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Continuation of the Revista Mexicana de Cardiología

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- COVID-19: What have we learned?
- Diastolic dysfunction in the left atrial strain
- Cardiac rupture during stress echocardiography
- Submitral aneurysm as a cause of mitral valve insufficiency
- Advantages of cardiac magnetic resonance over echocardiography
- The U wave: an ignored wave filled with information
- The role of microRNAs in the development of heart failure
- Electrocardiogram analysis to determine the site of origin of premature ventricular beats/contractions

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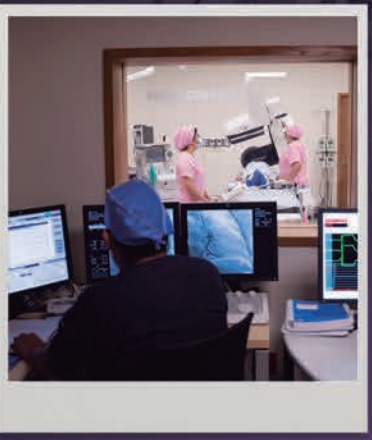

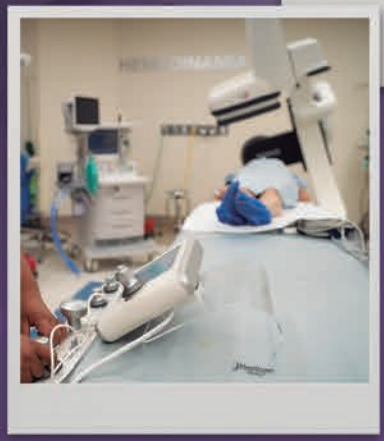

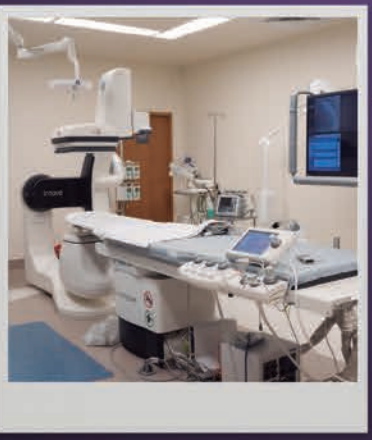

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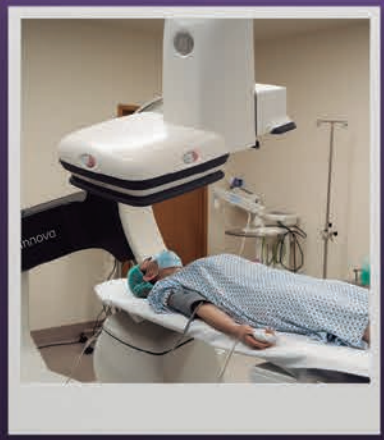

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Contents / Contenido

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Editorial

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What have we learned from the COVID-19 pandemic, once it fades away?

¿Qué hemos aprendido de la pandemia de COVID-19, una vez que se desvanezca?

Eduardo Meaney*

The SARS-CoV-2 pandemic has not been completely defeated. In several regions of the world, new waves of infections have emerged, and in our nation, another outbreak wave may reappear after the Christmas festivities. Perhaps the author of this text has an exaggerated optimism, but anyhow, it seems that the worst is over, fundamentally because of the «herd immunity» caused by both natural infections and the extensive vaccination. Although there is no possible comparison between the great plague epidemics (that of the era of Emperor Justinian and the so-called Black Death of the Middle Ages, that killed one out of two Europeans) and that of smallpox that Spanish conquerors brought to Mesoamerica, that almost extinguished the native inhabitants of this region of the world, COVID-19 pandemic was a worldwide catastrophe that caused millions of deaths and had disastrous economic effects. What lessons can we derive from this epidemiological catastrophe? The following list describes just a handful of these bitter and painful teachings.

1. Some governments of different nations, notorious universities, and the pharmaceutical industry carried out the remarkable achievement of creating a set of safe and effective vaccines in an exceptionally short time. Besides human ingenuity, this extraordinary accomplishment would not have been possible without a vast investment of financial resources. Medicine and science, like any other human inventions, require considerable resources to bear fruits. Unfortunately, some nations invest more in death and destruction than in health and life. Just imagine the medical, educational, cultural, and social progress that would be achieved with the money that costs a single nuclear aircraft carrier (about USD 13 billion). The yearly military spending of the world's greatest powers would be enough to end the hunger of millions of human beings and would banish or reduce diseases such as malaria, childhood cancer, and cardiovascular and neurodegenerative diseases, among many others.
2. In every country and in the international scenario, the tragedy of the COVID-19 pandemic was used unethically as a political tool to attack constituted governments or harm another nation politically and economically. The pandemic showed that solidarity and love to mankind, raised as sacred by various religious faiths, matters so little to vast sectors of human society. But it is fair to say that the performance of physicians, nurses, support personnel, and workers of no medical but essential tasks was heroic. The pandemic also showed that humanity can act the same, like angels or demons.
3. How the SARS-CoV-2 viruses, living in peace with bats, moved to affect the human population is unknown. But many new viral

* Editor in Chief. Cardiovascular and Metabolic Science. Mexico.

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infections (Ébola, Marburg and other severe acute respiratory syndromes caused by coronavirus) are secondary to the invasion to ecological reservoirs of our relatives, the no human animals. If the systematic destruction of the environment lasts, among many other disasters, new epidemic threats will appear, not as a divine punishment, but as a logical consequence of the imbalance caused by humans in the Nature order.

4. COVID-19 affected democratically to both rich and needed, but the latter (individuals and nations) suffer more and had higher rates of deaths and complications. The abysmal difference among rich and poor, individuals and nations, is not only immoral but rather the source of problems that can affect the entire world, from a health, socio-economic, geopolitical, and environmental point of view.
5. Not only in Mexico but in various countries like the United States and several European nations, the completely irrational anti-vaccine movements help to the propagation and persistence of the COVID-19 pandemic. This fact puts on the table of deliberation how far personal freedom can go. The author of this editorial thinks that there is no unlimited freedom, that my liberty ends where that of others begins, and that in many matters, the common wellness must prevail over personal prejudices, conveniences, or beliefs. But it is a rather complex topic that will continue to be discussed in the future.
6. The pandemic caught our weak health system totally unprepared. Neither the hospitals nor the health personnel were ready for a threat of this magnitude. This fact, plus the characteristics of our population ravaged by obesity, diabetes, hypertension, and dyslipidemia, explain the very high rate of mortality for COVID-19 seen in Mexico. The strongest pillars of society, besides the economy, are education and health. Every modern State must support, finance, and update educational and health establishments. It is known that a healthy and educated population better resists any epidemiological threat. For decades the epidemic of obesity (the mother of the other cardiovascular and cardiometabolic flagella) has been left untouched to not upset important economic power groups. It is time now, based on the teachings of this infectious epidemic, to turn to look at the pandemics that are and will be the main causes of death and disability in our country. Unfortunately, for these chronic-degenerative diseases, there are no vaccines, healthy distance, or face masks that can limit their spread. Cardiovascular and cardiometabolic prevention is more difficult and costly and needs the leadership of the State, the implementation of sounding public health policies, and the understanding and approbation of most of the population. Maybe, our people will see preventive medicine in a different and more rational way after the COVID-19 threat.
7. At the end of the pandemic of COVID-19, a long struggle awaits Mexican society to reduce cardiometabolic diseases that today threaten in the long term the national security and bonanza of our homeland. ANCAM and our allied societies will be there in the first trench of that fight.

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Original Research

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Impact of the diastolic dysfunction in the left atrial strain in patients with ischemic heart disease. A cross-sectional study

Impacto de la disfunción diastólica en el strain *de la aurícula izquierda en pacientes con cardiopatía isquémica. Un estudio transversal*

Tomás Miranda-Aquino,* Jorge Eduardo Hernández-del Río,* Silvia Esmeralda Pérez-Topete,‡ Christian González-Padilla,* Óscar Sergio Lomelí-Sánchez,* Carlos del Cid-Porras,* Michel Machuca-Hernández,* Ramón Miguel Esturau-Santaló*

Keywords:
Left atrial strain, diastolic dysfunction, ischemic heart disease, left atrial reservoir strain, left atrial conduct strain, left atrial pump strain.

Palabras clave:
Strain *de aurícula izquierda, disfunción diastólica, cardiopatía isquémica,* strain *reservorio de la aurícula izquierda,* strain *conducto de la aurícula izquierda,* strain *bomba de la aurícula izquierda.*

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ABSTRACT

Introduction: Left atrial strain (LAS) has been related to the grade of diastolic dysfunction. However, only a few reports exist about its relationship among patients with ischemic heart disease (IHD). **Objective:** To compare the LAS value among patients with normal and abnormal diastolic function. **Material and methods:** A cross-sectional, retrospective, observational, analytic, single-center study (Hospital Civil de Guadalajara). All patients with an ischemic heart disease diagnosis (acute and chronic) were included between June 2017 and July 2019. **Results:** Two hundred forty-eight patients were included. Among the study population, 58% had diastolic dysfunction. LAS was lower in the diastolic dysfunction group on the reservoir (39% vs 23%), conduit (22 vs 11%) and pump phases (16 vs 23%). As diastolic dysfunction progressed, the reservoir (39 vs 30% vs 22 vs 16%) and conduit (22 vs 12% vs 12 vs 9%) phases of left atrial strain decreased, and during the pump phase an improvement was noticed between grade 1 diastolic dysfunction compared with a normal diastolic function (16 vs 18% vs 11 vs 6%). We used the ROC curve to determine the cut-off value to predict diastolic dysfunction, and the cut-off was < 31.6%. The LAS also correlated with proBNP concentrations. **Conclusion:** As diastolic dysfunction progress, the three phases of LAS present a linear decline in IHD.

RESUMEN

Introducción: *El* strain *de aurícula izquierda se ha relacionado con el grado de disfunción diastólica, sin embargo, sólo pocos estudios existen de su relación en pacientes con cardiopatía isquémica.* ***Objetivo:*** *Comparar el valor del* strain *de aurícula izquierda en pacientes con función diastólica normal y anormal.* ***Material y métodos:*** *Estudio transversal, retrospectivo, observacional, analítico, unicéntrico (Hospital Civil de Guadalajara). Se incluyeron todos los pacientes con diagnóstico de cardiopatía isquémica aguda o crónica, en el periodo de junio 2017 a julio 2019.* ***Resultados:*** *Doscientos cuarenta y ocho pacientes fueron incluidos. El 58% de los pacientes tuvieron disfunción diastólica. El* strain *de aurícula izquierda fue menor en el grupo de disfunción diastólica en la fase de reservorio (39 vs 23%), conducto (22 vs 11%) y de bomba (16 vs 23%). Conforme progresó la disfunción diastólica, la fase de reservorio (39 vs 30% vs 22 vs 16%) y la de conducto (22 vs 12% vs 12 vs 9%) del* strain *de la aurícula izquierda fueron descendiendo; en la fase de bomba hubo un incremento en la disfunción diastólica grado 1 en comparación con función diastólica normal (16 vs 18% vs 11 vs 6%). El valor de corte del* strain *de reservorio para predecir disfunción diastólica fue de < 31.6%, utilizando curvas ROC. El* strain *de aurícula izquierda se correlacionó con las concentraciones de proBNP.* ***Conclusión:*** *Conforme la disfunción diastólica progresa, las tres fases del* strain *de la aurícula izquierda presentaron declive lineal en pacientes con cardiopatía isquémica.*

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INTRODUCTION

Ischemic heart disease (IHD) stands as the main cause of death in the world. The World Health Organization estimates that 17 million people die every year due to this condition, and the number increases year after year.[1] Ischemic heart disease can be broadly divided into stable ischemic heart disease[2] and acute coronary syndromes (ACS),[3,4] which can also be divided into unstable angina (UA), ST-segment elevation myocardial infarction (STEMI) and Non-ST-elevation myocardial infarction (NSTEMI).

