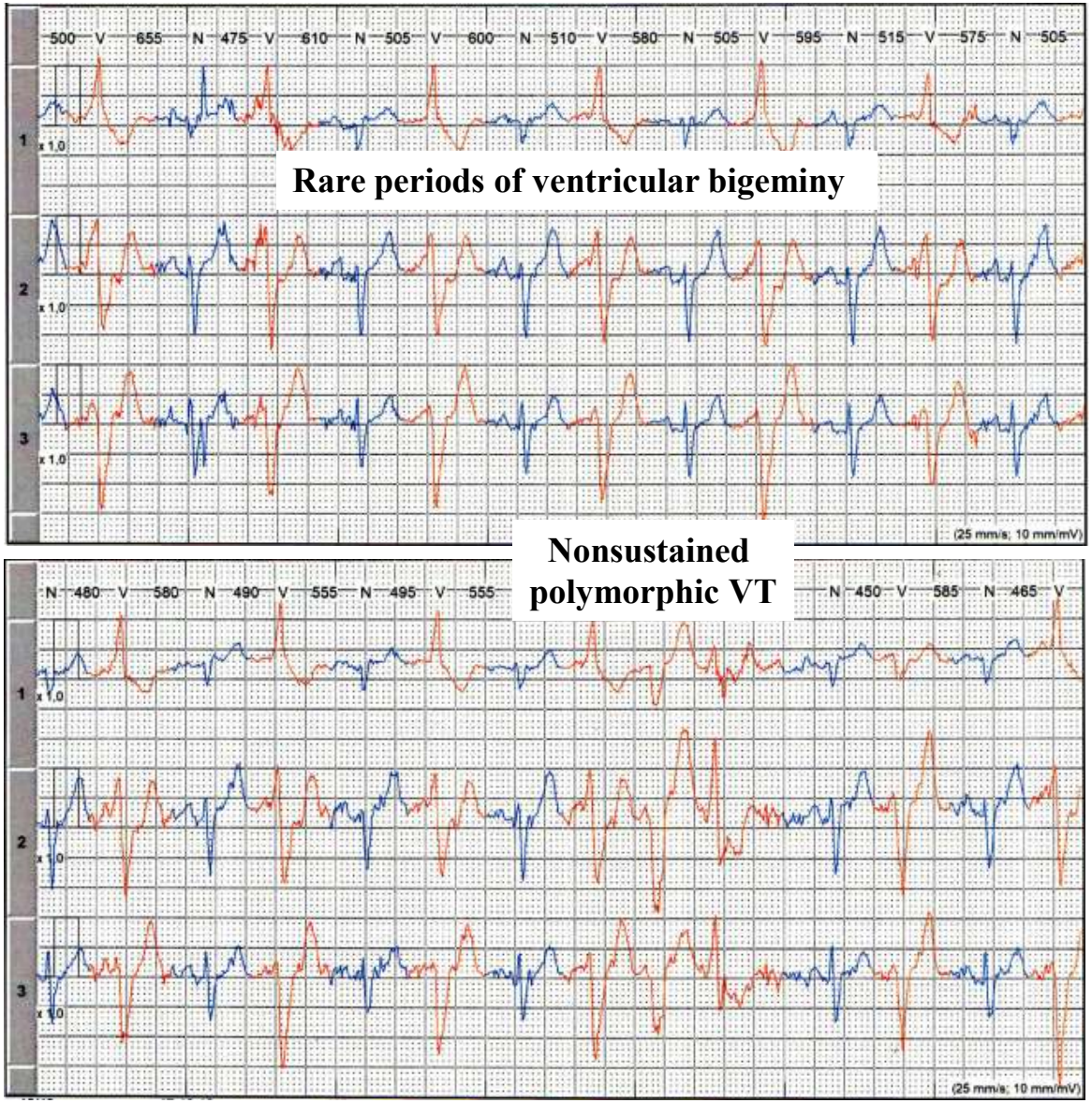
2D transthoracic Doppler echo



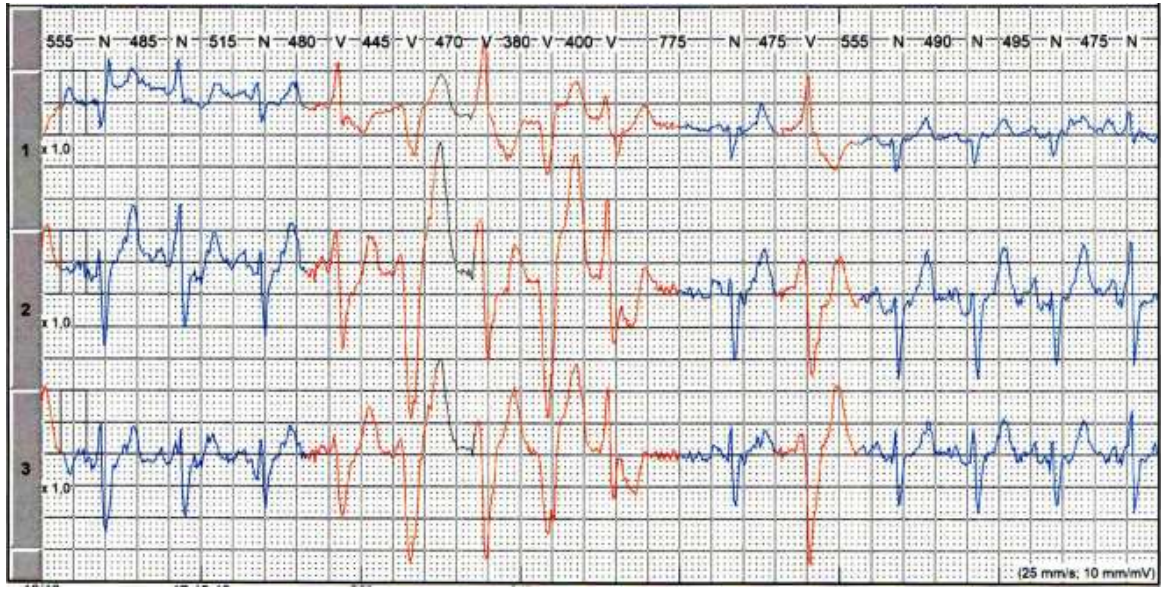


Cardiac chambers with normal dimensions, myocardium with normal thickness, preserved ventricular performance, bicuspid aortic valve with slightly thicker leaflets, and preserved opening and mild insufficiency in Doppler. LV ejection fraction = 70%; normal LV diastolic and systolic diameters, normal RV diameter. Normal LV mass and mass index.

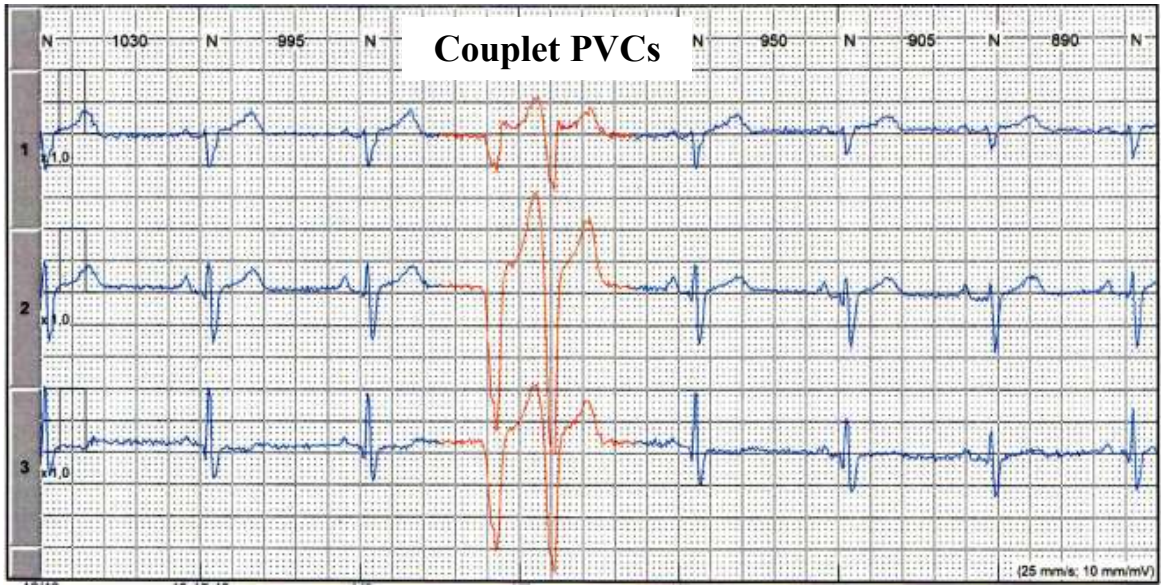
24-hour Holter monitoring

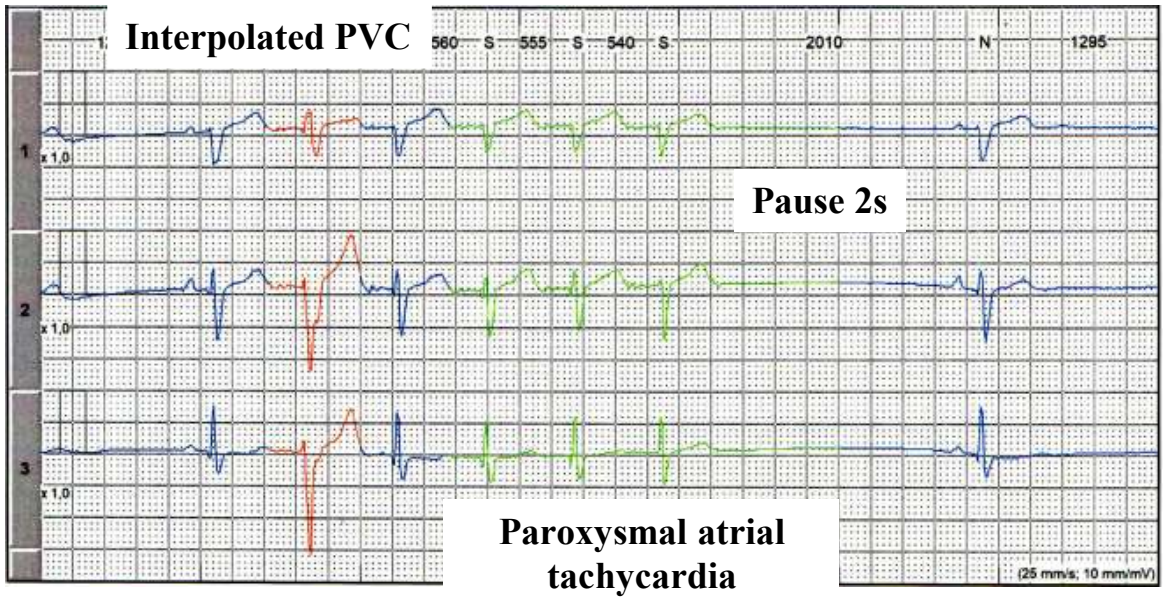


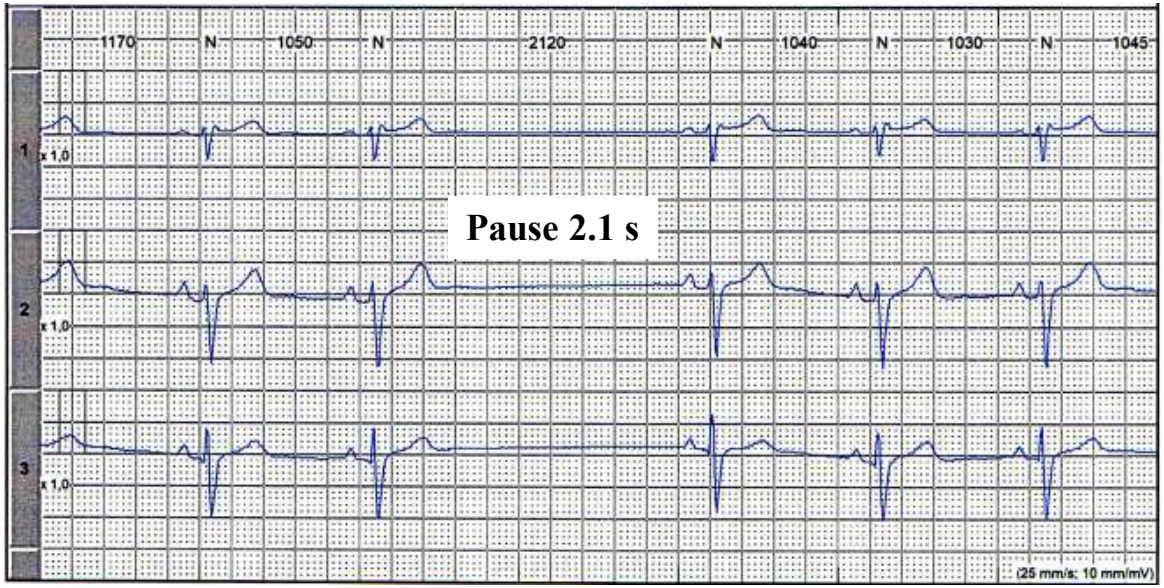
Nonsustained polymorphic VT



Couplet PVCs




Interpolated PVC
560 S 555 S 540 S
2010
N
1285
Pause 2s
Paroxysmal atrial tachycardia
(25 mm/s; 10 mm/mV)


1170 N 1050 N 2120 N 1040 N 1030 N 1045
Pause 2.1 s
(25 mm/s; 10 mm/mV)

Colleagues' opinion

Dear Andrés and Raimundo:
Thank you for sending this interesting case. At first, I was a little confused: according to lead V1, in the VCG, horizontal plane, there should be terminal anteriorly oriented forces that I do not see on the presented VCG. Is it possible that the V1 electrode was placed higher than in the 4th intercostal space?