Diastolic function comprises 4 phases: isovolumetric relaxation, early rapid diastolic filling, diastasis, and atrial contraction (also called a late diastolic filling). These four phases require an active myocardial relaxation, elasticity and distensibility of the left ventricle.[5]

Currently, the diastolic function can be easily assessed with an echocardiogram, following the American Society of Echocardiography guidelines.[6] Left atrial function has been historically related to the grade of diastolic dysfunction since, in the absence of mitral valve disease, an enlarged left atrium can be associated with an increased left ventricular diastolic pressure.[7] Left atrial function encompasses three physiological processes. In the reservoir phase, the left atrium is filled with blood coming from the pulmonary veins; the conduit phase, the diastasis; and the contraction phase (also called the pump phase), when the left atrium contracts.[8]

Patients with ischemic heart disease have an abnormal diastolic function, and it is known that diastolic function is affected even before the appearance of systolic dysfunction on the ischemic cascade.[9]

Left atrial strain (LAS) is a relatively new echocardiographic procedure. It represents the percent change of myocardial fibers on the spatial position in each phase of the atrial cycle.[10] This technique has the great advantage of non-invasively assessing all three phases of the atrial cycle, producing curves that accurately represent that function.

There have been discrepancies in the typical values of left atrial deformation (strain), with a mean reservoir strain of 40% among the larger studies.[11,12] Its relationship with the grade of diastolic dysfunction has been studied before, and it is proposed that a left atrial reservoir strain (LARS) below 35% can be associated with diastolic dysfunction.[13]

Among patients with IHD, the association between myocardial deformation and the degree of diastolic dysfunction has been barely studied. To our knowledge, there is only one report describing this relation.[14] The study included 109 patients with a NSTEMI and found that the three components of left atrial strain correlate with the classic parameters of diastolic function. Additionally, the LAS declines as the diastolic dysfunction grade increases.

Apart from IHD, another condition in which an association with left atrial strain is well documented is atrial fibrillation, where a decreased strain predicts the development of this arrhythmia.[15,16] After an ablation procedure can also be linked to a higher risk of recurrences.[17] Furthermore, it can predict the risk of systemic embolism in patients with atrial fibrillation.[8,10,18]

There is a broadly described linear relationship between a decline in left atrial strain and mitral valve regurgitation progression in valvular heart disease, mainly mitral valve disease. The association with survival has also been described.[19,20] It can predict the appearance of atrial fibrillation in mitral stenosis.[21]

LAS has also been described in patients with hypertension,[8] chronic kidney disease[22] and autoimmune diseases, such as lupus[23] and rheumatoid arthritis.[24]

This study´s importance implies the relevance of diastolic function stratification, using the LAS percentage in patients with IHD. This novel technique could lead to the re-stratification of those patients with an undetermined diastolic function. It is innovative as only a few papers describe this topic.

The objective of this study is to compare the LAS value among patients with normal and abnormal diastolic function.

MATERIAL AND METHODS

A cross-sectional, retrospective, observational, analytic, single-center study was performed. All patients older than 18 years old, hospitalized at the Cardiology Department of the "Hospital

Civil de Guadalajara Fray Antonio Alcalde" between June 2017 and August 2019, with a diagnosis of IHD (including UA, STEMI, NSTEMI and stable angina) were included. Every patient had an echocardiogram during the first 72 hours of their hospitalization. Exclusion criteria were: atrial fibrillation, poor acoustic window and mitral stenosis.

This study's main objective was to compare the percentage of LAS in patients with normal and abnormal diastolic function. The specific objectives were to contrast the percentage of LAS with the grades of diastolic dysfunction. To assess the capacity of LAS to predict diastolic dysfunction and compare these findings with the classic parameters of diastolic dysfunction. Also, to determine if there is a correlation between LAS and the classic diastolic dysfunction parameters and establish an association between the LAS and proBNP blood levels.

Demographic variables of our patients were age, gender, body mass index (BMI), co-morbidities such as hypertension, diabetes mellitus, dyslipidemia, smoking, blood analysis (HbA1c, Uric Acid, Creatinine, Cholesterol, triglycerides, proBNP). Moreover, initial diagnosis: UA, STEMI, NSTEMI and stable angina; and among the echocardiographic variables we had: left ventricle ejection fraction (LVEF), E/A ratio, e', E/e' ratio, left atrial indexed volume (LAVI), tricuspid regurgitation maximal velocity (TR Vmax), presence or absence of mitral regurgitation, and the severity of it.

A cardiologist performed echocardiographic studies, supervised by an echocardiographer, with a Siemens ACUSON SC2000 prime, using the 4v1c, 2.5 MHz probes. The LVEF was calculated by the biplane method (Simpson's rule). The LAVI was also calculated by a biplane method, and TR Vmax was determined using the continuous wave Doppler of the tricuspid regurgitation. E/e' ratio was calculated with the product of the division of the mitral inflow E wave (measured by pulsed wave Doppler) and the average of the medial and lateral e' waves (measured by tissue Doppler). Diastolic function was established according to the 2016 Left ventricular diastolic function guidelines of the American Society of Echocardiography 2016.[6]

LAS was obtained using the syngo®, Velocity Vector Imaging technology software. An apical 4-chamber view echo was predetermined to calculate myocardial strain. The left atrial endocardium was traced at end-systole, and the traced endocardial border was followed during the cardiac hole cycle. The R-R interval on EKG was used as the reference for strain assessment. A maximal longitudinal strain global was acquired, represented as the Left Atrial Reservoir Strain (LARS). Additionally, the other two values were obtained: The Left Atrial Conduit Strain (LACS) and the Left Atrial Pump Strain (LAPS). The maximum value represents LARS during the reservoir phase, the LAPS is the highest value in the contraction phase, and the difference between the former two is the LACS.

Qualitative variables are expressed in proportions, quantitative variables in mean (standard deviation) or median (interquartile range), according to their distribution (Kolmogorov-Smirnov). Qualitative values were compared using χ^2, while a Student's t-test, Mann-Whitney U test, ANOVA or Kruskal-Wallis were used for quantitative variables according to their distribution. According to the LAS, a ROC curve was used to establish a precise cut-off point to diagnose diastolic dysfunction, compared with the E/A ratio, E/e', LAVI, and TR Vmax. Spearman's correlation was used to determine LAS relation with E/A ratio, E/e', LAVI, and TR Vmax, along with proBNP. The inter-observe variability was determined by the kappa coefficient. Statistical significance was determined with a $p < 0.05$. The statistical program Medcalc statistical software, version 15.2, was used.

The Declaration of Helsinki ethical principles were followed.

RESULTS

During the study period, 248 patients were included. 58% of our study population *(Table 1)* had diastolic dysfunction. Among demographic features, the male gender was more prevalent. The diastolic dysfunction group had an older median age (57 vs 62 yr.), a lower BMI (27.8 vs 26.5) and a higher prevalence of diabetes mellitus (33 vs 54%). There was no significant difference in the prevalence of hypertension, dyslipidemia, and tobacco consumption. The most common diagnosis at hospital discharge was STEMI.

Table 1: Baseline characteristics of the patients. N = 248.

Parameter	Normal diastolic function n (%)	Diastolic dysfunction n (%)	p
Demographic characteristics			
N	105 (42)	143 (58)	
Age (years)	57 ± 11	62 ± 12	< 0.001
Male sex (%)	79	69	0.100
BMI (kg/m^2)	27.8 ± 4.0	26.5 ± 4.7	0.030
Hypertension (%)	48	61	0.060
Diabetes mellitus (%)	33	54	0.002
Dyslipidemia (%)	54	37	0.090
Smoker (%)	68	66	0.900
Admission diagnosis (%)			
STEMI	43	53	0.900
NSTEMI	14	22	0.900
UA	28	18	0.600
Stable angina	15	6	0.600
Laboratory data			
HbA1c (%)	7 (5-9)	7.6 (5-10)	0.100
Creatinine (mg/dL)	0.9 (0.3-1.4)	1.1 (0.5-2)	0.100
Cholesterol (mg/dL)	162 ± 37	159 ± 52	0.700
Triglycerides (mg/dL)	164 (110-190)	141 (101-182)	0.080
Uric acid (mg/dL)	6.1 ± 1.6	7 ± 2.4	0.020
Pro BNP (pg/mL)	933 (200-1530)	3432 (350-5450)	0.001

BMI = body mass index, STEMI = ST-elevation myocardial infarction, NSTEMI = Non-ST- elevation myocardial infarction; UA = unstable angina.

As we evaluated laboratory blood analysis, we documented that patients with diastolic dysfunction had higher uric acid levels (6.1 vs 7 mg/dL) and proBNP (933 vs 3432 pg/dL), and we found no difference among HbA1c, creatinine, cholesterol and triglycerides.

Among echocardiographic parameters *(Table 2)*, the population with diastolic dysfunction had a lower LVEF (57 vs 43%), a higher E/A ratio (1 vs 1.3), lower e' (8.1 vs 6.4 cm/s), higher E/e' ratio (9.2 vs 13.3), higher LAVI (23.4 vs 31.5 mL/m^2), and a higher TR Vmax (2.2 vs 2.6 m/s). Regarding LAS *(Figure 1)*, it was lower among the diastolic dysfunction group, with a LARS of 39 vs 23%, a LACS of 22 vs 11% and a LAPS of 16 vs 12%.

A total of 105 patients showed a normal diastolic function, 50 patients with grade 1 diastolic dysfunction, 57 on grade 2 and 36 on grade 3. Echocardiographic parameters were divided according to the grades of diastolic dysfunction *(Table 3)*. It was found that just as diastolic dysfunction advance, LVEF progressively declines (57 vs 46% vs 42 vs 39%), the E/A ratio increases, with the exception of grade 1 (1 vs 0.7 vs 1 vs 2.7), the e' decreases (8.1 vs 6.9 vs 6.2 vs 6 cm/s), E/e' relation worsens (9.1 vs 8.7 vs 14 vs 18.5), LAVI grows (23 vs 25 vs 32 vs 40 mL/m^2), and the TR Vmax rises (2.2 vs 2.3 vs 2.6 vs 2.9 m/s).

The LAS assessment showed a progressive decline as diastolic dysfunction increased *(Figure 2)*, in reservoir phase (39 vs 30% vs 22 vs 16%), and conduit phase (22 vs 12% vs 12 vs 9%). The pump phase on grade 1 diastolic dysfunction improved compared to a normal diastolic dysfunction (16 vs 18% vs 11 vs 6%) and decreased with higher grades of diastolic dysfunction.

When we used the ROC curve, the cut-off value to determine diastolic dysfunction was < 31.6% of LARS compared to other diastolic function parameters, and it was superior in predicting the presence of diastolic dysfunction *(Figure 3)*.

A correlation *(Figure 4)* between LARS, diastolic function parameters and proBNP values was examined. A slight correlation with e', E/e', LAVI and proBNP was found.

The interobserver variability for the left atrial strain assessment documented in our study was 0.85.

DISCUSSION

Our study's main objective was to investigate a difference in LAS values among patients with and without diastolic dysfunction. We found that patients with a normal diastolic function had a LARS of 39%, while patients with diastolic dysfunction had LARS of 23%. Morris et al.[25] documented a mean left atrial strain of 45% (± 11) on a healthy population and a reservoir strain of 28% on patients with diastolic dysfunction (± 11). Another healthy population

study reported a mean reservoir strain of the left atrium of 40% (± 6). A Metanalysis[11] that included 40 studies described a mean left atrial reservoir strain of 39% for a healthy population, the same value that we found on patients with a normal diastolic dysfunction in our study.

Comparing the reservoir and pump phases on both of our study groups, both values were lower on patients with diastolic dysfunction. We reported a LACS of 22% and a LAPS of 16% on patients with a normal diastolic function, values similar to the data described by Pathan et al,[11] as they demonstrated 23 and 17%, respectively.

Table 2: Echocardiographic parameters according to diastolic function.

Parameter	Normal diastolic function	Diastolic dysfunction	p
LVEF (%)	57 ± 9.0	43 ± 11.0	< 0.001
E/A ratio	1 ± 0.3	1.3 ± 0.9	0.001
e' (cm/s)	8.1 ± 1.6	6.4 ± 1.2	< 0.001
E/e´ ratio	9.2 ± 2.7	13.3 ± 6.9	< 0.001
LAVI (mL/m^2)	23.4 ± 6.8	31.5 ± 11.6	< 0.001
TR Vmax (m/s)	2.2 ± 0.4	2.6 ± 0.6	< 0.001
LARS (%)	38.7 ± 12.0	23.2 ± 9.0	< 0.001
LACS (%)	22.2 ± 9.5	11.1 ± 4.7	< 0.001
LAPS (%)	16.5 ± 7.0	12.1 ± 7.3	< 0.0001

LVEF = Left ventricle ejection fraction, LAVI = Left atrial volume index, TR Vmax = Tricuspid regurgitation velocity, LARS = Left atrial reservoir function, LACS = Left atrial conduction strain, LAPS = Left atrial pump function.

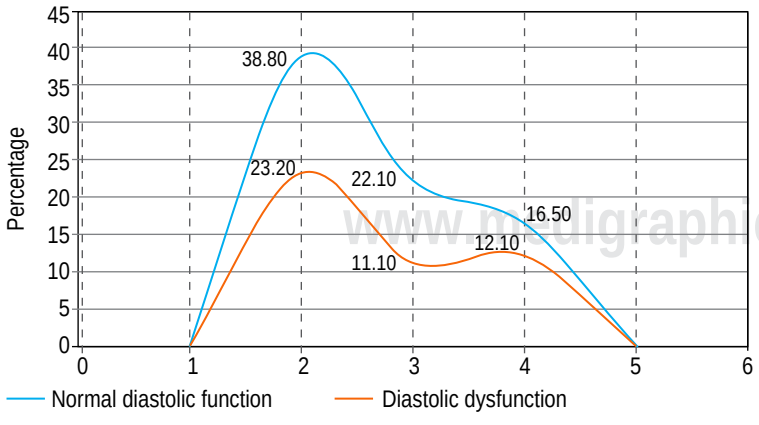


Figure 1: Left atrial reservoir strain and diastolic function.

Lower LAS values have been previously reported on patients with diastolic dysfunction and IHD.[21]

As detailed in other studies,[26,27] we also found that as diastolic dysfunction increases, the classic diastolic dysfunction parameters worsen. The interesting finding was that the 3 phases of LAS decreased progressively, just as diastolic dysfunction evolved. Brecht et al.[28] observed this inverse relationship of LAS deterioration as diastolic dysfunction advances and even suggested that it could be a sign of subclinical diastolic dysfunction. He also mentioned how the LAPS increases on grade 1 diastolic dysfunction, just as our study's findings. Singh et al.[13] and Thomas et al.[29] reported the same inverse relationship between LAS and systolic dysfunction. Another study on patients with an ACS[14] compared the relationship between LAS and the degree of diastolic dysfunction. They described a LARS of 27.7% for DD1, 17.8% for DD2 and 9.5% on DD3; a LACS of 17.8% DD1, 6.2% DD2, 3.3% DD3; and a LAPS of 18.6% for DD1, 8.2% for DD2, and 10.5% for DD3; being the reservoir phase values similar to our findings.

Moreover, in our study, it can be appreciated how LAS turns abnormal at an early stage of diastolic dysfunction, compared with an E/e' ratio that turned abnormal until stage 2 of diastolic dysfunction, whereas LAVI came abnormal until stage 3 diastolic dysfunction. These findings have been previously described,[13,29-31] suggesting that LAS could be a premature indicator of diastolic dysfunction, as it becomes abnormal before the appearance of classic diastolic dysfunction parameters, being even capable of reclassifying patients that could have a normal diastolic function on traditional algorithms or classifying patients on a higher diastolic dysfunction grade.

ROC curves were analyzed to determine the best parameter that could predict diastolic dysfunction. The left atrial strain was revealed to be the most significant, followed by the e' and the left atrial indexed volume. The cut-off point with the highest diagnostic accuracy was < 31.6%, with a sensitivity of 84% and a specificity of 71%. This cut-off value is similar to the value proposed by Singh et al.,[13] who suggested a value of < 35% with a sensitivity of 90% but a specificity of 59%. Furthermore, it

Table 3: Echocardiographic findings according to diastolic dysfunction grade.

Parameter	NDF	DD 1	DD 2	DD 3	p
N	105 (42%)	50 (20%)	57 (23%)	36 (15%)	
Echocardiographic parameters					
LVEF (%)	57 ± 9.0	46 ± 9.0	42 ± 10.0	39 ± 13.0	< 0.001
E/A ratio	1 ± 0.3	0.7 ± 0.2	1 ± 0.3	2.7 ± 0.8	< 0.001
e'	8.1 ± 1.5	6.9 ± 1.7	6.2 ± 2.1	6 ± 1.8	< 0.001
E/e´ ratio	9.1 ± 2.7	8.7 ± 2.7	14 ± 5.5	18.5 ± 8.7	< 0.001
LAVI	23.4 ± 6.8	25.3 ± 7.5	31.8 ± 9.6	39.8 ± 14	< 0.001
TR Vmax	2.2 ± 0.4	2.3 ± 0.5	2.6 ± 0.6	2.9 ± 0.6	< 0.001
LARS (%)	38.8 ± 12.0	29.7 ± 7.0	22.3 ± 8.0	15.7 ± 9.0	< 0.001
LACS (%)	22.1 ± 9.0	11.8 ± 5.0	11.6 ± 5.0	9.1 ± 4.0	< 0.001
LAPS (%)	16.5 ± 7.0	17.9 ± 6.0	10.7 ± 5.0	6.5 ± 6.0	< 0.001

NDF = normal diastolic function, DD = diastolic dysfunction, LVEF = left ventricle ejection fraction, LAVI = left atrial volume index, TR Vmax = tricuspid regurgitation velocity, LARS = left atrial reservoir function, LACS = left atrial conduction strain, LAPS = left atrial pump function.

showed accurate detecting an E/e' ratio higher than >14 on ischemic heart disease patients.[14]

Other studies indicated that compared with the classic diastolic function parameters, LAS could be a superior and more precise predictor of increased left atrial filling pressure.[32] It can also identify patients with heart failure with preserved LVEF,[33] which correlates with the pulmonary capillary wedge pressure.[34]

Additionally, the correlation level between LAS and other diastolic function variables was determined, with LAVI the highest correlation followed by e' and E/e' ratio. Nagueh et al.[5] reported the correlation previously demonstrated between the LARS and left ventricular end-diastolic pressures. Degirmenci et al.[35] described the correlation present with the LAVI. Among patients with IHD, there is also a recognized moderate correlation with LAVI, E/e' ratio and e'.[14]

Finally, we attempt to identify a correlation between the LARS and proBNP concentration, displaying an inverse relation. This exact inverse correlation has been found in patients with heart failure[33] and patients with NSTEMI.[35]

LAS evaluation demonstrated an echocardiographic technic with a straight correlation with diastolic function in patients with IHD. It can show a sudden change that can accurately categorize diastolic function, especially when the classic parameters seem unreliable or undetermined. This technic has the advantage of being unaffected by the angle of exploration and high reproducibility, even by inexperienced operators. The disadvantage is the lack of a well-defined consensus on normal values, the best imaging views, and the precise

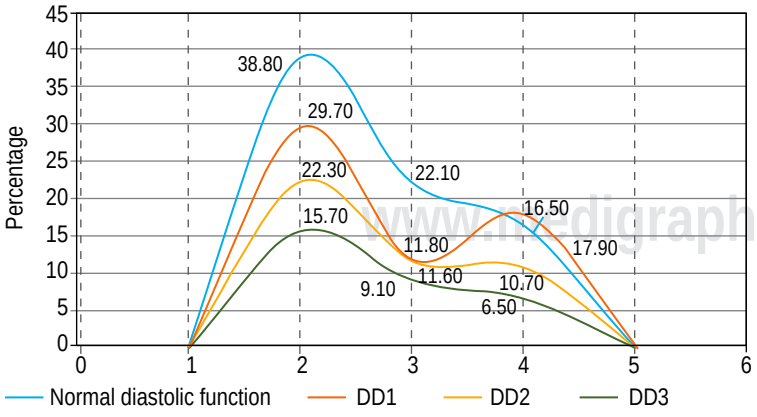
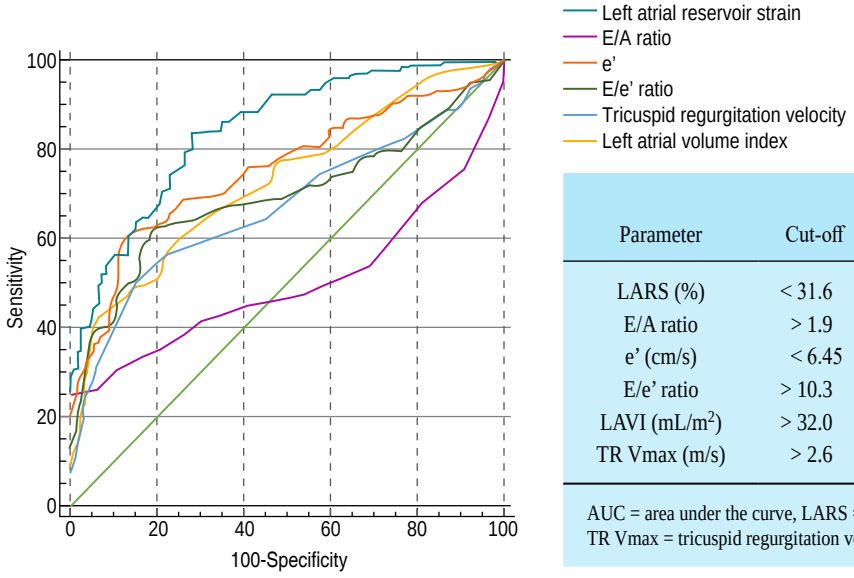


Figure 2: Left atrial strain according to the grade of diastolic dysfunction.



Parameter	Cut-off	AUC	Sensibility (%)	Specificity (%)	p
LARS (%)	< 31.6	0.846	84	71	< 0.0001
E/A ratio	> 1.9	0.506	25	100	0.8
e' (cm/s)	< 6.45	0.757	61	87	< 0.0001
E/e' ratio	> 10.3	0.699	62	81	< 0.0001
LAVI (mL/m^2)	> 32.0	0.731	43	93	< 0.0001
TR Vmax (m/s)	> 2.6	0.674	50	85	< 0.0001

AUC = area under the curve, LARS = left atrial reservoir strain, LAVI = left atrial volume index, TR Vmax = tricuspid regurgitation velocity.

Figure 3: ROC curves of echocardiographic and diastolic function parameters.