Ljuba Bacharova MD, DSc, MBA
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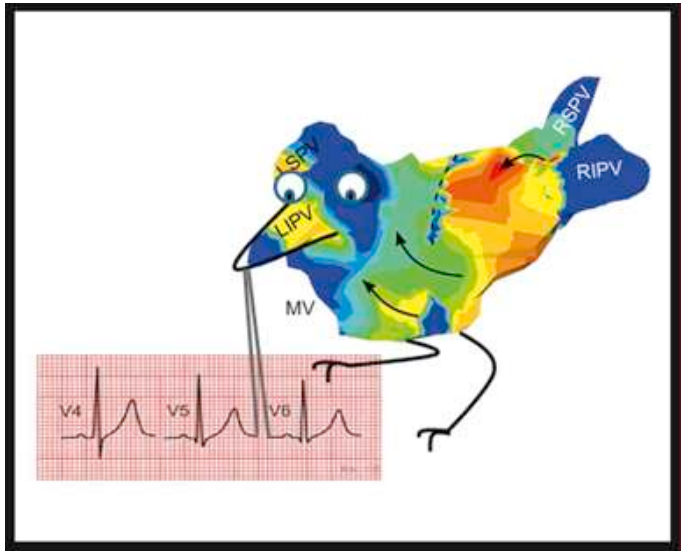
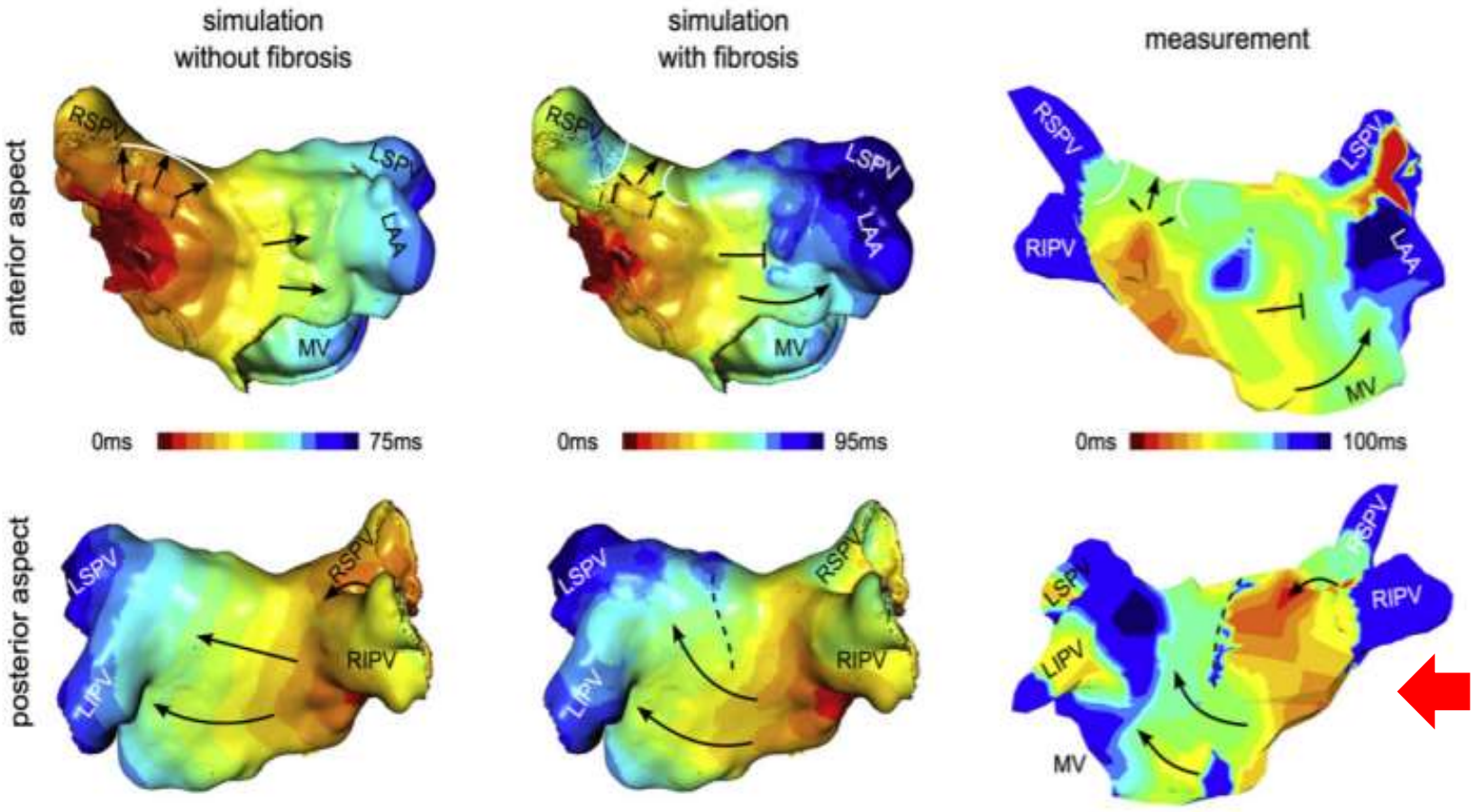
Answer
Dear Ljuba: your observation is very logical, however, we are sure that the location of the electrode of V1 is correct, because we had the same doubt and we repeated the tracing. There is an explanation for this apparent "mystery" that we will comment on at the end of the opinions. Please have a little patience.
Thanks for your comment.

Andrés and Raimundo.

Great dear Ljuba!!!

Ljuba Bacharova has morphed this colorful "ECG Pecking Bird" from the left atrial activation map presented in figure 4 of the manuscript on "Patient-specific modeling of atrial fibrosis..." by Krueger et al in this issue. (**Krueger 2014**) See the last figure in the next slide.





Simulated and measured local activation times in the left atrium of the AF patient. The simulation with fibrosis reproduced the measured local activation time more precisely, as the activation direction (arrows), zones of slow conduction (T) and the posterior line of conduction block (stroked) were only reproduced by inclusion of left atrial fibrosis in the model. Local activation times were only recorded in the left atriuM, therefore the right atrium is not shown in this visualization. L/R I/S PV: left/right inferior/superior pulmonary vein, MV: mitral valve, LAA: left atrial appendage.

Dear Andrés:
Regrettably, I have to tell you that this VCG is very confusing; where the first forces are not seen clearly and the planes are not coherent to each other. I made an interpretation of the vectorial forces, according to the attached ECG, where neither voltages nor angles or ms are preserved properly, with simpler trajectories of the loop than they should really have.
The first forces are headed downward and to the right and forward, and rotate clockwise in the frontal plane that because of the morphology of the rest of the loop makes us think of an area of inferior fibrosis. The maximum spatial vector is delayed in the right upper field; probably due to conduction disorders in this area or right antero-superior fascicular block.

The low voltage of QRS complexes in the frontal plane is due to the loop being perpendicular to it.
Warm regards,
Isabel

Reply:
Dear Isabel,
You are not the only one to have this doubt. But let me tell you that I obtained a tracing with the same exact pattern before this one. For this reason, I decided to send the patient to the excellent Center in SP, the *Instituto do Coração*. This tracing comes from this institution, being identical to mine, with a difference of 5 days. You may read our rationale throughout this text. I think the final conclusion is certain. I am sending a VCG performed at Instituto do Coração (InCor) in São Paulo. This is the most prestigious institution on Cardiology. The tracing is identical to the one with my equipment about one week before. Please see next slide.

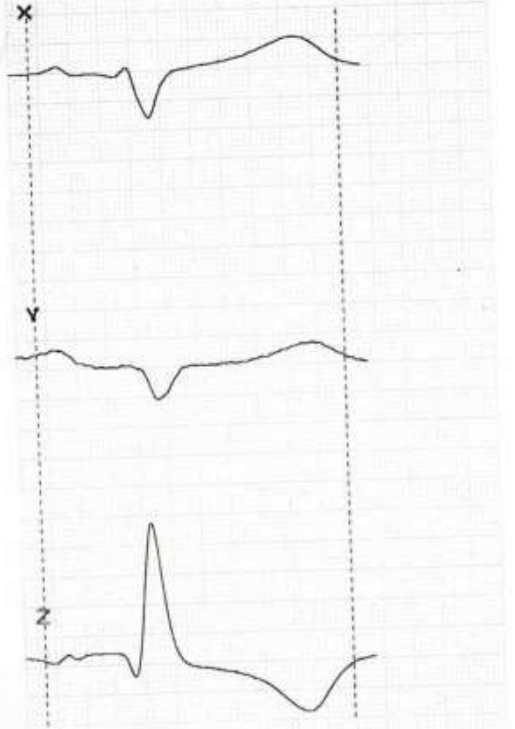
FRANK LEAD VCG

Date: 6/10/17 10:30
Name:

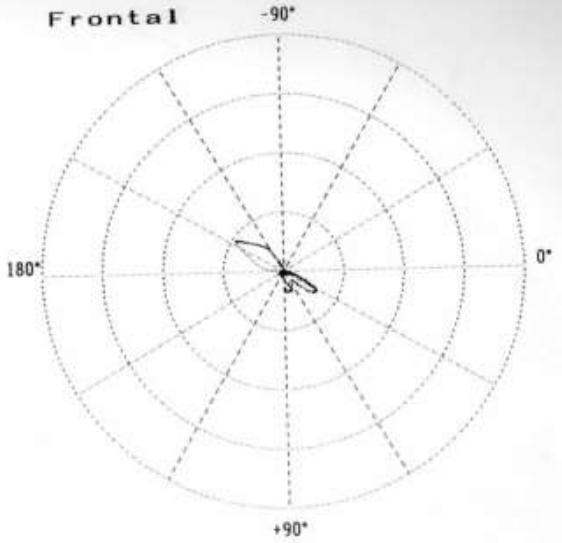
I/D : 3723610
Age : 36 yr.

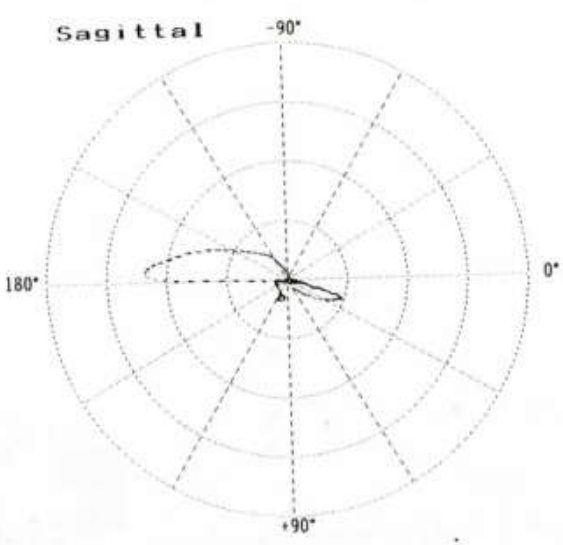
Heart Rate: 0 bpm
Sex : Male

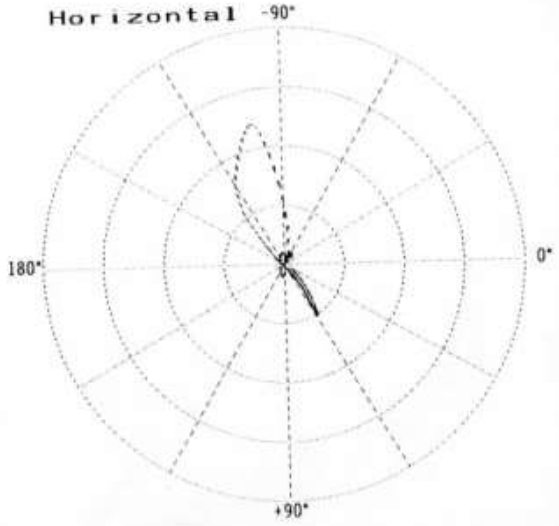
Comment:



Sensi.	2
Timer	2 msec
Loop	All Loop
Sagittal	Right
Z Axis	Front
Filter	Hum
	Muscle
	Drift







Spanish
Querido Potro:Presenta una bradicardia sinusal de alrededor de 60 por minuto con disminución de los voltajes en las derivaciones de los miembros del QRS y un bloqueo del fascículo posterior izquierdo y un Bloqueo incompleto de la rama derecha.
Refiere ECO normal.
Mi interpretación es que la bradicardia que presenta y los microvoltajes del ECG pueden ser atribuibles a hipotiroidismo asociado y no a a miocardiopatia chagasica.
Un abrazo
Martín Ibarrola

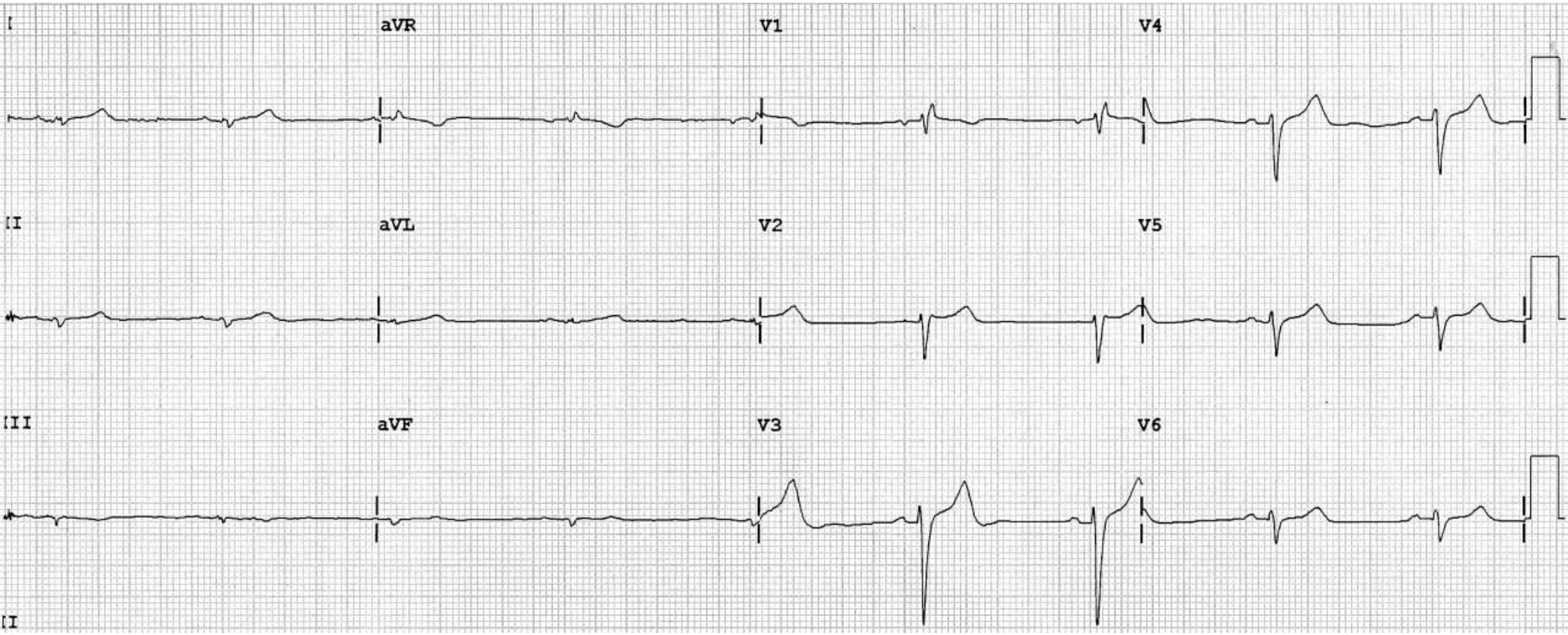
English
Dear Andrés:
It presents a sinus bradycardia of around 60 bpm with lowQRS voltage in limb leads and LAFB + incomplete RBBB.
It refers to normal ECO.
My interpretation is that the bradycardia and ECG micro-voltages presented may be attributable to associated hypothyroidism and not to chagasic myocardiopathy.
A hug
Martín Ibarrola

Spanish
Queridos amigos:
Pienso que este joven informático está severamente afectado. Me pregunto si al compromiso dado por el Chagas no se suma una miocardiopatía no compactada, sugerida por el aumento de las trabeculaciones en el VI observadas en la RNM
Coincido en descartar hipotiroidismo como propone Martín, y también me permito delirar preguntándome además si el bajo voltaje observado no podría deberse a edema existente en el miocardio que estuviera dado por cierta actividad inflamatoria, agregada a la fibrosis ya existente en el ápex, que seguramente devendrá en un aneurisma durante la evolución.
Por ahora se halla afectado predominantemente el sistema de conducción, pero creo que el músculo también lo está, aunque aún ha dado pocas manifestaciones, siendo el bajo voltaje y la arritmia ventricular expresiones precoces.
Un abrazo
Edgardo

English
Dear friends:
I think that this young computer technician is severely affected. I wonder if the commitment given by Chagas does not add a non-compacted cardiomyopathy, suggested by the increase in trabeculations in the LV observed in the NMR.
I agree to rule out hypothyroidism as proposed by Martin, and I also allow myself to be delirious, also wondering if the low QRS voltage observed could not be due to edema existing in the myocardium that was caused by certain inflammatory activity, added to the fibrosis already existing in the apex, which will surely become in an aneurysm during evolution.
For now the conduction system is predominantly affected, but I believe that the muscle is also, although it has still given few manifestations, being the low voltage and the ventricular arrhythmia precocious expressions.
A hug
Edgardo

Final comments

By Andrés Ricardo Pérez-Riera & Raimundo Barbosa-Barros



Sinus bradycardia (heart rate 53 bpm), QRS axis in the right upper quadrant -118° (only aVR and aVL are predominantly positive: aVR > aVL), very low QRS voltage in the frontal plane, triphasic QRS pattern in V_1 (rsR') and rS from V_2 to V_6, transition R-wave progression (isodiphasic R/S ratio) not present across the unipolar precordial leads. This phenomenon could be attributed to clockwise rotation of the heart around the longitudinal axis, consequence of right ventricular hypertrophy, or intraventricular conduction disturbance associated with fibrosis.

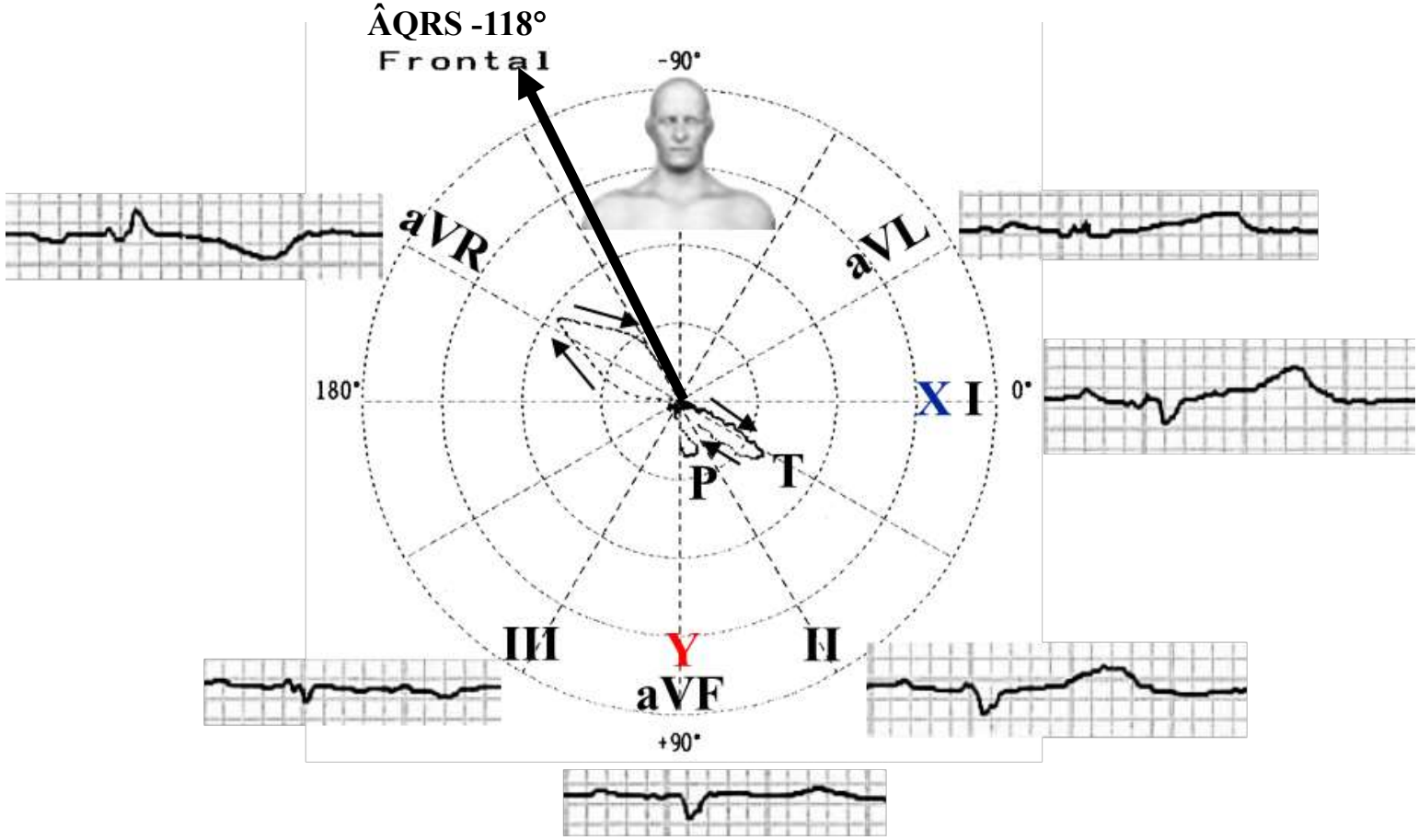
Conclusion: atypical left anterosuperior fascicular block + RBBB + low QRS voltage in the FP.

Why are we sure that this patient has bifascicular block (LAFB+RBBB)? Explanation in the next slide.

Extreme axis deviation = QRS axis between -90° and ±180° AKA Northwest axis, or no man's land. I, II, aVF and III are predominantly negative. Only aVR and aVL are positive and aVR>aVL. Consequently, the axis is located in -118°.

Possible causes for QRS loop located in the right upper quadrant in the FP; (between -90° and ±180°).

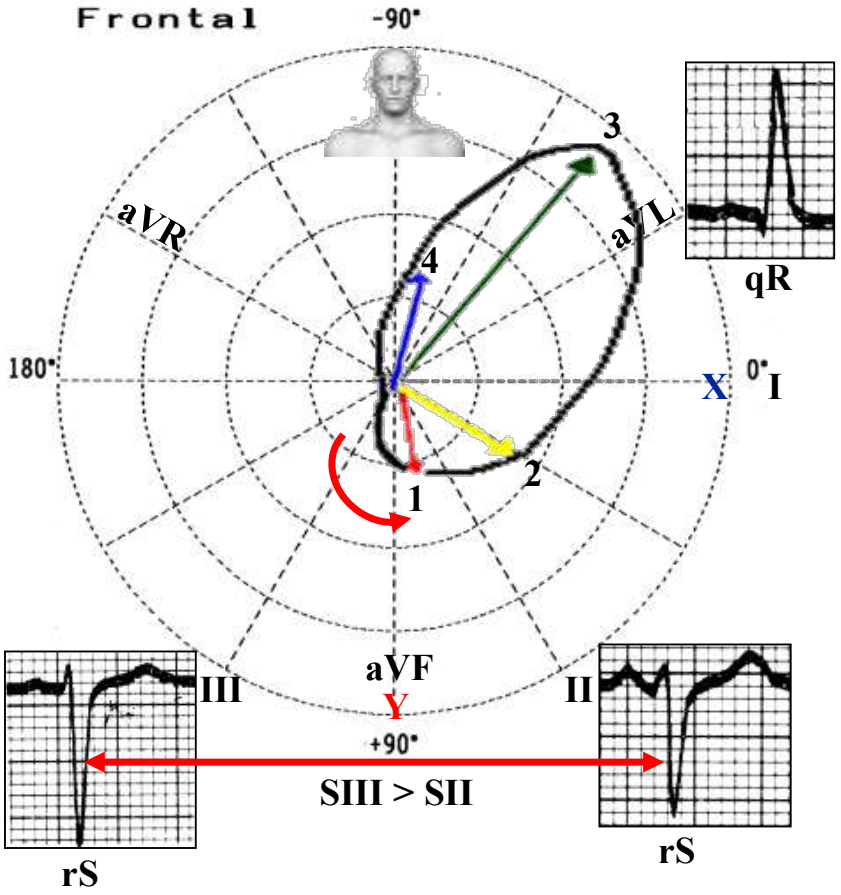
1. Dextrocardia
2. Premature ventricular contractions (PVCs)
3. Accelerated idioventricular rhythm (AIVR)
4. Ventricular tachycardia (VT)
5. Right end conduction delay by one of the divisions of the His bundle right branch
6. Hyperpotassemia
7. Severe RVH/enlargement
8. This case: fibrosis in inferobasal and lateral walls + LAFB.



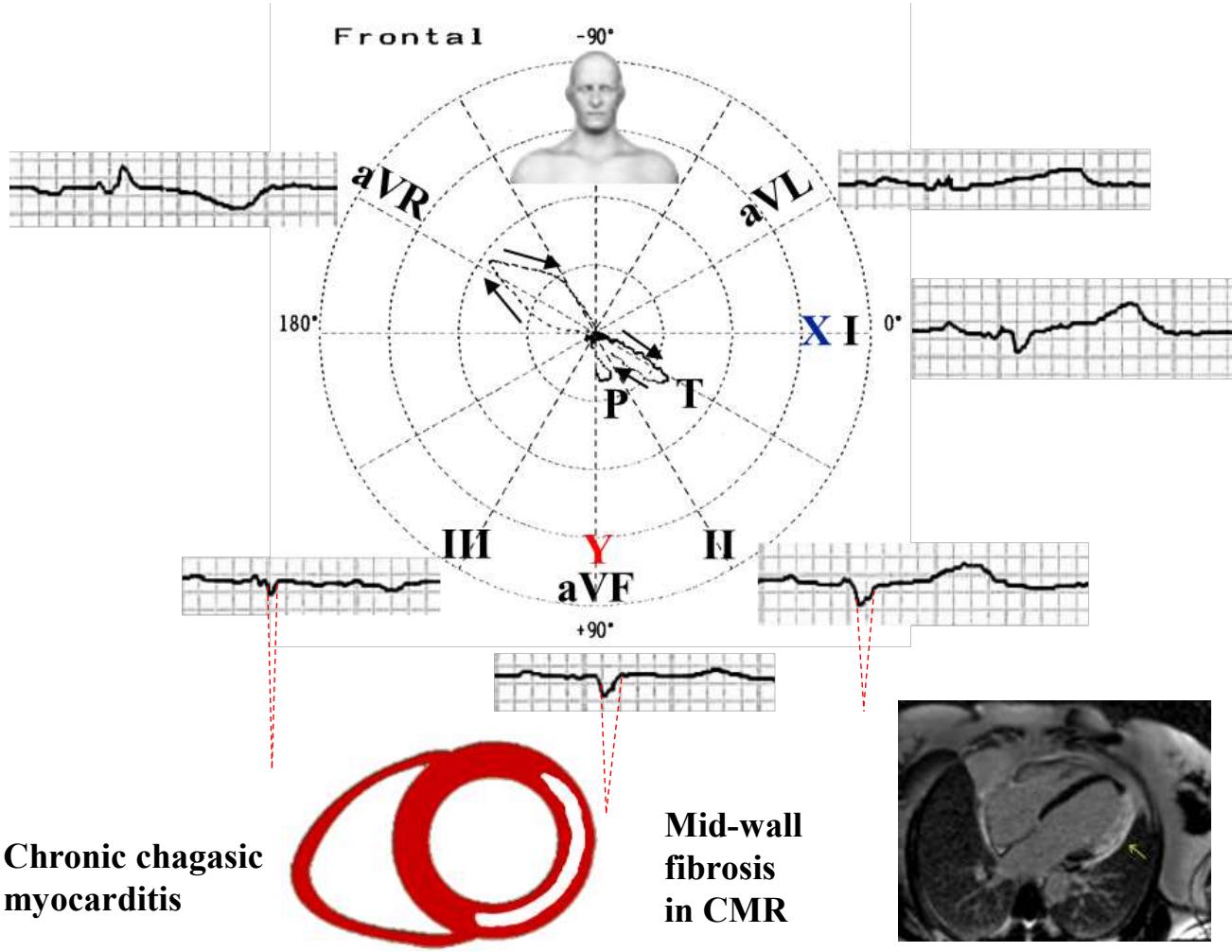
Lead I	Lead aVF	Quadrant	0◦ to +90◦
Positive	Positive	Left inferior	Possible LAD 0◦ to - 90◦
Positive	Negative	Left superior	+90◦ to +90◦
Negative	Positive	Right inferior	+91◦ to ±180◦
Negative	**Negative**	**Right superior**	-90◦ to ±180◦

Why LAFB? In the presence of LAFB the QRS pattern in inferior leads is rS in II, III and aVF, qR or qRs in I and aVL (Figure **A**).