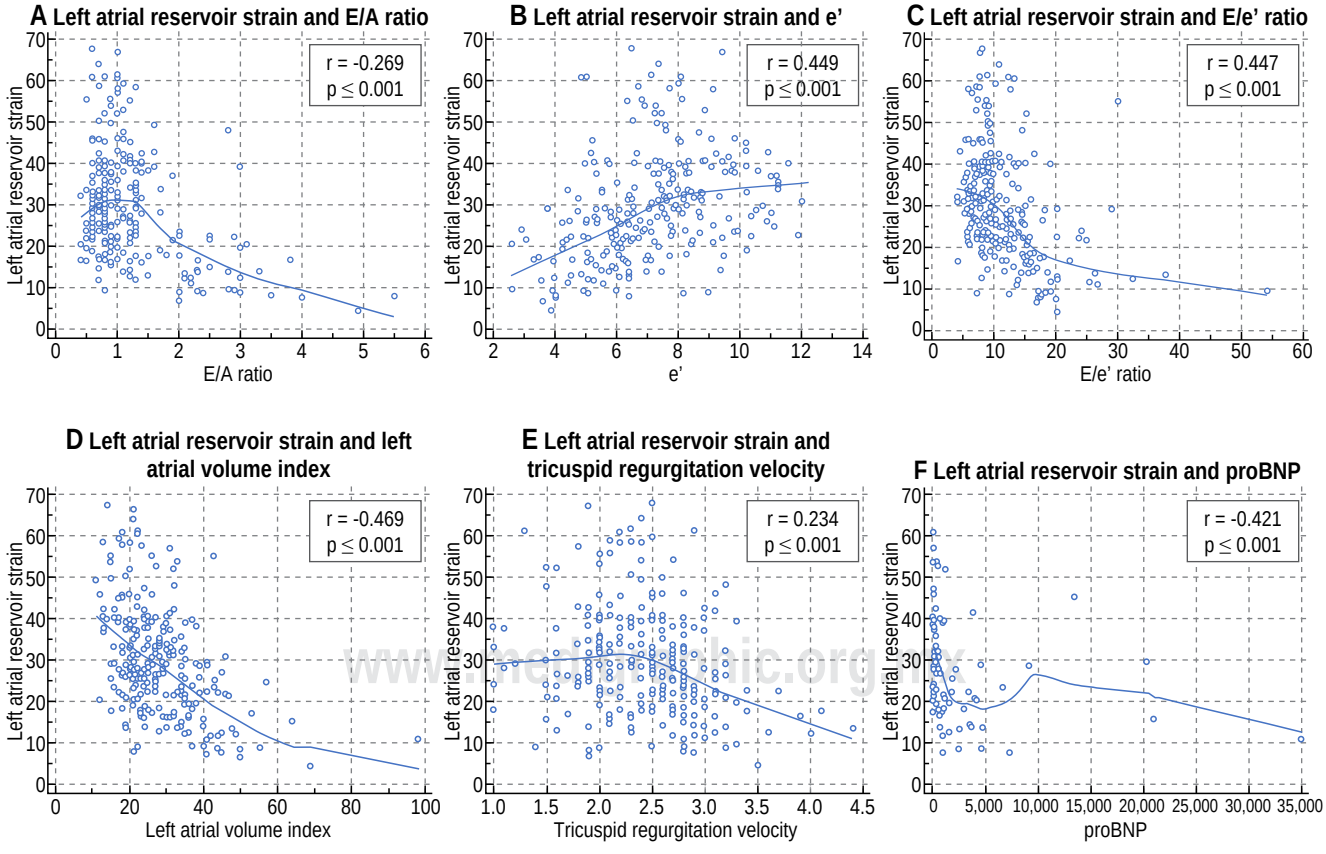


Figure 4: Correlation between left atrial strain and echocardiographic parameters.

echocardiographic reference point that should be used.

Our study´s limitations are the retrospective, single-center design, exclusive to patients with IHD, and its modest sample size. However, it has the advantage of being one of the first studies in Latin America to use this technic to evaluate diastolic function. Our results encourage us to continue exploring this tool on prospective trials to estimate cardiovascular events and their performance in pathologies other than ischemic heart disease.

CONCLUSION

The left atrial strain, on its three phases, is decreased among patients with IHD and diastolic dysfunction. These three phases show a linear decline just as diastolic dysfunction progresses. Left atrial function is an important emerging entity and carries significant clinical and prognostic implications. The left atrial strain measurement is feasible, and the findings of this study suggest that left atrial strain could be a proper parameter in the evaluation con diastolic dysfunction in patients with IHD.

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Cardiac rupture during dobutamine stress echocardiography as stratification after acute myocardial infarction

Ruptura cardiaca durante ecocardiograma de estrés con dobutamina como estratificación posterior a infarto agudo al miocardio

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Keywords:
Cardiac rupture, dobutamine stress echocardiogram, acute myocardial infarction.

Palabras clave:
Ruptura cardiaca, ecocardiograma estrés con dobutamina, infarto agudo al miocardio.

ABSTRACT

Dobutamine stress echocardiography is widely used in stratification after an acute myocardial infarction. Complications that can be life threatening have been reported, ventricular arrhythmias being the most frequent. Cardiac rupture is a rare but fatal complication. We report the case of a 68-year-old male with an inferior infarction without a reperfusion strategy, who underwent a dobutamine stress echocardiogram 6 days after the infarction. During the initial recovery, the patient presented cardiac rupture due to the presence of a pericardial effusion with a hematic appearance and electro-mechanical dissociation. Emergency pericardiocentesis was performed, eventually the patient died. Recent inferior infarction and a dyskinetic zone have been reported in the literature as high-risk characteristics to present. Proper selection of the patient, a baseline echocardiogram without risk characteristics for rupture, and the time to perform the study after the infarction can reduce the incidence of this complication.

RESUMEN

El ecocardiograma de estrés con dobutamina es ampliamente utilizado en la estratificación posterior a un infarto agudo al miocardio. Se han reportado complicaciones que pueden ser potencialmente mortales, siendo las arritmias ventriculares las más frecuentes. La ruptura cardiaca es una complicación rara, pero fatal. Se presenta el caso de un masculino de 68 años con un infarto inferior sin estrategia de reperfusión, el cual fue sometido a un ecocardiograma de estrés con dobutamina a los seis días del infarto. Durante la recuperación inicial el paciente presenta ruptura cardiaca por presencia de derrame pericárdico de aspecto hemático y disociación electro mecánica. Se realizó pericardiocentesis de urgencia, finalmente falleciendo el paciente. En la literatura se ha reportado el infarto inferior reciente y una zona discinética como las características de alto riesgo para presentarse. La selección adecuada del paciente, un ecocardiograma basal sin características de riesgo para ruptura y el tiempo de realización del estudio posterior al infarto puede disminuir la incidencia de esta complicación.

INTRODUCTION

The dobutamine stress echocardiogram is a widely used study in the diagnosis of coronary artery disease and myocardial viability. It is considered safe, however serious life-threatening complications have been reported, such as cardiac rupture, myocardial infarction, ventricular arrhythmias, asystole, cerebrovascular accident, supraventricular tachycardia, symptomatic bradycardia, coronary spam1. We present the case of a patient who suffered a cardiac rupture during dobutamine stress echocardiography in the stratification after an acute myocardial infarction.

CASE PRESENTATION

A 68-year-old man with a history of chronic smoking, systemic arterial hypertension

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and diabetes mellitus 2, the rest of the antecedents were denied. He was admitted to the emergency department due to an episode of typical angina pectoris of more than 24 hours of evolution, attending due to persistence of symptoms. The initial electrocardiogram showed Q waves in DII, DIII, AVF, V5-V6 with ST elevation 2 mm in the same leads. In his studies, CK 485 and CK MB 69 stand out, not having troponin in the hospital. A Killip Kimball I inferolateral myocardial infarction of 24 hours of evolution was considered.

Given the time of evolution, it was stabilized with optimal medical treatment (We do not have a cardiac catheterization lab in the hospital and our tertiary referral hospital is six hours away).

A transthoracic echocardiogram was performed that showed septoapical, apical, inferior apical akinesia, no thinned cardiac segments. Left ventricular ejection fraction (LVEF) 45%, type 1 diastolic dysfunction E/A 0.6, E/e 10, normal dimensions of the right heart chambers with normal right ventricular ejection fraction at rest. Systolic pulmonary artery pressure 26 mmHg, estimated by tricuspid reverse gradient. No pericardial effusion at rest *(Figures 1 to 3)*. The patient evolved to be hemodynamically stable, so a stress echocardiogram was performed to search for viability/residual ischemia on the 6th day after

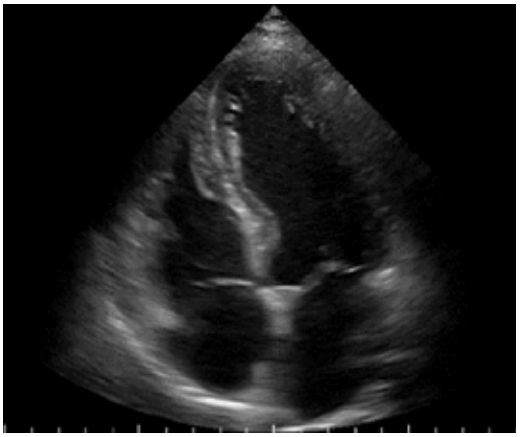

Figure 1: Apical 4-chamber image. There is no pericardial effusion or areas of thinning.

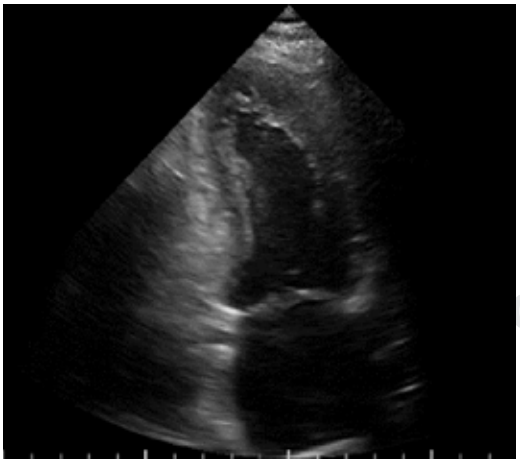

Figure 2: Apical 2-chamber image. There is no pericardial effusion or areas of thinning.

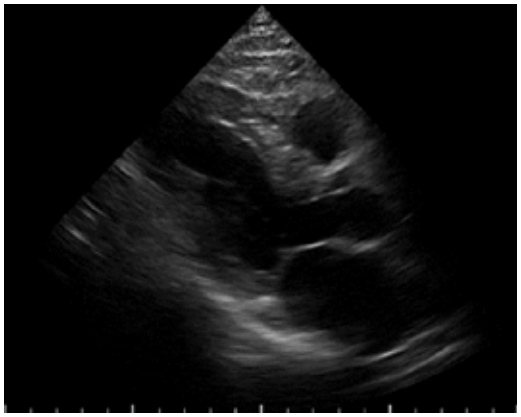

Figure 3: Long parasternal axis image.

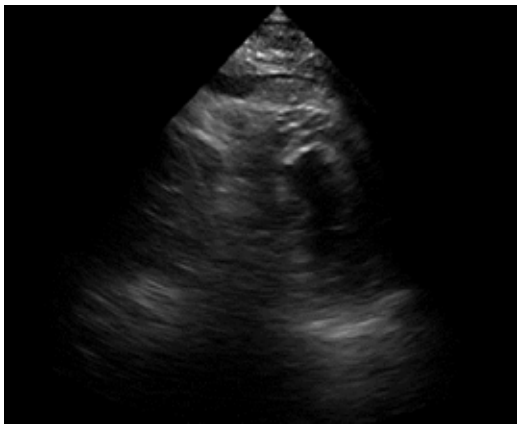

Figure 4: Short axis in the initial recovery. Minimal pericardial effusion.

admission to hospitalization. A 5-stage protocol was initiated, starting at 5 µg/kg/min, reaching 20 µg/kg/min. The patient persisted with septoapical and apical akinesia and developed an ischemic response due to developing basal and medial inferior hypokinesia. No changes were recorded in the electrocardiogram at this dose of dobutamine. Esmolol 30 mg intravenous single dose was administered at the beginning of the recovery phase and the study was terminated. In first minutes of recovery, the patient showed sudden deterioration in alertness and pulseless electrical activity. The echocardiogram showed pericardial effusion with a hematic appearance and echocardiographic data of tamponade *(Figures 4 to 6)*. The patient presented cardiorespiratory arrest, so intravenous fluids were administered and an emergency pericardiocentesis was performed, achieving expansion of the right ventricle but with rapid formation of a new pericardial effusion. Later on, he presented asystole which did not revert to basic or advanced cardiovascular resuscitation.