A) Typical LAFB in the Frontal Plane



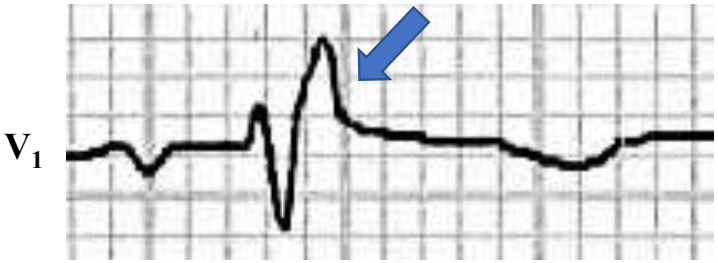
B) Atypical LAFB in the Frontal Plane (the present case)



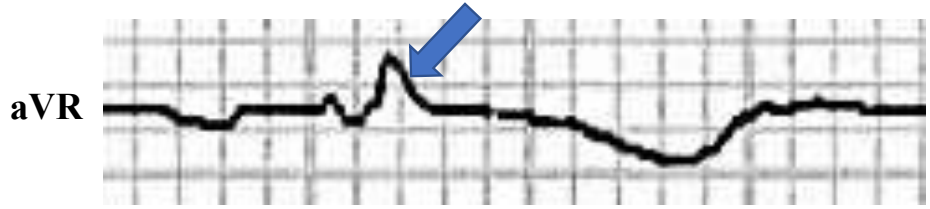
Inferior and lateral middle fibrosis cause reduction of S wave in inferior leads, hiding the typical LAFB pattern. The QRS axis in the upper right quadrant is consequence of association with inferolateral middle fibrosis + LAFB.

What supports the diagnosis of RBBB? Answer:

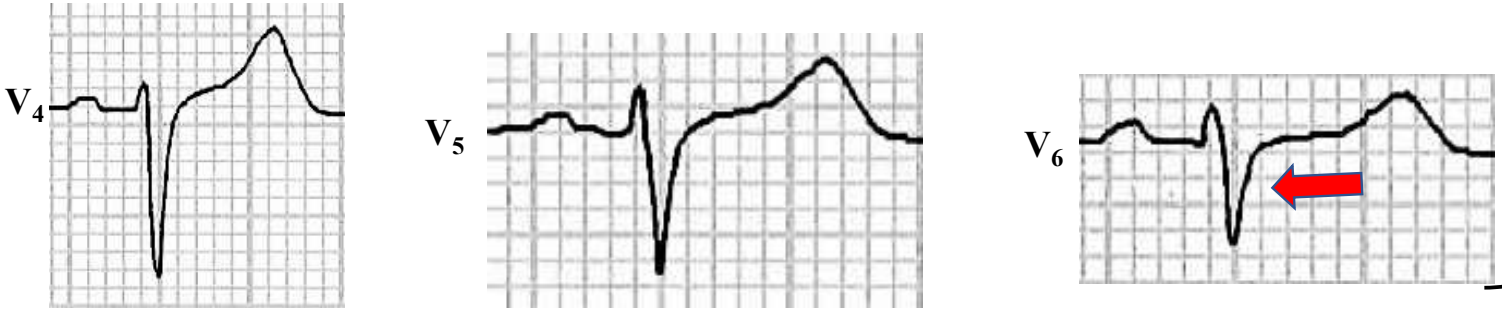
1. Triphasic QRS pattern in V1 (rsR') indicating predominant rightward forces



2. Triphasic pattern rsR' in aVR: broad final R wave indicating predominant rightward forces



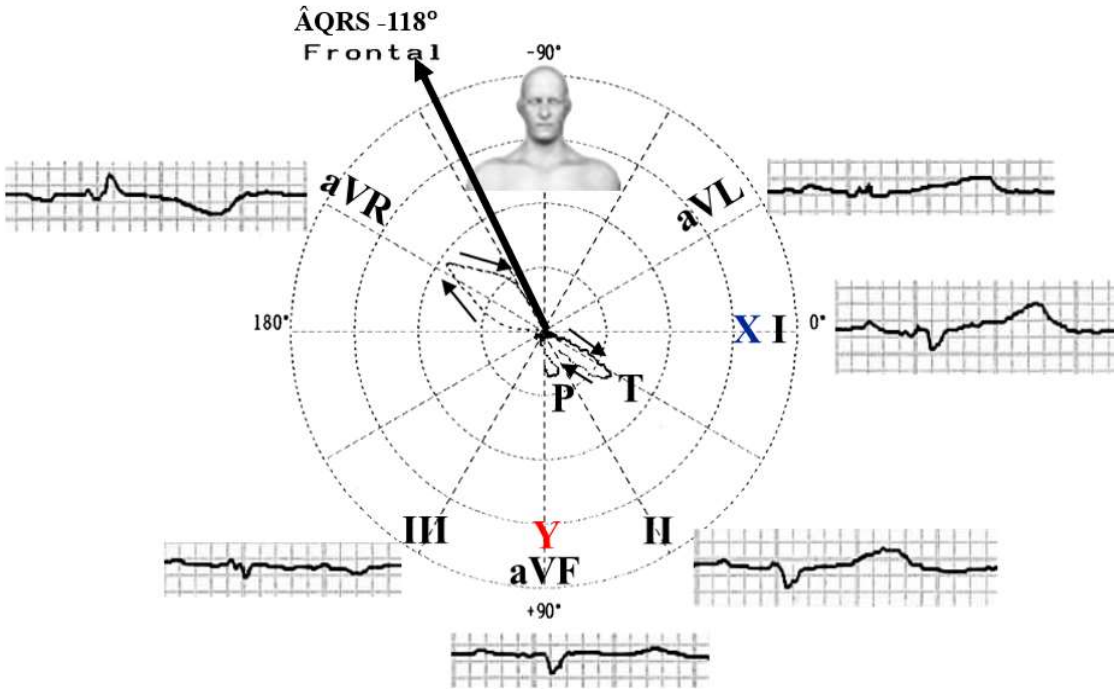
3. rS with broad final S wave in left precordial leads indicating predominant rightward forces



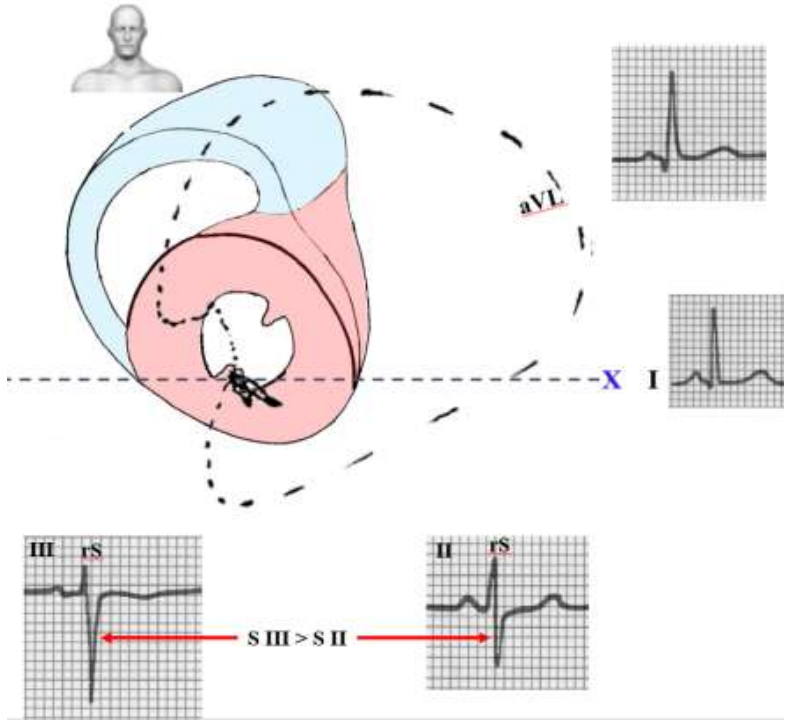
RBBB criteria

When RBBB and LAFB are present, ventricular activation occurs through the left septal (or middle septal) and left posterior fascicle; consequently, the initial 10 to 20 ms QRS vector is directed inferior, anteriorly and to the right: causing an initial small r wave in III and a q wave in left leads I and aVL. In the present case there is fibrosis in the inferolateral-septal-medial segment and subepicardium of the LV apex. Consequently, the small initial r wave in lead III and the q initial wave of I and aVL leads decrease or disappear as in the present case. Then; the stimulus is directed towards the anterolateral wall of the left ventricle and through the so-called "crossing zones of Rosembaum". However; the partial lateral fibrosis displaces the forces to the right (reinforced in the final part by the slow final forces of the RBB located to the right). This pathway behavior explains why the counterclockwise QRS loop of the FP is dislocated predominantly in the upper right quadrant and not the left superior quadrant as in isolated LAFB.

The present case

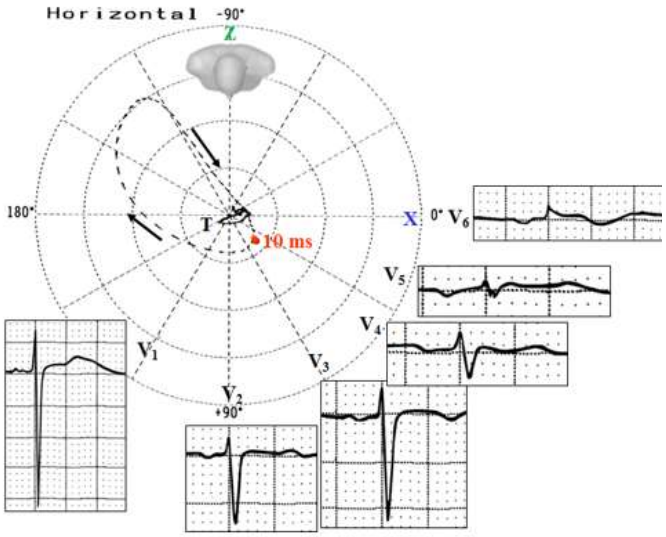


Isolated LAFB



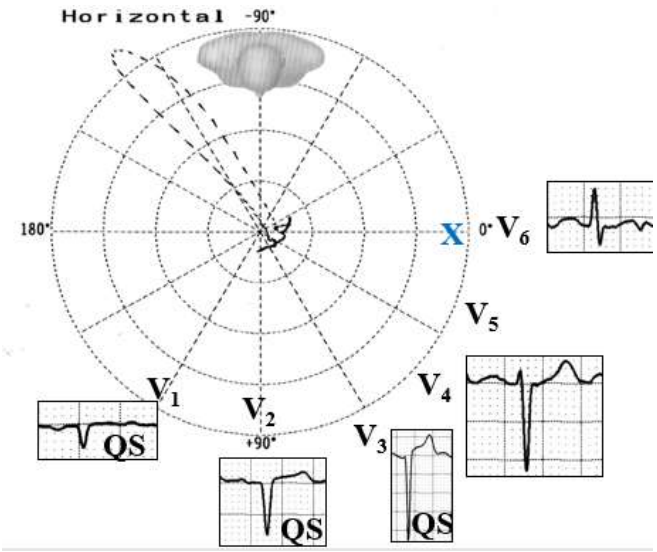
Comparative study with QRS loops of dextrocardia and RVH of type C of emphysema in the HP

Dextrocardia



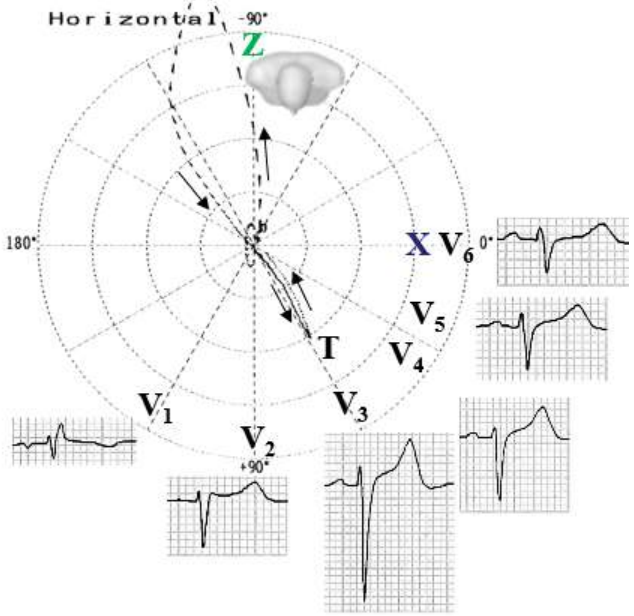
HP - The following stands out: initial 10 ms vector heading forward and to the left; QRS loop of clockwise rotation and predominantly located in the right posterior quadrant; reversed progression of the R wave in the precordial leads V_1 to V_6 (decreasing); maximal vector located in the right posterior quadrant; negative P wave in V_5-V_6; negative T wave in V_5-V_6.

RVH of type C or special



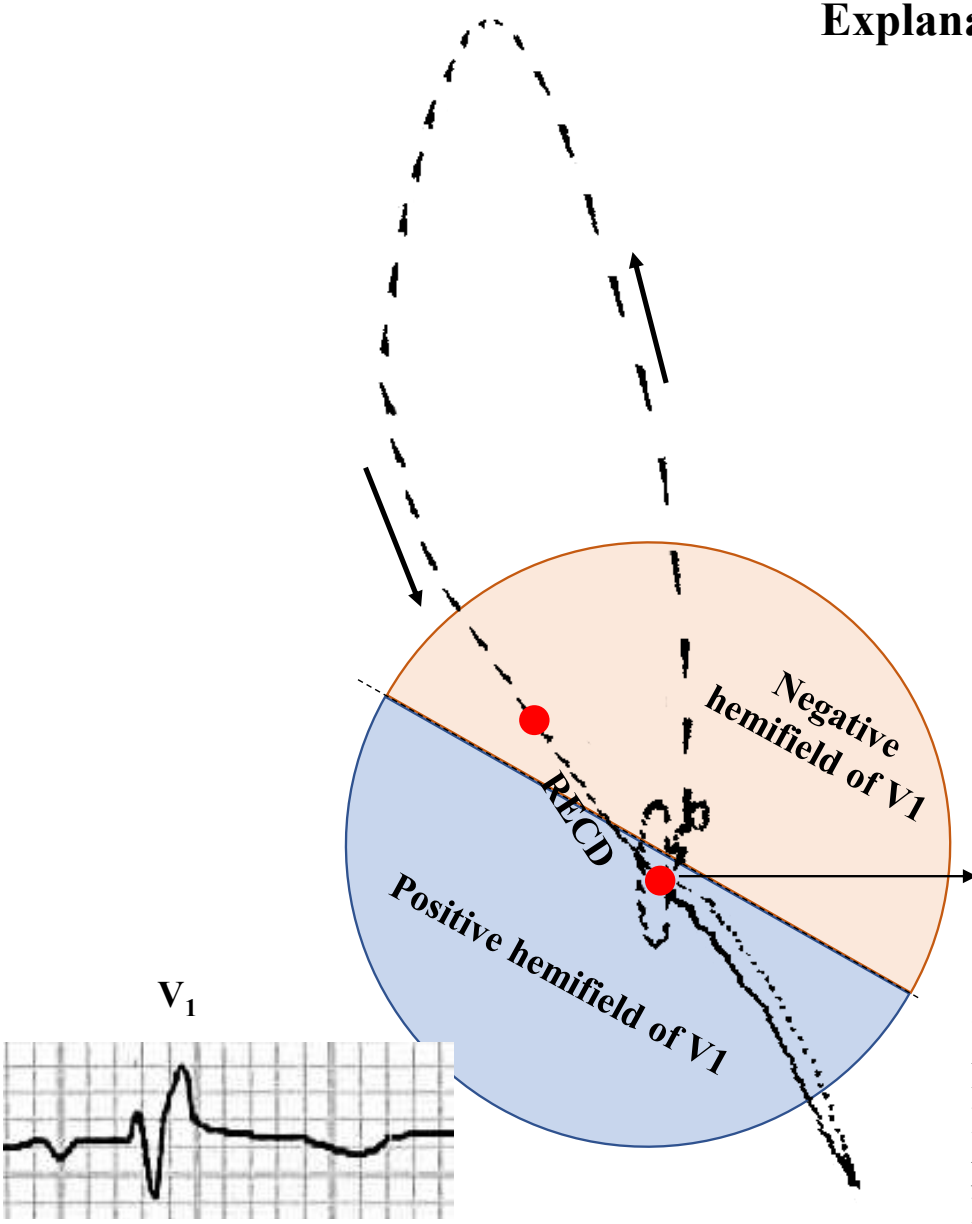
Characterized by: counterclockwise rotation or in eight, posterior shift: more than 70% of the area of the loop in posterior quadrants and more than 20% in the right posterior one. In this extreme case, 100% of the QRS loop is in the right posterior quadrant. QS pattern from V_1 to V_3: pseudo anteroseptal infarction, by the relatively high position of the precordial electrodes in relation to the height of the heart as a consequence of diaphragm descent pushed by hyperinsufflated lungs.
Tendency to low voltage in left precordial leads.

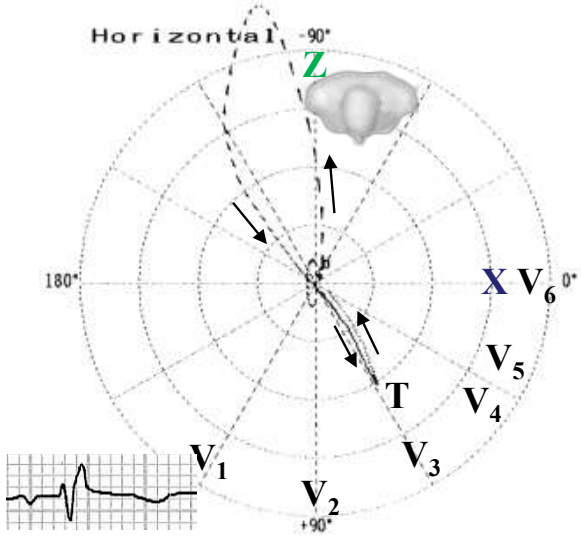
The present case



Atypical RBBB, transition R-wave progression (isodiphasic R/S ratio) not present across the unipolar precordial leads. This phenomenon could be attributed to clockwise rotation of the heart around the longitudinal axis, consequence of right ventricular hypertrophy, or intraventricular conduction disturbance associated with severe fibrosis.

Explanation of atypical RBBB





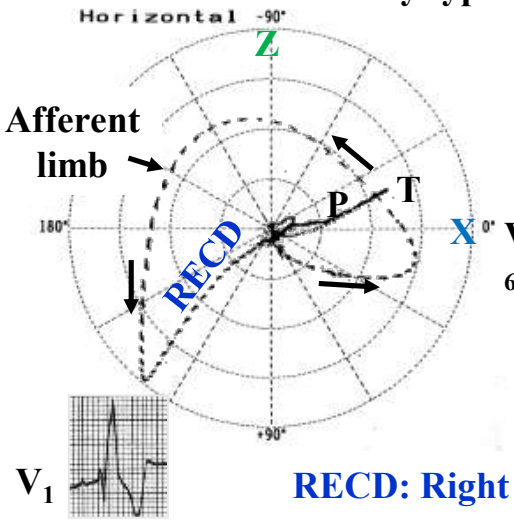
Triphasic QRS pattern in V1 (rsR') because R wave is located in the positive hemifield of V1.

RECD: Right End conduction delay (RBBB with atypical location on right posterior quadrant).

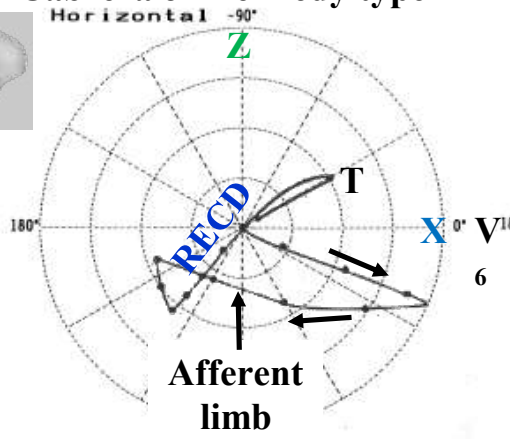
R' wave located in the positive hemifield of V1

Typical VCG variants of RBBB

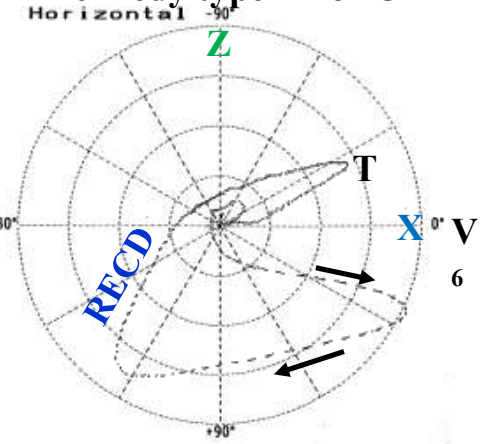
Grishman or Kennnedy type I



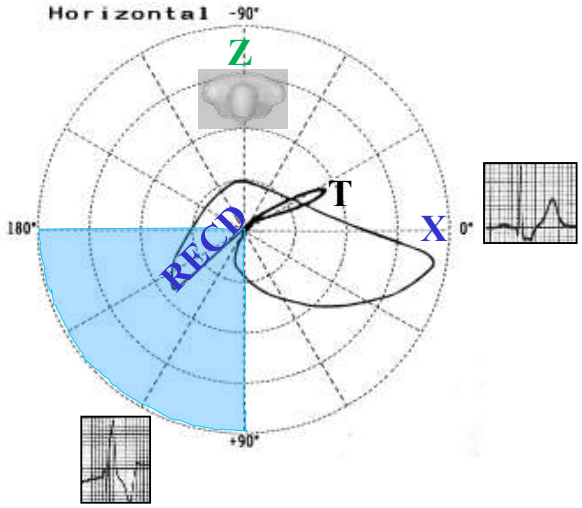
Cabrera or Kennedy type II



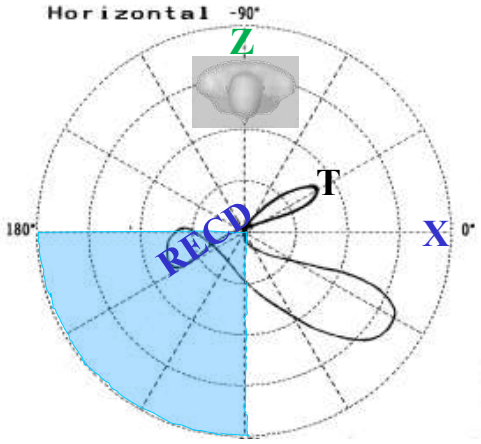
Kennedy type III or C



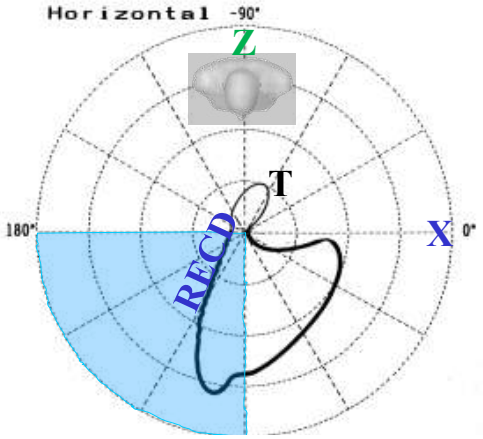
RECD: Right End Conduction Delay



Right Anterior Quadrant



We find type II in ASD, PS, in COPD and more rarely in chronic Chagasic myocardits.



Initial vector to the front, QRS loop of CW rotation and main body located in anterior quadrants.

In November 2015 (2 years and 2 months ago), a full electrophysiology study was made. It revealed sinus bradycardia (HR 57 bpm), normal sinus automaticity, and so was AV conduction. A discrete His-Purkinje system lesion was observed, with minimum prolongation of the HV interval (58 ms; normal value up to 55 ms). Intraventricular conduction presented conduction disorder through the right bundle branch associated to left anterior fascicular block. Ventricular repolarization was normal with the expected alterations secondary to repolarization with normal duration.

Ventricular stability test: Several programmed ventricular pacing protocols were conducted on the RV tip and RVOT, with no pharmacological sensitization (isoproterenol) with 3 different basic cycles of 500, 400 and 330 ms, with up to 3 extrastimuli. All these tests were normal.

Mapping: Mapping of the His bundle was made in a normal anatomical position. No anomalous bundles were identified.

Electrophysiology study with drugs

The pharmacological test was made with ajmaline (75 mg), displaying a good functional reserve of the His-Purkinje system and absence of type-1 Brugada pattern.

Main electrophysiology parameters: HR 57 bpm; PR interval 147 ms, QRS duration 116 ms, normal Wenckebach point 178 bpm (normal up to 180), corrected sinus node recovery time 486 ms (normal up to 500), PA interval 49 ms (normal up to 55), short AH interval 40 ms (normal between 55 and 125 ms), H potential or H-H' interval duration 25 ms (normal ≤35), HV or HQ interval 58 ms (normal up to 55 ms), AV anterograde refractory period 360 ms (normal of 250 to 400 ms), effective refractory period of the RV 220 ms (normal), normal QT interval.
Negative pharmacological test with ajmaline and ventriculo-atrial conduction present through normal pathways.
Negative ajmaline challenge for Brugada syndrome.

Conclusions

Normal sinus function.
Mild involvement of the His-Purkinje system, good reserve in the ajmaline test, conduction disorder through the right bundle branch, and left anterior fascicle: LAFB.
Stable ventricles, even after sensitization with isoproterenol.

Causes of Low QRS voltage in the frontal plane

The QRS is said to be low voltage when the amplitudes of all the QRS complexes in the limb leads are < 5 mm; or the amplitudes of all the QRS complexes in the precordial leads are < 10 mm. Lead V4 usually has the tallest R-wave amplitude. QRS voltage is measured from the nadir of the QRS complex to its peak. Low voltage often occurs in the frontal plane without low voltage in the precordial leads (voltage discordance). Voltage discordance is defined as a QRS amplitude ≤ 5 mmm present on the FP leads, while at least 2 contiguous precordial leads have voltages greater than 10 mm. Low voltage can be present on the initial ECG, or it can develop progressively over time due to changing conditions such as pericardial effusion or bleeding; comparison of serial ECGs is useful for the diagnosis of such conditions. Low voltage isolated to the limb leads is associated with the same conditions that cause diffuse low voltage in only half of patients. In the remainder, more than 60% have dilated cardiomyopathies (**Chinitz 2008**).

Possible causes

1. **Normal variant** In the absence of pathological cause, low-voltage QRS in the ECG can be caused by electrical malfunction of the recorder or cable connections, or it can be related to electrode misplacement and cable transposition (**Hannibal 2014**).
2. **Emphysema/chronic obstructive pulmonary disease (COPD):** Low voltages in the limb leads are classically seen in patients with emphysema. Other features of emphysema include: rightward QRS axis, peaked or peaked and tall P waves (P *pulmonale*) and clockwise rotation (persistent S wave in V6), RV afterload and BMI correlated with horizontal QRS-axis clockwise rotation. Increased airway obstruction and RV afterload mainly increase the Sokolow-Lyon Index for RV mass and associate with clockwise rotation of the horizontal QRS-axis, whereas emphysema reduces the QRS amplitudes. Body mass index (BMI) is an equally important determinant for the majority of the ECG changes (**Larssen 2017**).

Emphysema	Electrocardiographic features commonly related to COPD
Right-atrium enlargement (**Holtzman2011**)	P amplitude in II, III or aVF ≥2.5 mm ; P amplitude in V1 ≥1.5 mm (**Rodman 1990**)
RVH *(**Scott1955**)*	R in V1 ≥7 mm; R/S in V1 >1; VAT or R-wave peak time in V1 >35 ms
Sokolow-Lyon: RVH	R in V1 + S in V5 or V6 >10.5 mm (**Sokolow M, Lyon 1949**)
Low voltage limb leads	QRS (R+S) <5 mm in I, II, aVF, III (all)*
Low voltage precordial leads	QRS <10 mV in V1–V6 (all)

Clockwise rotation	R/S ratio in V5 ≤1
$S_1S_2S_3$ pattern	Dominant S in I, II, III (all) (**Rodman 1990**)
QS complex	Lead III
Right-axis deviation:	>90°
Left-axis deviation:	<-30° to −90°(**Rodman 1990**)
<-30° to −90° (**Rodman 1990**)	HR >80 beats/min**Minnesota Code (**Wright-PSG J 1982**)

1. **Left spontaneous pneumothorax (LSP):** characterized by sinus tachycardia, longer QTc interval, greater QRS and T axes. With regard to RS amplitudes, greater R in lead aVR and V1, and deeper S in lead II indicating predominant rightward forces, and smaller R in lead I and V3-V6 indicating inferior leftward forces. Of these ECG findings, heart rate, S voltage in lead II and R voltage in V1 in the large LSP but not in the small LSP had greater values than that in the unaffected group (**Liu 2017**).
2. **Chronic constrictive pericarditis (Fuster 1983)**
3. **Massive pericardial effusion (Anah 2011):** triad of low QRS voltage, tachycardia and electrical alternans
4. **Pleural effusion (Seashore 2015)**
5. **Constrictive pericarditis (Durmus 2013)**
6. **Addison 's disease (Dubiel 1972)**
7. **Myocardial atrophy (Hellerstein 1950)** It is a decrease in the size, strength, weight, and activity of the heart. Causes: mitral stenosis (gives rise to a local atrophy, the left ventricle being the part affected). Caquexia, hyponutrition, anorexia nervosa, cancer, senile atrophy, phthisis pulmonalis, chronic suppurative processes
8. **Endocardial fibroelastosis (Arya 2012)** refers to a pronounced, diffuse thickening of the ventricular endocardium and presents as unexplained heart failure in infants and children. The disease can be primary or secondary to various congenital heart diseases, most notably hypoplastic left heart syndrome, aortic stenosis, or atresia. Reduced electrical potentials may occasionally be encountered. Such factor as myocardial anoxia, pleuropericardial effusion or edema due to cardiac failure in its terminal stage may be responsible for low QRS voltage (**Vlad 1955**).