DISCUSSION

The dobutamine stress echocardiogram is associated with a low rate of complications, with a mortality rate of less than 0.01%, mainly due to ventricular arrhythmias.[1] Cardiac rupture has been reported in patients with akinesia or inferior dyskinesia, as result of a recent inferior infarction within 4-12 days. There are reports of cases in which the patient develops sudden chest pain and loss of consciousness accompanied by pulseless electrical activity due to electromechanical dissociation.[2-5] In most of the reported cases, the result is fatal. Inotropic stimulation of necrotic and thinned tissue can increase wall stress and result in rupture at the site of least resistance.[6] It has been reported of cases where stimulation at low doses (10 µg/kg/min) produces a powerful inotropic stimulation that causes myocardial rupture, observing that the infarction of the inferior wall is more susceptible to rupture.[3,4] In this case, the baseline study did not find thinned segments, pericardial effusion or any echocardiographic data compatible with cardiac rupture.[7]

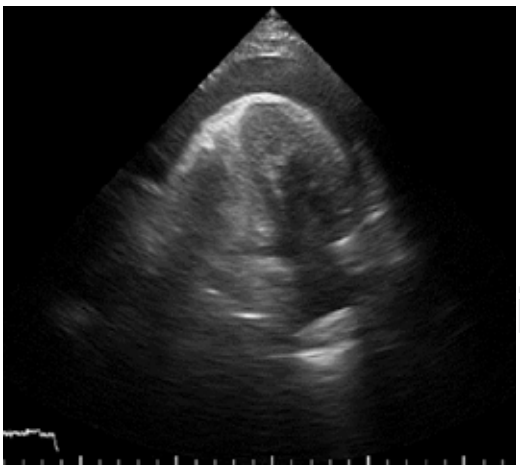

Figure 5: Apical 4-chamber image. Severe global pericardial effusion.

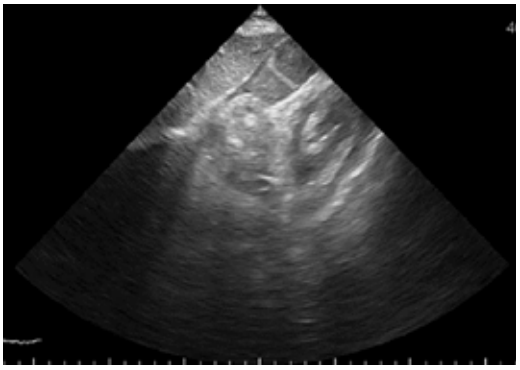

Figure 6: Subcostal window. Severe pericardial effusion with a hematic appearance that collapses right cavities.

The characteristics found coincide with what has been reported in the literature, where it has been carried out in the early stratification of the infarction and with cardiac rupture at low doses of dobutamine, with the difference that occurred in the early recovery immediately after the suspension of dobutamine and administration of esmolol.

CONCLUSIONS

Excluding ventricular tachycardia, the occurrence of complications during stress echo that can be life threatening is 1 in 1,573. Cardiac rupture during stress echo is a fatal complication, fortunately extremely rare.

Recent inferior infarction and a dyskinetic zone have been reported in the literature as high-risk characteristics to present.

Proper selection of the patient, a baseline echocardiogram without risk characteristics for rupture, and the time to perform the study after the infarction can reduce the incidence of this complication.

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CLINICAL CASE

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Submitral aneurysm as a cause of mitral valve insufficiency

Aneurisma de presentación como causa de insuficiencia de la válvula mitral

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Keywords:
Cardiac ventricular aneurysm, mitral subvalvular aneurysm, mitral valve insufficiency, heart failure, congenital heart disease.

Palabras clave:
Aneurisma ventricular cardiaco, aneurisma subvalvular mitral, insuficiencia valvular, falla cardiaca, cardiopatía congénita.

ABSTRACT

The mitral subvalvular ventricular aneurysm is a rare cardiac condition with an origin not yet well defined. Since the first report by Corvisart in 1812, several reports have coincided with pointing out the significant incidence among Africans, which has been the scene of several discussions until today. There are several controversies around this issue; the current consensus is several interrelated factors such as the weakness of the posterior fibrous ring of the mitral valve is at the basis of its occurrence, which can be based on a sustained basis, congenital aneurysm, infectious, inflammatory or degenerative processes involving the endocardium. The diagnosis of certainty is made by echocardiogram, and the treatment is eminently surgical. 28-year-old Angolan patient with a mitral subvalvular aneurysm is described as the cause of severe mitral regurgitation and heart failure, which was successfully corrected surgically.

RESUMEN

El aneurisma ventricular subvalvular mitral se considera una rara afección cardiaca con un origen aún no bien definido. Desde su primer informe por Corvisart en 1812, varios informes han coincidido en señalar su mayor incidencia entre los africanos, lo que ha sido escenario de varias discusiones hasta hoy. Existen varias controversias en torno a este tema, el consenso actual es de varios factores interrelacionados como la debilidad del anillo fibroso posterior de la válvula mitral está en la base de su aparición que puede ser de base sostenida, aneurisma congénito, procesos infecciosos, inflamatorios o degenerativos que involucran el endocardio. El diagnóstico de certeza se realiza mediante ecocardiograma y el tratamiento es eminentemente quirúrgico. Se describe el caso de una paciente de 28 años, de nacionalidad angoleña, con aneurisma subvalvular mitral como causa de regurgitación mitral severa e insuficiencia cardiaca, que fue corregida quirúrgicamente con éxito.

INTRODUCTION

Mitral subvalvular ventricular aneurysm (AVSM) is considered a rare heart disease, the origin of which is not yet well defined.[1] However, there are several etiological hypotheses associated with this condition. It is currently accepted that it originates from congenital mitral valve annulus and endomyocardial weakness in susceptible individuals who are exposed to certain biological agents or chronic inflammatory phenomena that cause remodeling and fibrosis of the subvalvular structures, resulting in the formation of aneurysms with varying degrees of mechanical involvement of the mitral valve (MV).[2]

Corvisart et al. first reported this clinical entity just over two centuries ago, and since then, several studies have suggested a link between this mitral valve anomaly and varying degrees of mitral regurgitation (MR).[3] For years, it was associated almost exclusively with young adults of African descent, which has been losing legitimacy in the last decade due to reports of patients of a wide range of races, ages, and nationalities.[1-3]

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AVSM constitutes the lowest reported incidence among all isolated MV diseases, with about 1% of cases.[3] On the African continent, it was first described in Nigeria in 1962 with a series of 12 cases.[4] According to the classification of Singh et al., taking into consideration the location and extent, it is classified into three types: Type I (localized single neck), type II (multiple necks), and type III (entire mitral annulus).[5]

Clinically, patients may remain asymptomatic for many years and maybe detected incidentally; in other cases, they may present with classic symptoms of heart failure (HF), mitral regurgitation (MR), ventricular arrhythmias, thrombotic events and/or myocardial ischemia secondary to extrinsic compression of the coronary arteries, and sudden death in the worst cases.[1-5]

Today, with new cardiac imaging technologies, as well as the wide availability of transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE), computed tomography (CT) and recently three-dimensional (3D) echocardiography and magnetic resonance imaging, this entity has disappeared from myth to an increasingly frequent reality within its limited spectrum. These techniques are able to accurately define the location, extent and severity of MR, as well as the degree of communication with the left ventricle (LV).[1,3,5,6]

Surgical resection is considered the corrective method of choice when performed by experienced personnel, with encouraging success rates and very low mortality.[6]

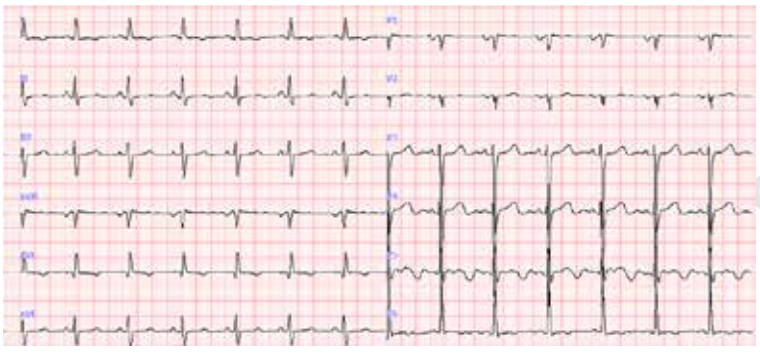

Figure 1: 12-lead electrocardiogram shows sinus rhythm, narrow QRS complexes, with signs of left chamber overload.

The present report refers to the case of a 28-year-old Angolan patient with severe MR due to AVSM.

CASE PRESENTATION

A 28-year-old Angolan woman with a history of pulmonary tuberculosis six years ago was referred to the cardiology department for progressive worsening of dyspnea over the past ten months, associated with easy fatigue and considerable weight loss. She had no known history of endocarditis and multiple admissions to a tertiary care unit for HF. She was evaluated at the cardiology service of the Girassol clinic to define the origin of the diagnosed MR; initially, rheumatic valve disease was considered, given the local epidemiological context. The physical examination drew attention to the weight loss and the presence of a regurgitant murmur at the mitral level.

Tests performed

A 12-electrocardiogram was performed, showing sinus rythm but with signs of left chamber overload *(Figure 1)*. A transthoracic echocardiogram was then requested, which revealed an image suggestive of aneurysm formation in mitral subvalvular projection located at the level of the posterior leaflet (in submitral projection) communicating freely with the LV and presence of severe MR with the enlarged left atrium *(Figure 2)*. The transesophageal echocardiogram (TEE) confirmed a severe MR, and the single neck of the aneurysm connected to the LV is better visualized without a thrombus image within the aneurysm *(Figure 2)*. Cardiac angiotomography *(Figure 3A-C)*: illustrates mitral subvalvular aneurysmal dilatation and a communicating aneurysm *(Figure 3D)*.