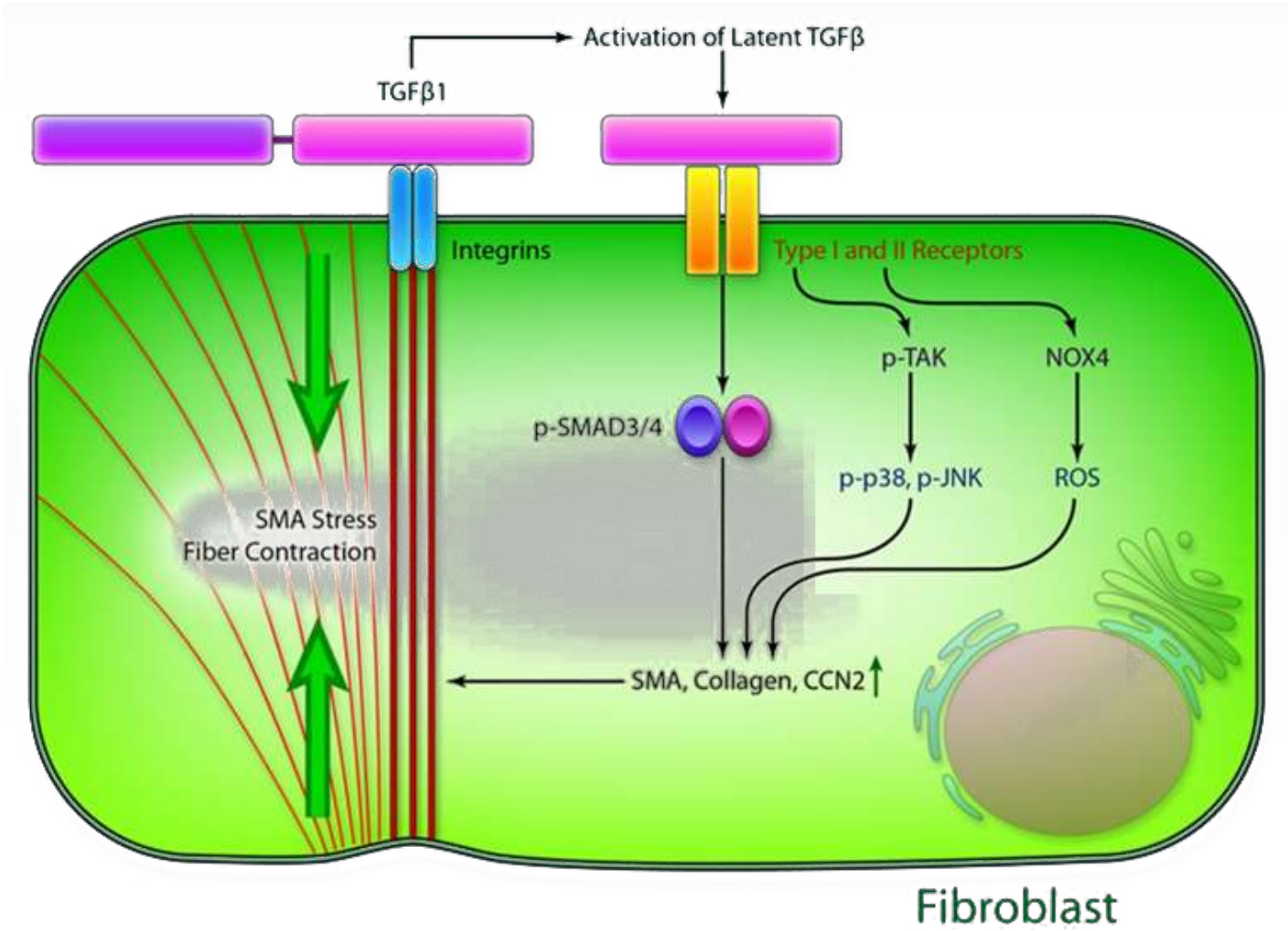
1. **Cardiac sarcoidosis (Roberts 2018; Seward 2010).** Low-voltage QRS complex is not a uniform finding with the infiltrative cardiomyopathies. The clinical presentation, along with functional and morphologic features, often provides enough insight to establish a working diagnosis. In most circumstances, however, tissue or serologic evaluation is needed to validate or clarify the cardiac diagnosis and institute the appropriate therapy (Seward 2010).
2. **Cardiac Amyloidosis (Sangal 2017; Mussinelli 2013)** Low-voltage QRS complex was the sine qua non of infiltrative cardiomyopathy (i.e., cardiac amyloid). In cardiac AL amyloidosis, myocardial infiltration is typically associated with low QRS voltages at the ECG. Although considered as one of the hallmarks of the disease, its reported prevalence varies from 45% to 70%, mainly because of nonhomogeneous definitions. Low voltage is a relatively late finding in cardiac amyloidosis and may not be useful for early identification (Cyrille 2014).
3. **Coronary artery disease** Low QRS voltage was reported to predict adverse outcomes in AMI in the pre-thrombolytic era. Low QRS voltage is associated with multi-vessel disease and in-hospital CABG in anterior STEMI (Kobayashi 2017).
4. **Previous massive myocardial infarction** Diffuse loss of R wave height suggests extensive myocardial loss from a prior anterior MI. (Madias 2008)
5. **End-stage dilated cardiomyopathy (Brieler 2017)**
6. **Myocarditis (Madias 2007)**

14. **Morbid obesity (da Costa 2008).** Electrocardiographic features occurring with significantly higher frequency in morbidly obese patients are low QRS voltage, leftward shift of the P, QRS, and T axes, left ventricular hypertrophy and left atrial enlargement. None of voltage-based ECG criteria are of value for LVH. Only Romhilt-Estes score and Cornell indices could be helpful for the identification of LVH in the group of patients with morbid obesity (Alpert 2000), but their value is far from being satisfactory (Domienik-Karłowicz 2011).
15. **Myocardial fibrosis:** Diffuse myocardial fibrosis interferes with ECG voltage measures. There is a positive relationship between ECG voltage amplitude and LVMI as well as an inverse relationship between ECG voltage amplitude and myocardial extracellular volume fraction (Maanja 2017). This phenomenon could explain the decreased sensitivity of LVH detectable by ECG, a fundamental diagnostic tool in cardiology. Fibrotic diseases are a significant global burden for which there are limited treatment options. The effector cells of fibrosis are activated fibroblasts called myofibroblasts, a highly contractile cell type characterized by the appearance of α-smooth muscle actin stress fibers. The underlying mechanism behind myofibroblast differentiation and persistence has been under much investigation and is known to involve a complex signaling network involving transforming growth factor-β, endothelin-1, angiotensin II, CCN2 (connective tissue growth factor), and platelet-derived growth factor (Leask 2015).

Cardiac fibrosis, characterized by the excessive production and deposition of scar tissue, is often a result of conditions such as hypertension. diabetes mellitus myocardiopathies and myocarditis. The cells ultimately responsible for the development of scar tissue are mesenchymal cells resident within connective tissue called myofibroblasts, which possess the highly contractile protein α-smooth muscle actin (α-SMA) (**Gabbiani 2003**). In myofibroblasts, α-SMA is assembled into stress fibers that can remodel the surrounding extracellular matrix (ECM) because they are connected to ECM through specialized cell surface structures called focal adhesions (**Gabbiani 2003**). In the diseased heart, cardiomyocytes are lost to necrotic cell death, and myofibroblasts are activated to initiate a reparative fibrosis. The adult mammalian heart has negligible regenerative capacity, and thus, normal cardiac repair, is dependent on the clearance of dead cells and on the formation of a scar tissue to help preserve heart integrity. Conversely, a hyperactive repair program has been hypothesized to cause pathological fibrosis. A complex interaction among a network of growth factors/cytokines and hormones is responsible for initiating and maintaining fibrotic responses in vivo. In particular, angiotensin II (Ang-II), endothelin-1 (ET-1), transforming growth factor-β (TGF-β), and platelet-derived growth factor (PDGF) work together to induce activation of resident interstitial fibroblasts, promote persistence of myofibroblasts and induce the expression of a wide variety of ECM components, including collagen type I (**Leask 2010**). The ultimate origin of myofibroblasts is unclear, but it could result from a variety of processes including growth factor–mediated differentiation of resident mesenchymal cells, recruitment of pericyte-like progenitor cells, or by epithelial–mesenchymal transition (**Hinz 2012**). The cellular microenvironment also plays a critical role in promoting pathological responses to these growth factors/cytokines and hormones. For example, the role of elevated mechanical loading/tension and elevated proadhesive signaling, promoted by matricellular proteins, such as CCN2 or connective tissue growth factor, seems to be extremely important (**Leask 2010**). Matricellular proteins are nonstructural ECM components that modulate growth factor responses to aging, mechanical loading, and regeneration, and hence, they promote angiogenesis, inflammation, tissue repair, and fibrosis (**Frangogiannis 2012**). As a result of this complexity, the appropriate intervention points to base rational antifibrotic therapies remain unclear.

Transforming Growth Factor-β

There are 3 TGF-β ligands, TGF-β1, TGF-β2, and TGF-β3. TGF-β1 expression is upregulated in both normal tissue repair and pathological fibrosis (**Leask 2004**). TGF-β1 is initially produced as a secreted latent form, which is proteolytically activated in a fashion that involves integrin-mediated ECM contraction (**Sarrazy 2014**). Once activated, TGF-β binds to TGF-β type I and TGF-β type II receptors. The TGF-β type I receptor is a kinase, and in the case of fibroblasts, it is termed activin-linked kinase (ALK) 5. ALK5 phosphorylates Smad2 and 3; phosphorylated Smad2/3 bind to Smad4, translocate into the nucleus, and activate gene transcription. In addition to this so-called canonical pathway, TGF-β activates noncanonical signaling pathways(eg, mitogen-activated protein kinase pathways) that appear to modify gene expression in a promoter-specific fashion (**Trojanowska 2009**)

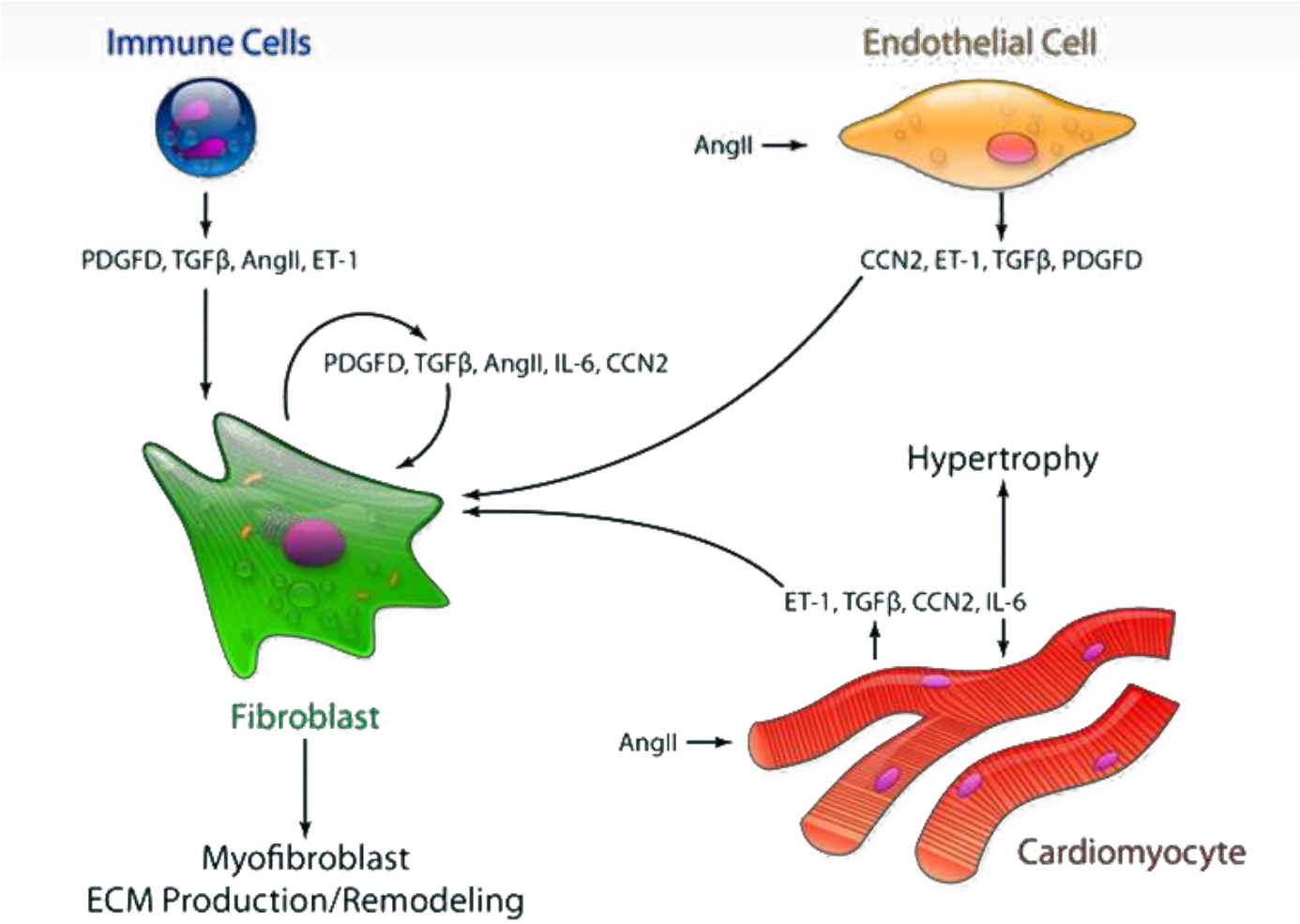


Transforming growth factor-β (TGF-β) signaling in fibroblasts. TGF-β is a major fibrogenic cytokine. Latent TGF-β is released by integrin-mediated contraction, binds to its type I and II receptors, and activates the canonical Smad3/4 pathway and the noncanonical TGF-β–activated kinase-1 (TAK1)/p38/c-Jun N-terminal kinase (JNK) and NADPH oxidase 4 (NOX4)/reactive oxygen species (ROS) pathway resulting in induction of fibrogenic genes, such as α-smooth muscle actin (α-SMA), collagen, and CCN2. Myofibroblasts may perpetuate their fibrotic phenotype at least in part via this pathway (illustration credit: Ben Smith).