DISCUSSION

AVSM is a rare anomaly diagnosed in any age and ethnic group, but with a higher documented incidence among young African adults.[1] Since its first description,[3,7] AVSM has been the subject of numerous debates in an attempt to discover its true etiology and to

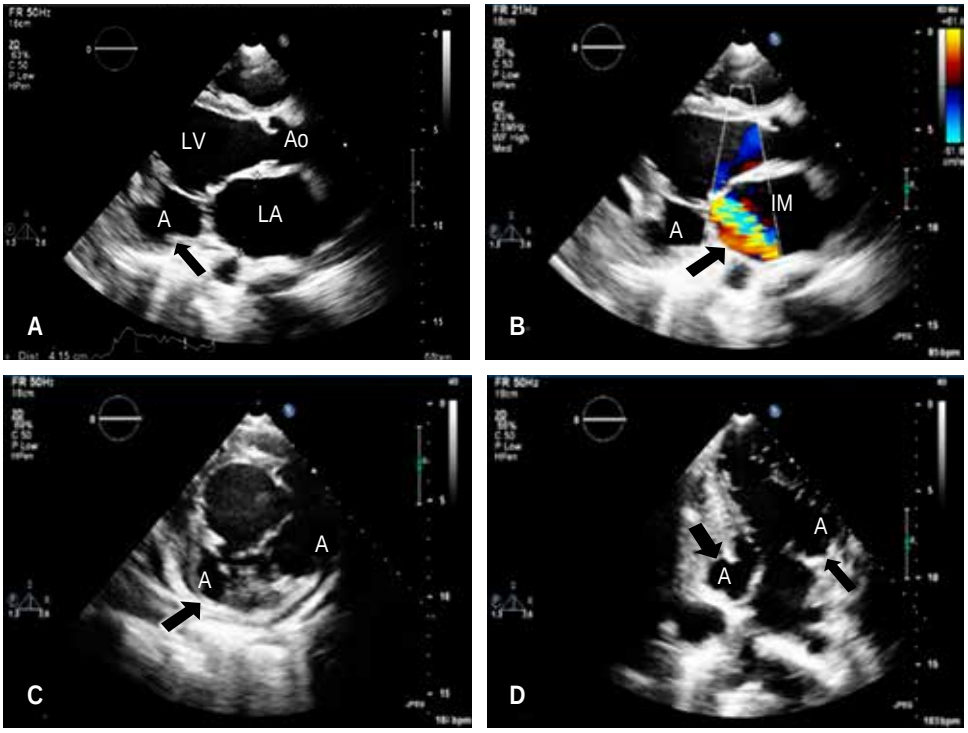

Figure 2:

Transthoracic echocardiogram. **A)** Two-dimensional mode in long-axis parasternal view with the presence of an aneurysm in the basal portion of the LV posterolateral wall at the mitral subvalvular level (arrow). **B)** Colorful Doppler image with severe mitral regurgitation (arrow). **C)** Aneurysm (arrow). **D)** Fistulated aneurysm (arrow). A = aneurysm; LA = left atrium; Ao = aorta; LV = left ventricle; IM = insuficiency mitral.

clarify its relationship primarily in this group of individuals.[1-4]

Although its incidence is certainly underestimated worldwide,[7] several recently published reports show a variable prevalence in different countries.[3-6] Humberto et al., in a systematic review of all relevant articles worldwide between 1962 and 2018, identified 150 patients diagnosed with a subvalvular aneurysm, with the majority being submitral aneurysms (140) and 125 of these of congenital origin.[1]

It is now generally accepted that AVSM is related to the presence of congenital weakness of the posterior MV annulus fibrosus, and this phenomenon could constitute the fundamental anatomical substrate for conditioning individuals susceptible to this condition, especially when exposed to certain infectious and inflammatory processes or degenerative processes involving the perivalvular endocardium.[1,4-7] This raises some the questions: why is there such a predisposition in black African individuals, are they only discovered and reported incidentally in our environment, or is the exclusive genetic basis of the disease in our environment? Or is the exclusive genetic basis at the heart of these questions?

Contradictorily, Africa is a predominantly poor continent, with few technological resources to diagnose this disease. In this particular sense, a Brazilian study contradicts the hypothesis that AVSM is an exclusive phenomenon of African ancestry, comparing this reality with the degree of research in the region on a given topic, as in the case of Chagas' cardiopathy in that country.[8]

Several cases are diagnosed incidentally, probably because in the early stages, there is usually no symptomatology that draws the attention of professionals to this entity, which delays the best approach to these patients.[9] This may have occurred with the patient in question. However, we had already received her with symptoms of severe HF.

Angolan authors report a wide range of age groups of these patients, and based on these reports; we can infer that the incidence in Angola seems to be considerably high if we take into account the numerous published cases in relation to other African countries to be due to the high burden of

infectious diseases, where rheumatic heart disease, syphilis, and tuberculosis continue to have the greatest negative impact on morbidity and mortality, with a possible causal relationship in the etiopathogenesis of AVSM, as mentioned above.[1,6,9] In this regard, Wolpowitz et al. state that syphilis initially causes the formation of pulsatile diverticula in susceptible individuals (congenital weakness of the LV wall in the vicinity of the atrioventricular groove), but this granulomatous disease is not considered a common cause of AVSM among Africans.[10]

Amidst these controversies about the origin of AVSM, it can be admitted that a multifactorial phenomenon seems to be the explanation for the supposed predisposition of Africans. From the point of view of an anatomical vulnerability of LV structures at the mitral subvalvular level linked to the peculiar epidemiology of the aforementioned infectious diseases, which present a pathophysiological link resulting in chronic inflammation, progressive degeneration of the endocardial junction with the mitral-aortic ring.[6-8]

The clinical image is varied, but the MR and the resulting varying degrees of HF motivate the search for medical attention, all caused by volume overload of the left chambers, highlighting the importance of including AVSM as an etiological diagnosis in patients with MR.[1-3] Other less common symptoms are lethal arrhythmias, precordial pain, the presence of thromboembolic phenomena, and myocardial ischemia due to compression of the coronary arteries by the aneurysm.[5] Treatment is eminently surgical with excellent long-term survival worldwide.[1,6,8,10]

This clinical case presented a clinical image of HF associated with severe MRI, later confirmed by echocardiography. The dyspnea and progressive fatigue were related to valve dysfunction, in addition to the size of the aneurysm that can accommodate large regurgitant volumes during systole. MRI is considered secondary to the displacement of

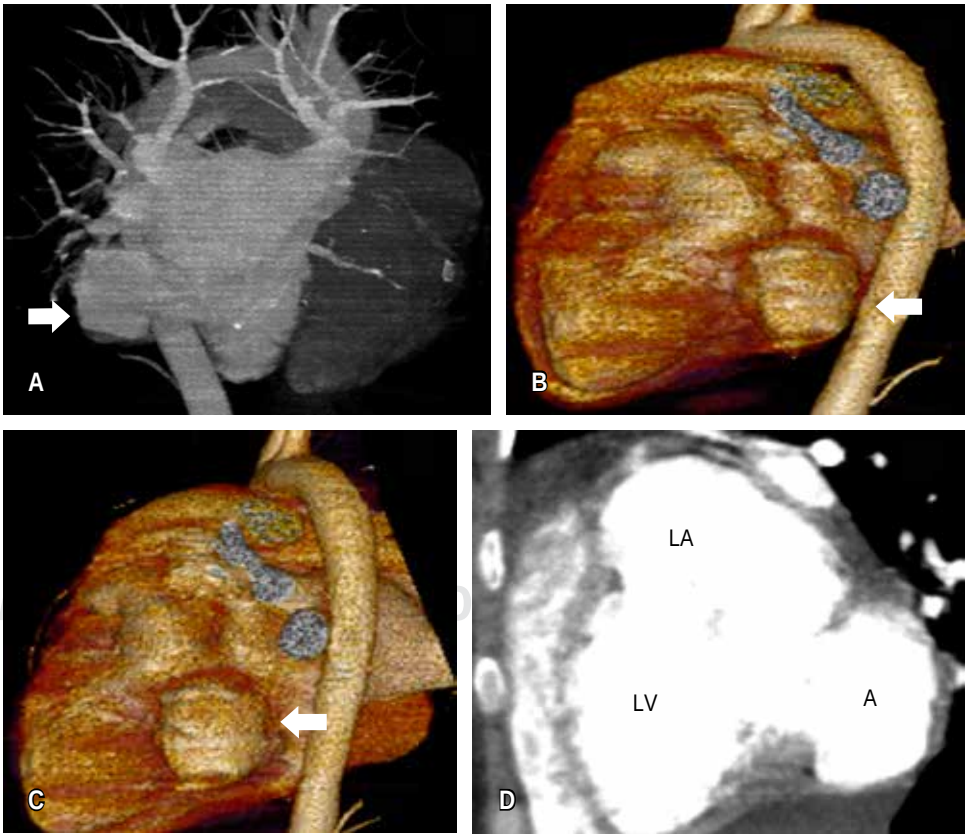

Figure 3:

A-C) Cardiac computed axial tomography angiography. Illustrate submitral aneurysmal dilation (white arrow). **D)** The aneurysm communicates with the left chambers.
A = aneurysm; LA = left atrium; LV = left ventricle.

the posterior mitral annulus and separation of the subvalvular apparatus, resulting in mitral leaflet coarctation failure, a finding consistent with recently published reports.[1,8,10]

It is clear from the present report that diagnosis and treatment, in this case, were late, as the patient was already in NYHA functional class IV. The patient was referred to the Girassol Clinic Cardiovascular and Thoracic Center for surgical correction.

Resection of the aneurysm was performed, and an attempt was made to perform MV plastic surgery, which was not possible due to the advanced degree of dislocation of the posteromedial papillary muscle and its respective chordae tendineae. The patient presents a good clinical evolution with one year of follow-up and is in NYHA functional class I.

CONCLUSIONS

Many clinical and pathophysiological aspects of this rare entity related to mitral regurgitation in individuals who are usually young and, interestingly, from the African continent remain unknown, and the reasons remain unclear. We believe that future research can shed light on these facts so that it will be possible to identify vulnerable individuals early and thus avoid extreme repercussions on the heart of those affected.

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REVIEW

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The emerging added value of cardiac magnetic resonance over echocardiography in the assessment of functional mitral regurgitation

El valor añadido emergente de la resonancia magnética cardiaca sobre la ecocardiografía en la evaluación de la insuficiencia mitral funcional

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Keywords:
Functional mitral regurgitation, multimodality cardiac imaging, cardiac magnetic resonance, regurgitant fraction.

Palabras clave:
Insuficiencia mitral funcional, imagen multimodal cardiaca, resonancia magnética cardiaca, fracción regurgitante.

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ABSTRACT

According to a new conceptual viewpoint, functional mitral regurgitation (FMR) is consistent with a variety of structural and dynamic characteristics in several clinical scenarios regarding the involvement of the left ventricle (LV) and the mitral valve (MV) integrity. Echocardiography is, for sure, the first-line cardiac modality to the classification of the etiology and the severity of FMR. However, it does not provide complete and accurate information on the LV compromise and tends to have some methodological errors in calculations. Cardiac magnetic resonance (CMR) is the gold standard technique for LV volumes, left ventricular ejection fraction (LVEF) and could fully integrate LV tissue characterization in several cardiomyopathies and allow the quantitative estimation of the severity valve insufficiency and could help to guide better clinical decision-making.

RESUMEN

De acuerdo con un nuevo punto de vista conceptual, la insuficiencia mitral funcional es consistente con una variedad de características estructurales y dinámicas en varios escenarios clínicos con respecto a la afectación del ventrículo izquierdo (VI) y la integridad de la válvula mitral. La ecocardiografía es sin duda, la modalidad cardíaca de primera línea para la clasificación de la etiología y la gravedad de la insuficiencia mitral funcional. Sin embargo, no proporciona información completa y precisa del compromiso del VI y tiende a tener algunos errores metodológicos en los cálculos en su estimación. La resonancia magnética cardíaca es la técnica de referencia para la estimación de los volúmenes y la fracción de eyección del VI y podría integrar el estudio de la caracterización tisular del VI en varias miocardiopatías; permite la estimación cuantitativa de la gravedad de la insuficiencia valvular y podría mejorar la toma de decisiones clínicas.