Transforming growth factor beta (TGF-β) is a multifunctional cytokine belonging to the transforming growth factor superfamily that includes four different isoforms (TGF-β 1 to 4, HGNC symbols TGFB1, TGFB2, TGFB3, TGFB4) and many other signaling proteins produced by all white blood cell lineages. Activated TGF-β complexes with other factors to form a serine/threonine kinase complex that binds to TGF-β receptors, which is composed of both type 1 and type 2 receptor subunits. After the binding of TGF-β, the type 2 receptor kinase phosphorylates and activates the type 1 receptor kinase that activates a signaling cascade. This leads to the activation of different downstream substrates and regulatory proteins, inducing transcription of different target genes that function in differentiation, chemotaxis, proliferation, and activation of many immune cells. TGF-β promotes ECM deposition by upregulating ECM and tissue inhibitors of matrix metalloproteinase (TIMP) gene expression and suppressing matrix metalloproteinase (MMP) gene expression. In cell adhesion and integrin-dependent fashion, TGF-β causes fibroblasts to differentiate into myofibroblasts (**Thannickal 2003**). Dermal wounds treated with anti-TGF-β strategies (eg, antibodies or antisense oligonucleotides) show reduced ECM and scar tissue deposition (**Cordeiro 2003**). Similarly, Smad3-deficient mice display accelerated rates of cutaneous wound healing, decreased granulation tissue formation, and reduced inflammation (**Flanders 2002**). Fibroblasts derived from Smad3-deficient mice are relatively resistant to the ability of TGF-β to induce collagen and other ECM genes (**Yang 2003**).

The canonical TGF-β pathway contributes to cardiac fibrosis. In the border zone of healing infarcts, the TGF-β/Smad3 pathway is activated and induces remodeling (**Dobaczewski 2010**). In cardiac fibrosis and remodeling, TGF-β is initially derived from immune cells and is subsequently produced by myofibroblasts (**Thannickal 2003**). In cultured cardiac fibroblasts, the ability of TGF-β to induce procollagen type III and tenascin-C depends on Smad3, and Smad3-deficient hearts are relatively resistant to interstitial fibrosis (**Bujak 2007**). TGF-β1 inhibition of cardiac fibroblast proliferation requires Smad3 (**Dobaczewski 2010**). Moreover, TGF-β1 induction of collagen lattice contraction and α-SMA expression also requires Smad3 (**Dobaczewski 2010**). Finally, TGF-β prevents cardiac fibroblast apoptosis in response to infarction through Smad3 and also extracellular signal–regulated kinases 1/2 and Akt (**Vivar 2013**). Intriguingly, in cardiac fibrosis observed postmyocardial infarction, decreased miR-24 expression exists in hypertrophic hearts; in cardiac fibroblasts, TGF-β increases miR-24 expression, whereas overexpression of miR-24 reduces TGF-β secretion and Smad2/3 phosphorylation. The likely target of miR-24 is furin, a protease that is implicated in processing of latent TGF-β (**Wang 2012**). In the canonical pathway, the three TGF-β ligand isoforms, TGF-β1, TGF-β2, and TGF-β3, are synthesized as precursors and bind to form the latent TGF-β complex before being secreted (**Derynck1985**.) After extracellular activation, TGF-β ligands bind to the membranous TGF-β type III receptor or the TGF-β type II receptor (TGF-βRII) homodimers with high affinity. TGF-βRII binding allows dimerization with TGF-β type I receptor (TGF-βRI) homodimers, activation of the TGF-βRI kinase domain and signal transduction via phosphorylation of the C-terminus of receptor-regulated SMADs (R-SMAD), SMAD2 and SMAD3. The TGF-βR dimer then forms a heterotrimeric complex with SMAD4 which translocates and accumulates in the nucleus (**Ross2008**). TGF-β dependent signalling can activate or

repress hundreds of target genes through the interaction of SMADs with various transcription factors (TF). SMAD activities are regulated through several mechanisms: SMAD2/3 nucleocytoplasmic shuttling, binding to anchor proteins such as SARA, phosphorylation (e.g., by ERK, JNK, and p38 MAPK), Smurf (SMAD-ubiquitination-regulatory factor)-dependent degradation, or via expression of inhibitory SMAD6 and SMAD7 (**Inman 2002**). In the non-canonical pathway, TGF-β signalling activates SMAD-independent pathways such as PI3K/AKT, MAPK pathways (ERK, JNK, and p38 MAPK) as well as NF-κB, Rho/Rac1, Cdc42, FAK, Src, Abl (**Derynck 2003**). Moreover, transversal signaling, especially at the SMAD level, allows TGF-β pathway activation to integrate signals from integrins, Notch, Wnt, TNF-α, or EGF-dependent pathways as well as signals from cellular processes such as the cell cycle or apoptosis machineries (**Bierie 2006**). The TGF-β signaling pathway thus has pleiotropic functions regulating cell growth, differentiation, apoptosis, cell motility, extracellular matrix production, angiogenesis and cellular immune response (**Yingling 2004**).



Cellular interactions in cardiac fibrosis. The cells involved with the interactions. Note that profibrotic proteins can originate from several different sources; however, the final effector cell of scarring is the myofibroblast. Ang-II indicates angiotensin II; ECM, extracellular matrix; ET, endothelin-1; IL, interleukin; PDGFD, platelet-derived growth factor D; and TGF-β, transforming growth factor-β.

ALK5 inhibitors have been developed as potential antifibrotic agents. In a rat coronary artery ligation model of myocardial infarction, the ALK5 inhibitor GW 788388 decreased TGF-β activity and reduced both systolic dysfunction and left ventricular (LV) remodeling (**Tan 2010**). Similarly, the ALK5 inhibitor SM16 attenuated pressure load–induced fibrosis in vivo and TGF-β–induced Col1a2 and lysyl oxidase expression in vitro (**Engebretsen 2014**). However, although SM16 treatment improved diastolic function and cardiac output, this compound also caused a significant increase in inflammatory heart valve lesions (**Engebretsen 2014**). Neutralizing anti-TGF-β antibodies, when used in a model of experimental myocardial fibrosis, decreased fibroblast activation and collagen mRNA expression, but did not appreciably affect myocyte hypertrophy, blood pressure, and systolic function (**Kuwahara 2002**). In a related yet separate study, neutralizing anti-TGF-β antibodies decreased collagen production and increased matrix metalloproteinase expression but worsened vascular remodeling and resulted in increased mortality (**Frantz 2008**). Collectively, these data obtained using both ALK5 inhibitors and anti-TGF-β antibodies provide support for the idea that targeting the canonical TGF-β signal pathway might not be viable clinically.

Instead of blocking canonical TGF-β signaling, a better alternative might be to block noncanonical signaling pathways. For example, TGF-β activates TGF-β–activated kinase (TAK) 1, a mitogen-activated protein kinase kinase kinase. Supporting the hypothesis that TAK1 contributes to cardiac fibrosis, it has been shown that TAK1 is activated in cardiomyocytes after pressure overload generated by aortic constriction and that cardiac-specific overexpression of activated TAK1 in mice causes cardiac hypertrophy and heart failure (**Zhang 2000**). In addition, dominant negative TAK1 inhibits TGF-β–induced hypertrophic events in mouse cardiomyocytes and fibroblasts, including ECM production (**Ono 2003**). One of the targets of TAK1 is p38; p38 is activated in heart failure evolving in response to sustained hemodynamic overload and contributes to cardiac fibrosis (**Yan 2009**). Another noncanonical pathway may involve the generation of reactive oxygen species. Matrix remodeling by TGF-β is amplified by increases in oxidative stress; TGF-β induces myofibroblast differentiation in cardiac fibroblasts via NADPH oxidase (NOX) 4 (**Cucoranu 2005**). In myxomatous mitral valve disease in humans, elevated oxidative stress is observed associated with increases in NOX2 and 4 (**Hagler 2013**). Treatment of cardiac fibroblasts with small interfering RNA against NOX4 suppresses the expression of TGF-β target genes, including fibronectin, collagen I, α-SMA, and CCN2, indicating that NOX4 was involved in TGF-β–induced myofibroblast differentiation (**Cucoranu 2005**). TGF-β activates noncanonical signaling pathways, including the mitogen-activated protein kinase members c-Jun N-terminal kinase and p38. As c-Jun N-terminal kinase and p38 are redox sensitive and can be activated by reactive oxygen species in the cytoplasm, it is possible that reactive oxygen species may activate these pathways and augment the TGF-β signaling response (**Jiang 2011**). Collectively, these data suggest that targeting TAK1 or NOX4 downstream of TGF-β might be viable antifibrotic approaches.

Angiotensin II

The levels of Ang-II, an oligopeptide that causes vasoconstriction and increased blood pressure, are elevated in fibrotic hearts (**Schnee 2000**). In rats with myocardial fibrosis, Ang-II is both expressed and activated by macrophages and myofibroblasts (**Sun 1994**). In cardiac myocytes and fibroblasts, Ang-II induces expression of TGF-β1 through the angiotensin type 1 receptor (**Campbell 1997**), and, in vivo, TGF-β is required for Ang-II to cause both cardiac hypertrophy and fibrosis (**Schultz 2002**). Indeed, in cardiac fibroblasts, Ang-II induces expression of collagen through TGF-β/Smad3 and extracellular signal–regulated kinase by an interleukin 6 (IL-6)–dependent mechanism (**Ma 2012**). The ability of Ang-II to induce IL-6 expression also seems to involve nuclear factor κB activation (**Xu 2011**). Supporting the idea that IL-6 is important for the fibrogenic function of Ang-II is a recent publication showing that IL-6 knockout mice, although not displaying altered development of Ang-II high salt–induced hypertension and cardiac hypertrophy, were resistant to Ang-II–induced cardiac dysfunction, myocardial inflammation, and fibrosis (**González 2015**).

Another mechanism underlying the fibrotic ability of Ang-II may involve miR-29b. Loss of miR-29b occurs in cardiac fibrosis; in vitro knockdown of miR-29b enhances whereas overexpression of miR-29b inhibits Ang-II–induced collagen type I and α-SMA expression (**Zhang 2014**). The basis of this observation may be that miR-29b targets a sequence within the TGF-β1 coding region (**Zhang 2014**). Ang-II suppresses both miR-29b and miR-133a in vivo; mutation of miR-133a binding sites in the 3′-UTR of Col1A1 mRNA abolished miR-133a–mediated repression of reporter gene activity, showing that Col1A1 is a bona fide target of miR-133a (**Castoldi 2012**). Collectively, these data are consistent with the hypothesis that Ang-II is upstream of TGF-β and IL-6 in driving cardiac fibrosis.

Angiotensin receptor inhibitors, such as losartan, are effective in reducing cardiac fibrosis in both animals and humans (**De Mello 2006**). Losartan inhibits endothelial-to-mesenchymal transformation in mitral valve endothelial cells by blocking TGF-β–induced phosphorylation of extracellular signal–regulated kinase (**Oliveira-Junior 2014**). Moreover, losartan attenuates obesity-induced metabolic and cardiovascular changes (**Wylie-Sears 2014**). Importantly, in a small study, losartan was shown to diminish progression of myocardial hypertrophy and fibrosis in patients with nonobstructive hypertrophic cardiomyopathy (**Shimada 2013**). The protective effects of losartan may be due, in part, to its ability to suppress cardiac fibrosis.

Endothelin-1: ET-1, cleaved to a physiologically active peptide by endothelin-converting enzyme, is the significant endothelin isoform in humans and possesses powerful promitogenic and vasoconstriction activities. ET-1 activates the endothelin-A (ETA) and the endothelin-B (ETB) receptors and is predominantly produced by endothelial cells, macrophages, cardiomyocytes, and fibroblasts (**Dashwood 2011**). Through the ETA receptor, ET-1 decreases DNA synthesis and increases collagen production in cardiac fibroblasts (**Hafizi 2004**). In isolated valves, ET-1 increases compliance of aortic cells but does not effect cells on the ventricular side of the valves, consistent with the observation that cells on the aortic side possess elevated levels of actin protein (**Miragoli2014**). Myofibroblasts cultured from explants of scar tissue resulting from MI scars produce increased levels of ET-1, endothelin-converting enzyme-1, and the ETA and ETB receptors; these cells, in an endothelin-dependent manner, also significantly overexpress type I collagen protein (**Katwa 2003**). In vivo, in a rat model of myocardial ischemia and reperfusion, bosentan (a dual endothelin receptor antagonist used in the treatment of pulmonary artery hypertension) slightly improved hemodynamic effects, decreased myocardial O_2 consumption, significantly reduced the percentage area of fiber loss and infarct area (**Singh 2006**). In a similar model, the ETA/B bosentan showed a protective effect as assessed by histological evaluation of the myocardium and also attenuated myocardial oxidative stress (**Gupta 2005**). Aditionally, bosentan reduced hypertrophy and fibrosis, including collagen deposition in animal models of heart disease (**Choudhary 2011**). The development of cardiac fibrosis and hypertrophy in response to Ang II is impaired in mice with vascular endothelial cell–specific ET-1 deficiency (**Adiarto 2012**). These results are consistent with observations that Ang-II induces ET-1 via extracellular signal–regulated kinase and reactive oxygen species and the serum-responsive transcription factor myocardin-related transcription factor (MRTF) A (**Weng 2014**). MRTF-A is recruited to the ET-1 promoter by c-Jun/c-Fos (activator protein 1) in response to Ang-II treatment; moreover, MRTF-A deficiency improved Ang-II–induced cardiac hypertrophy and fibrosis in mice (**Weng 2014**). ET-1 increases nuclear enrichment and activity of MRTF-A in cultured vascular SMCs; furthermore, MRTF-A silencing attenuated ET-1–induced synthesis and release of proinflammatory mediators, including IL-6 and monocyte chemoattractant protein-1 (**Yang 2014**). Thus, ET-1 and MRTF-A are likely to work in a feed-forward manner to promote inflammation and fibrogenic activity. Initial reports in humans showed that short-term administration of bosentan to patients with severe heart failure resulted in hemodynamic and cardiac benefits (**Sütsch 1998**). However, a series of randomized controlled clinical trials examining the effects of ET receptor antagonists on coronary artery disease and heart failure have not generated positive results; in many studies, endothelin receptor antagonism resulted in harmful effects, generally attributable to enhanced fluid retention (**Rodríguez-Pascual 2014**). For example, the ETA antagonist darusentan, in the Endothelin A Receptor antagonist Trial in Heart failure study (EARTH), or enrasentan (a dual ET_A/ET_B antagonist) did not show any favorable effects, despite improved hemodynamics (**Prasad 2006**). These divergent results could occur because of the bioavailability or stability of the drugs thus far developed (ie, they arose because of compound class effects) or to the differences between acute and chronic disease models (ie, they arose because of the indications examined). Thus, it is unclear at present whether ET-1 and its receptors represent viable antifibrotic therapeutic targets.