INTRODUCTION

The comprehensive assessment of FMR requires integrating MV anatomy features, regurgitant severity by quantitative parameters, LV volumes, and LVEF that are primarily best evaluated by the transthoracic echocardiography (TTE). MV morphology should be carefully assessed in multiple views using B-mode imaging to evaluate structure and motion; color flow Doppler is utilized to localize MR jet origin. However, if the image quality is poor with TTE, transesophageal echocardiography (TEE) may be needed to define anatomy and valvular function more precisely.[1] Therefore, TEE may identify lesions such as vegetations or flail segments not detected by TTE for determining the etiology of mitral regurgitation (MR).[2,3] The measurements of LV dimensions, volumes, and LVEF are performed according to the American Society of Echocardiography (ASE) guidelines for chamber quantification.[4]

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MR can have a primary (organic) or secondary (functional) etiology.[5] The primary MR is generally due to degenerative disease, also is characterized by direct damage to the structure of the leaflets (prolapse or rupture), which leads in the progression to an increase in volumes and a decrease in LVEF directly related to the primary MV involvement, and these patients will benefit from the direct intervention of this etiological cause (repair or replacement of the mitral valve).[1] In the setting of FMR, it reflects the severity of an underlying LV disease, which is the primary determinant of disability and death, and MR is a simple biomarker of advanced ventricular myopathy. For that reason, we traditionally interpret it as secondary or functional MR.[5,6]

The estimation of MR by quantitative measures is strongly recommended for assessing MR severity.[7] The calculation of effective regurgitant orifice area (EROA) is a quantitative marker of severity, as well as regurgitant volume (RV) and regurgitant fraction (RF). The echocardiographic assessment by several parameters, including the proximal iso-velocity surface area (PISA) method, volumetric methods, and 3-dimensional imaging, commonly define MR severity.[1]

It is crucial to recognize some technical limitations and imprecision of each method and the overlap of values obtained. PISA or vena contracta width are parameters that allow the estimation of EROA, RV, RF and are obtained by a single-frame measurement for

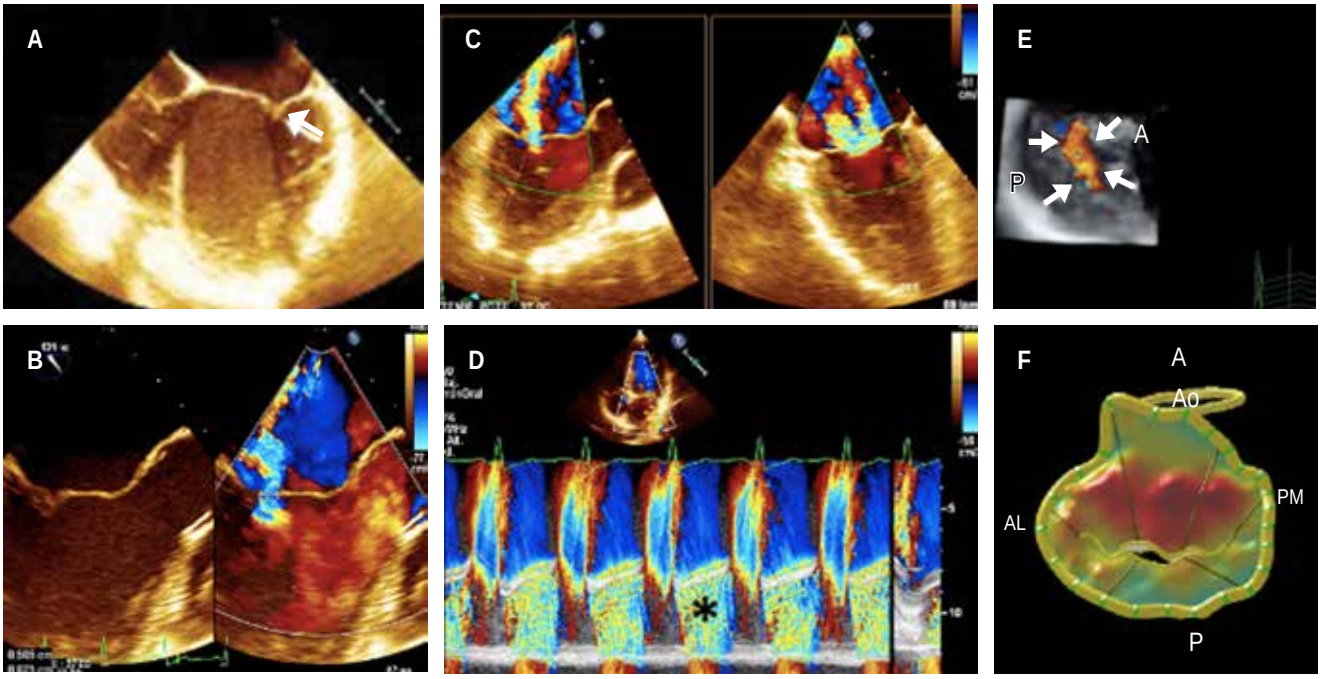
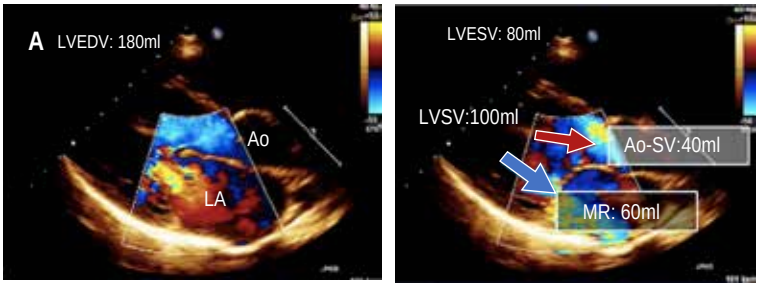


Figure 1: Echocardiographic assessment of the etiology of functional mitral regurgitation by 2-dimensional and 3-dimensional transesophageal echocardiography. All measures were obtained in a single frame during systole for estimation of mitral regurgitation severity. **A)** Mid-esophageal (0 degrees) four-chamber view showing a restricted posterior leaflet motion compatible with a Carpentier IIIb mitral regurgitation. (white arrow). **B)** Mid-esophageal three-chamber view (120 degrees) with an anteroposterior orientation of the mitral valve (A2-P2) showing underestimation of severity with a PISA of 6.7 mm a vena contracta width of 5 mm compatible with moderate mitral regurgitation. **C)** Simultaneous (X-plane) views of mitral valve with 3D assessment in an anteroposterior (three-chamber view) and bi-commissural (two-chamber view) orientation denoting an extensive MR in the bi-commissural two-chamber view. **D)** Color Doppler M-mode in mitral regurgitation with a holosystolic duration of the jet (black asterisk). **E)** Transesophageal echocardiography 3-dimensional in-face view of mitral valve with color Doppler evaluation confirming a large effective regurgitant orifice area that occupied the almost complete coaptation line in a commissural orientation. **F)** Schematic mitral valve model obtained by 3-dimensional transesophageal echocardiography.
P = posterior; A = anterior; AL = anterolateral; PM = posterior medial.



B

Left ventricle and mitral regurgitation, parameters	MITRA-FR	COAPT
Left ventricular ejection fraction (%)	Reported	31	31
Effective regurgitant orifice area (cm^2)	Reported	0.3	0.4
Left ventricular end-diastolic volume (mL)	Reported	245	193
Left ventricular end-systolic volume (mL)	Calculated: (LVEDV-LVESV) in MITRA-FR (calculated from LVEDV and LVEF	76	51
Regurgitant volume (mL)	Reported	45	60
Aortic stroke volume (mL)	Calculated: LVSV-RV	31	-9
Regurgitant fraction (%)	Calculated: (RV/LVSV)	59	118

LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, LVEF = left ventricular ejection fraction, LVSV = left ventricular stroke volume, RV = regurgitant volume.

Figure 2: Illustrative findings of functional mitral regurgitation in MITRA-FR and COAPT trials. **A)** In quantitative mitral regurgitation severity assessment, the left ventricular end-diastolic volume (upper left) and left ventricular end-systolic volume (upper right) allow the estimation of left ventricular stroke volume. This left ventricular stroke volume is ejected in systole throughout the aorta, and other parts of blood flow return to the LA representing the RV. **B)** Left ventricle and regurgitant volume parameters of quantitative evaluation in both trials.
LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, LVSV = left ventricular stroke volume, LA = left atrium, Ao = aorta, RV = right ventricle, LV = left ventricle.

TTE or TEE that can markedly overestimate MR severity when the jet is limited to early or late systole.[8] Nevertheless, when MR is holosystolic, properly measured values of EROA > 0.4 cm^2, RV > 60 mL, or RF > 50% are precise for severe MR. In the setting of FMR, a lower value of EROA and RV may underestimate lesion severity associated with markedly crescentic orifice geometry, where PISA yields a falsely low value for EROA due to its inherent assumption of a round orifice.[9-13] 3-dimensional TEE can directly visualize of these characteristics and precise quantification of EROA *(Figure 1)*.

The results of two recent transcatheter mitral valve repair trials in FMR with MitraClip® compared with medical therapy alone concerning all-cause mortality and the rate of hospitalization for heart failure showed different and contradictory results. In the MITRA-FR, investigators did not observe any effect on death and hospitalization within 12-month follow-up,[14] and in the COAPT trial, it was documented a 29% reduction of death and a 46% reduction of hospitalization within a 24-month follow-up.[15]

The disparity results of these two trials arrived in discussions in this setting addressed in different recent published data.[16,17] A part of these discussions made special attention to the inconsistencies in the assessment of MR severity when assessed by echocardiography in both trials. It is known that echocardiographic parameters are highly predisposed to methodological errors when defining MR severity by EROA and RV determined by the PISA method.[18-20] According to this technique, MR severity is estimated by a single snapshot during the cardiac cycle when it is better and larger visualized. Nevertheless, the PISA method was the parameter used in the two trials when defining MR severity.

When comparing and analyzing parameters of LV and MR in both trials, we found several inconsistencies. The reported LVEF was similar in both trials, about 31% compatible with severe LV dysfunction. The MR severity estimated by EROA in the MITRA-FR trial was lower than COAPT (0.3 vs 0.4 cm^2). In the MITRA-FR, the mean value of LV end-diastolic volume was about 245 mL (reported indexed value of 135 mL/m^2), and in the COAPT trial, a lower value of 195 mL. The total LV stroke volume in MITRA-FR

was about 76 mL (calculated from LVEDV and LVEF) and was reported in 51 mL in the COAPT trial. The RV in MITRA-FR was informed to be 45 mL and in COAPT of 60 mL.[21] Therefore, based on these MITRA-FR parameters, if the LV stroke volume was 76ml, and the RV was 45 mL, the estimated aortic stroke volume was 31 mL (LV stroke volume-RV). Whereby, the calculated RF (RV to LV stroke volume) was about 59%, while in the COAPT trial, if the LV stroke volume was 51 mL and the RV was 60 mL, the estimated aortic stroke volume (LV stroke volume - RV) had an inconsistent value of -9 mL during systole, and the calculated FR was about 118% (RV to LV stroke volume). Because of these considerations and errors, the MR severity assessment by semiquantitative parameters has to be reconsidered.[18,19] Also, this indicates the difficulties in the estimation of LV volumes, the stroke volume, and the severity of MR by quantifying with a value that represents only a single shot of MR with a lack of data for dynamics quantitative evaluation echocardiography in FMR *(Figure 2)*.