CCN2(connective tissue growth factor, CTGF)

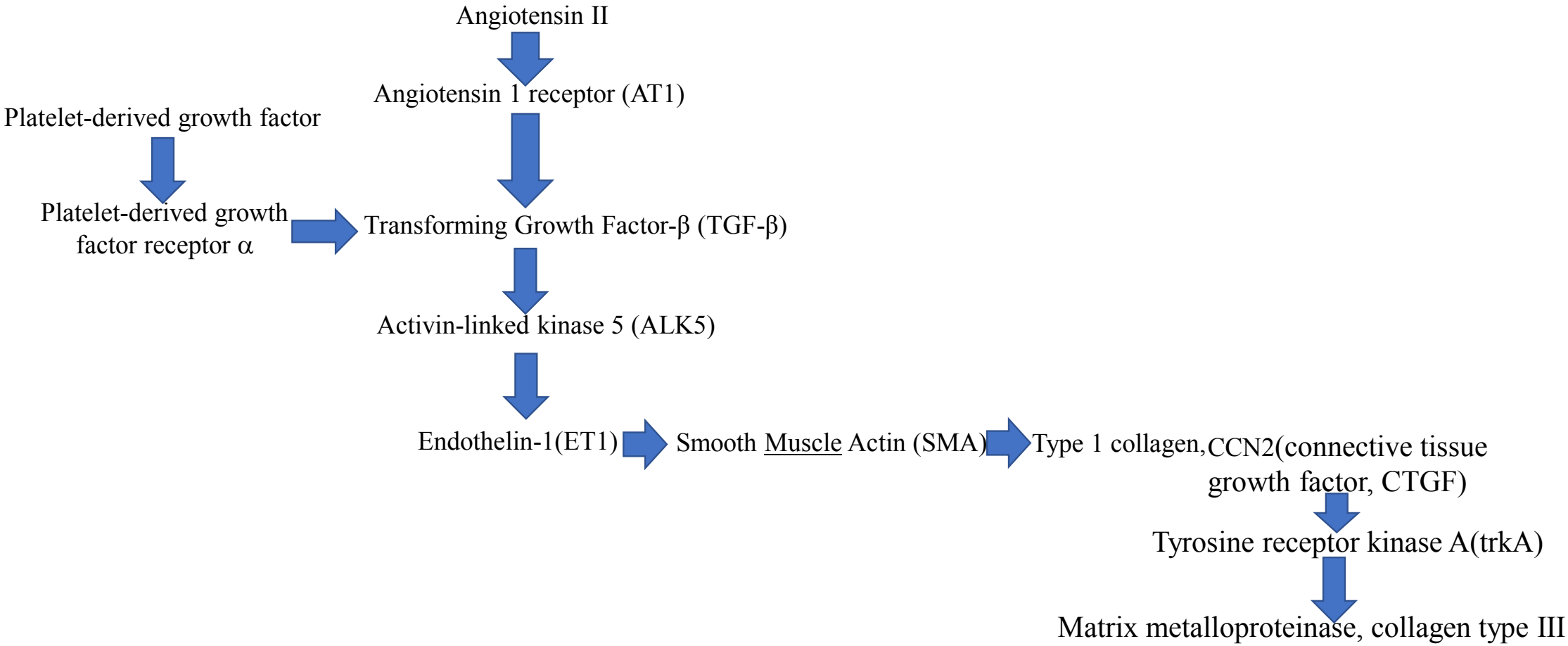
It is a matricellular protein of the CCN family of extracellular matrix-associated heparin-binding proteins. CTGF has important roles in many biological processes, including cell adhesion, migration, proliferation, angiogenesis, skeletal development, and tissue wound repair, and is critically involved in fibrotic disease. Fibrosis is a common feature of several chronic diseases, and is characterized by exacerbated accumulation of extracellular matrix (ECM) (**Riquelme-Guzman 2017/8**). Matricellular proteins are highly spatiotemporally regulated nonstructural components of the ECM that, in a context-dependent fashion, modulate cellular responses to signaling molecules, such as cytokines and ECM components (**Murphy-Ullrich 2014**). Formerly referred to as connective tissue growth factor, CCN2, a member of the CCN family of matricellular proteins, is upregulated in fibroblasts in response to TGF-β and is overexpressed in fibrotic disease, including those caused by myocardial infarction, diabetes mellitus, tumors, muocarditis and hypertrophy (**Tsoutsman 2013**). In animals exposed to Ang-II, myocardial CCN2 mRNA peaked at 6 hours, whereas TGF-β peaked at 3 days compared with saline control (**Rosin 2013**). CCN2 expression occurred before fibrocyte migration (1 day) into the myocardium or ECM deposition (3 days). CCN2 protein expression was observed localized to resident cells by day 3 of Ang-II exposure (**Rosin 2013**). Ang-II, when exposed to cultured cardiomyocytes and microvascular endothelial cells, caused an increase in CCN2 expression that was blocked by an anti-TGF-β–neutralizing antibody (**Rosin 2013**). Indeed, in atrial fibroblasts, Ang-II increases CCN2 expression via mitogen-activated protein kinases/TGF-β1/tumor necrosis factor receptor–associated factor 6 pathway (Gu 2012). Intriguingly, in uninjured hearts, CCN2 is specifically localized to endothelial cells (**Lang 2008**). In several studies, it has been shown that CCN2 promotes the fibrogenic activity of TGF-β, likely through promoting adhesive signaling (**Wang 2011**).

CCN2 both in vitro and in vivo causes hypertrophy of rat cardiomyocytes (**Panek 2009**). Expression of CCN2 mRNA is induced by both high glucose and palmitate in H9c2 cells and in mouse neonatal cardiomyocyte primary cultures. Small interfering RNAs against CCN2 reduced the abilities of high glucose and palmitate to induce hypertrophy and apoptosis. These CCN2 effects were shown to rely on the activity of the tyrosine kinase A receptor that has previously been implicated in CCN2-dependent signaling (**Wang 2009**). CCN2 silencing using small interfering RNA of activated primary cardiac fibroblasts resulted in strongly reduced expression of stretch-induced chemokines (Ccl2, Ccl7, and Ccl8), matrix metalloproteinases (MMP2 and MMP9), ECM (Col3a1), and a cell-to-cell contact protein (Cx43) (**Tank 2014**). Ang-II–induced expression of hypertrophic marker genes or collagens was not affected by treatment with anti-CCN2 monoclonal antibodies, whereas anti-CCN2 monoclonal antibodies caused resistance to adverse LV remodeling and LV dysfunction in hearts resulting from pressure overload caused by thoracic aortic constriction. Conversely, when a thoracic aortic constriction model was used, anti-CCN2 antibodies reduced both collagen levels and hypertrophic marker gene expression, reduced cardiomyocyte crosssectional area and LV dilatation, and preserved LV systolic function (**Szabó 2014**). Collectively, these results indicate that, in cardiac fibrosis, strategies targeting CCN2 might be considered.

Platelet-Derived Growth Factor

PDGF consists of a complex family of homodimeric or heterodimeric growth factors, including PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD. These collectively signal through 2 PDGF receptors, α and β (**Grimminger 2010**). After myocardial infarction, PDGF-A and D are significantly increased in endothelial cells, macrophages, and myofibroblasts. Enhanced PDGF-A, PDGF-D, and PDGF receptors are coincident with angiogenesis and inflammatory and fibrogenic responses in the infarcted myocardium, suggesting their regulation on cardiac repair (**Zhao 2011**). Transgenic mice overexpressing the active core domain of PDGF-D in the heart displayed enhanced proliferation of both cardiac interstitial fibroblasts and arterial vascular smooth muscle cells resulting in cardiac fibrosis followed by dilated cardiomyopathy and, subsequently, cardiac failure (**Pontén 2005**). In vitro, PDGF-D significantly enhanced TGF-β1 synthesis, which was eliminated by TGF-β blockade with small interfering RNA; moreover, the stimulatory role of PDGF-D on fibroblast proliferation and collagen synthesis was abolished by TGF-β blockade (**Zhao 2013**). In infarcted heart, the perivasculature and mononuclear-like cells show activation of the PDGF signaling pathway (**Zymek 2006**). This pattern is interesting given the potential involvement of pericyte activation as source of activated myofibroblasts in fibrosis (**Hinz 2012**). Injection of a neutralizing PDGF receptor α–specific antibody attenuated atrial fibrosis in pressure-overloaded hearts, whereas PDGF-AA stimulated both atrial fibrosis and fibrillation in normal hearts (**Liao 2010**). In infarcted heart, TGF-β1, TIMP1 and 2, and type I collagen mRNA were all significantly increased in a PDGF receptor–dependent fashion; moreover, the ventricular dysfunction present in infarcted hearts and was mildly improved in the presence of the PDGFR/c-Abl inhibitor imatinib (**Liu 2014**). Similarly, PDGF-A, PDGF-C, or PDGF-D, when introduced into the heart using adenovirus-mediated delivery, significantly upregulated TGF-β1 mRNA expression and also accelerated cardiac fibrosis and arteriosclerosis (**Tuuminen 2009**). Collectively, these data indicate that PDGF may promote fibrosis by elevating TGF-β levels. These results strongly suggest that PGDF may be a good target for antifibrotic therapy in the heart; however, given the complexity of the molecules involved with the PDGF signaling pathway, developing antifibrotic agents against this pathway may be difficult.

The accumulation of interstitial collagen fibers in chronic chagasic myocarditis may be expected to decrease myocardial compliance and disrupt synchronous contraction of the ventricles during systole, contributing to a spectrum of ventricular dysfunction that involve either the diastolic or systolic phase of the cardiac cycle or both. Myocardial fibrosis can be also implicated in the genesis of malignant ventricular tachyarrhythmias, major causes of sudden death among these patients. The increase in myocardial fibrosis could be directly related to an inflammatory reaction mainly composed of T lymphocytes and macrophages(**Rossi 1998**).



Signaling molecules driving cardiac fibrosis. A series of direct and indirect interactions among growth factors and matricellular proteins drive fibrogenesis. The growth factors and matricellular proteins and their associated cell surface receptors are shown, along with major profibrotic effectors/end points.

5. What is the proper approach and risk stratification? Let´s see the Rassi score in this patient.

Risk factors	Points
Clase III o IV de la New York Heart Association	5
Cardiomegaly (Thorax RX)	5
Segmental or global wall anomalous movement (echocardiography)	3
Nonsustained ventricular tachycardia (Holter 24h)	3
Low QRS voltage (ECG)	2
Male	2
Total points in our case	**6**

Conclusion: Low risk because he has a Rassi score between 0 to 6 points

Total of points	Mortality in 5 years
0-6 (low risk)	2%
7-11 (intermediate risk)	18%
12-20 (high risk)	63%

This patient is categorized in stage B1.
As for left ventricular (LV) dysfunction and HF manifestations, the chronic phase can be further classified into stages (A, B, C and D), according to international recommendations adapted to the Chagas' disease.
The stage A includes indeterminate form (not accepted currently) patients with no present or previous symptoms of HF, without structural heart disease (normal ECG and chest X-ray). As long as the patient remains in this form of the disease, prognosis is not compromised.
The stage B includes those patients with structural heart disease, who have never had signs or symptoms of HF. This stage is divided into:
B1 - patients with ECG changes (arrhythmias or conduction disorders) may present mild echocardiographic abnormalities (abnormalities of regional contractility), but global ventricular function is normal.
B2 - patients with global ventricular dysfunction (decreased LV ejection fraction).
Stage C includes patients with LV dysfunction and prior or current symptoms of HF (NYHA I, II, III and IV).
Stage D includes patients with symptoms of HF at rest, refractory to maximized medical therapy (NYHA IV) requiring specialized and intensive interventions (**Andrade 2011**).

Pharmacological approach
The goal of pharmacological treatment of arrhythmias in chagasic chronic cardiomyopathy is the control of symptoms without concrete evidence of effectiveness in preventing SCD and overall mortality. In general, the presence of these arrhythmias in asymptomatic patients with preserved ventricular function eliminates the need for antiarrhythmic treatment. For symptomatic patients without ventricular dysfunction, antiarrhythmic treatment can be individualized and in those with LV dysfunction, amiodarone is the only safe drug. In usual doses of 200 to 400 mg/day, it may be associated with β-blockers to reduce serious events.
Does this patient have a new electrophysiological study? Remember that this test was performed 26 months ago and showed no major problems, only minimal prolongation of the HV + incomplete RBBB + LAFB.
The electrophysiological study (EPS) allows investigating the sinus function and the AV conduction, and is indicated for clarifying syncope of undetermined origin after noninvasive evaluation, and reversed sudden death, as well as mapping ventricular refractory tachycardia for potential ablation, not yet present. It could be useful to know the current situation, given the evolutionary character of chronic chagasic cardiomyopathy.

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