Determination of different phenotypes in functional MR

Defining several phenotypes of FMR may help determine the efficacy of different interventions. Severe MR in the setting of new-onset cardiomyopathy often resolves with aggressive medical optimization. However, a subgroup of patients persists despite optimal medical treatment, in whom the eventual benefit of MR correction arises. In the COAPT trial, 40% of the candidates screened were categorized to have severe MR that was truly medically refractory.[15] Another essential part of the discussion regarding the discordant results of MITRA-FR and COAPT trials is the relation of EROA and RV to LV end-diastolic volume and to distinguish between new conceptual discrimination in FMR proportionate and disproportionate according to the LV size[16] with less LV remodeling after treatment secondary to higher LV dimensions. When quantifying LV volumes using 2D TTE, we have a standard error of 20% using Simpson's method generally due

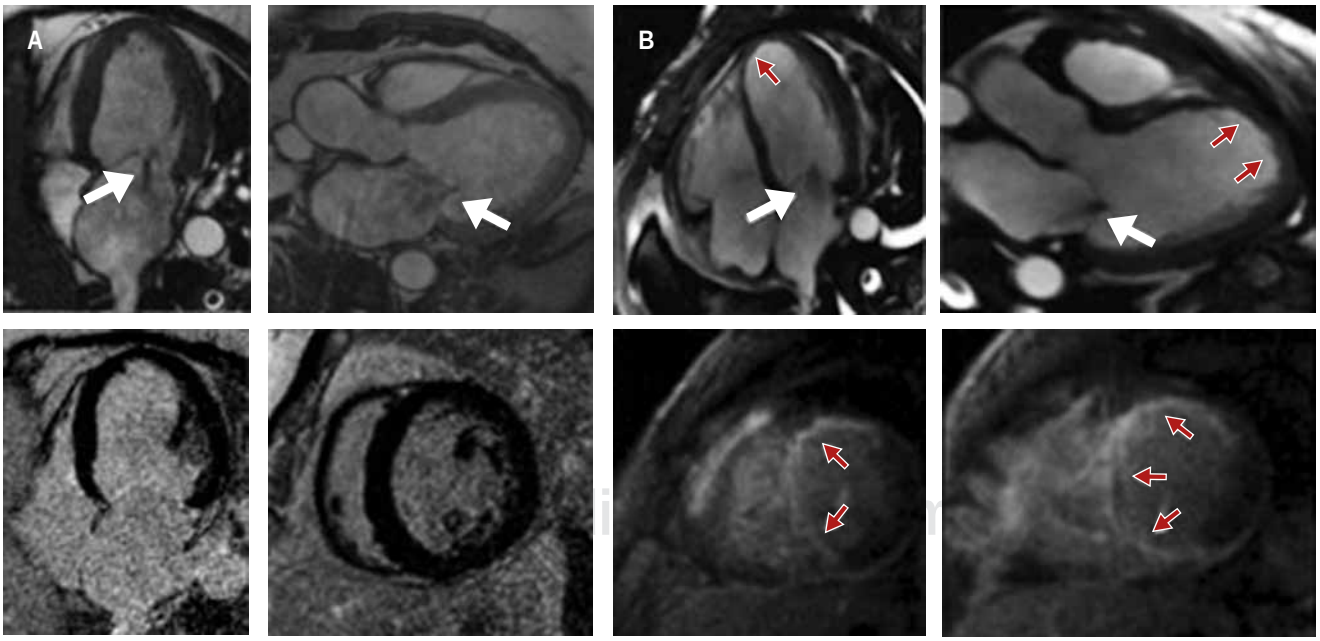


Figure 3: «Ventricular functional mitral regurgitation» (white arrows) in the setting of: **A)** non-ischemic cardiomyopathy with the absence of late gadolinium enhancement, **B)** ischemic cardiomyopathy with the presence of transmural late-gadolinium enhancement in left descending coronary artery left ventricle territory (red arrows).

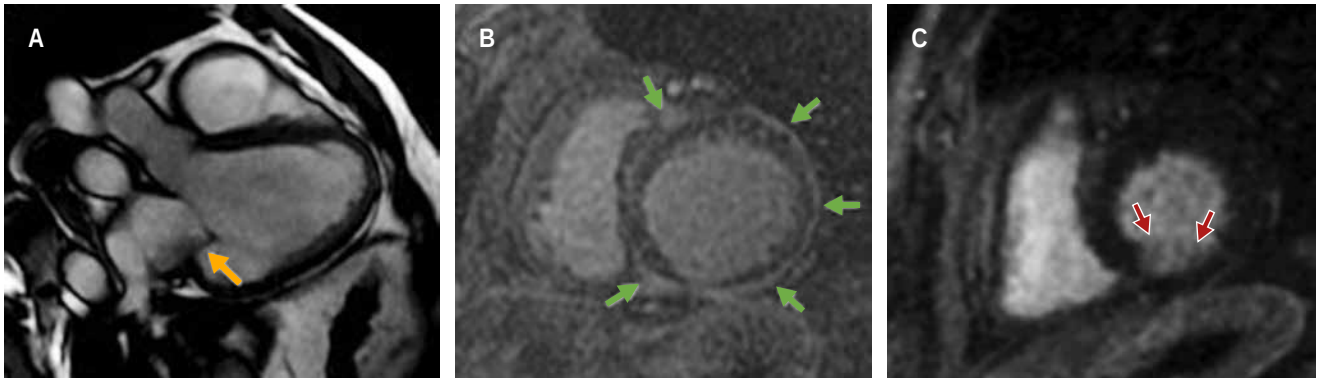


Figure 4: A) «Ischemic» functional mitral regurgitation presenting with restricted posterior leaflet motion leads to a homolateral excentric jet (yellow arrow). **B)** Non-ischemic cardiomyopathy showing subepicardial late-gadolinium enhancement distribution (green arrows). **C)** Showing ischemic cardiomyopathy with subendocardial inferior late-gadolinium enhancement by prior myocardial infarction (red arrows).

to foreshortening views. The mean difference of LV end-diastolic volume in both trials was «only» 45 mL, making this distinction difficult to determine precisely by 2D TTE. Thus, conclusions should be drawn with care based on LV end-diastolic volume and LVEF in FMR patients in MITRA-FR and COAPT.[21] Other parameters to analyze reverse LV remodeling after treatment were not reported in both trials and limits the interpretation of results, such as parameters of LV systolic function as peak power index, global longitudinal peak systolic strain, and papillary muscle involvement as the lateral and posterior dislocation, interpapillary muscle distance, tenting mitral valve area, and tethering mitral valve angles.

The more prevalent FMR arises due to symmetric retraction of the leaflets due to ventricular dilation with a centrally directed regurgitant jet, often aggravated by ventricular dyssynchrony. This type of MR has been called by some authors «ventricular functional MR». It could respond to medical therapy directed by guidelines or cardiac resynchronization,[22] these patients may have an ischemic-type etiology with altered contractility of the most apical segments or a non-ischemic type etiology with different degrees of ventricular dilation, to be considered as a true alteration of the LV and not of the MV itself *(Figure 3)*.

Another subgroup of patients presents abnormal contractility of the most basal segments of the inferior wall, predominantly due to coronary disease in an ischemic etiology, causing a restrictive movement and retraction of the posterior leaflet that results in a generally eccentric MR with posterior and lateral direction known as «ischemic MR».[22] Forming part of a structural anomaly of the valvular apparatus itself less susceptible to respond to medical treatment alone, in these cases surgical valve resolution has been associated with a better quality of life and a reduced amount heart failure events,[23] which supports its independent pathophysiological importance *(Figure 4)*. More recently, a functional MR of an atrial origin has been recognized, frequently associated with atrial fibrillation resulting from atrial remodeling and associated mitral annular dilation, leading to a central jet's appearance due to central coaptation deficit, without significant ventricular dilation.[24,25] So, likely, this atrial functional MR responds less to LV-directed medical therapy.

CMR imaging is not only the gold standard non-invasive imaging modality for assessing LV volumes, LVEF, and determining the etiology of several cardiomyopathies by late-gadolinium enhancement distribution, but also is a valuable technique allowing to quantifying flow to determine an accurate assessment of valvular regurgitation in discordant cases.[26,27] Assessment of valvular regurgitation is calculated on CRM by qualitative, semiquantitative, or quantitative methods. Qualitative determination of valvular regurgitation can be visually estimated as the extension of signal loss due to spin dephasing

in the left atrium on cine CRM images. However, this parameter can underestimate regurgitant severity.[28] Quantitative estimation of EROA can be calculated from the cine images after correct alignment and angulation of MV in an end-systolic frame.[29] Nevertheless, this method depends on appropriate MV plane alignment and angulation during imaging acquisition. Therefore, quantitative determination of RV and RF is the most utilized and accurate technique to define severity, mostly calculated using an indirect approach by comparing ventricular stroke volume to forward aortic flow or comparing LV and RV stroke volume in the absence of other valvular lesions.[30] This type of regurgitant valve regurgitation assessment had the advantage of being highly reproducible, and robust being not affected by some jet regurgitant features such as the direction or eccentricity, the presence of concomitant aortic regurgitation, and did not make LV geometry assumptions when estimating LV volumes and systolic stroke volume as present in echocardiography. The area under the curve of this volumetric method to define regurgitant severity was higher compared by 3D-echo, 2D-echo, and direct phase-contrast CMR (AUC: 0.98, 0.96, 0.90, and 0.83 respectively).[30]

These echocardiographic MR severity inconsistencies in valvular regurgitation assessment by semiquantitative non-accurate methods, highly

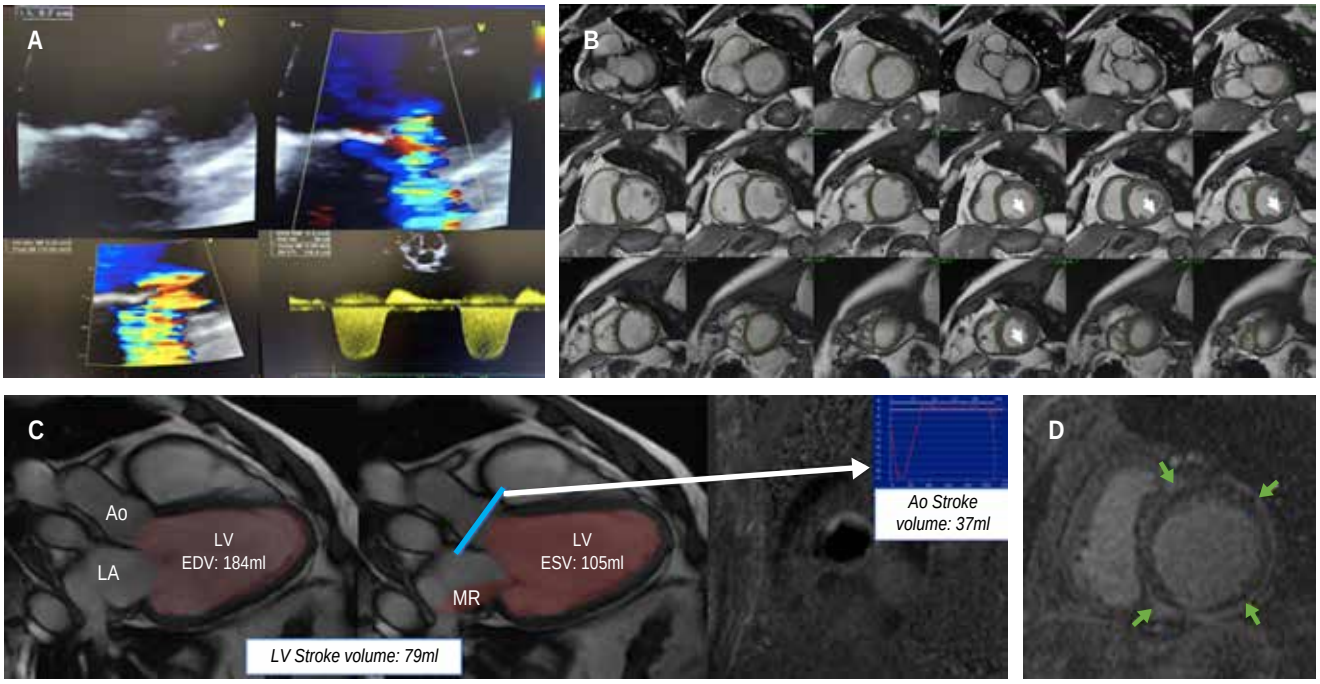


Figure 5: Representative case of the usefulness of regurgitant fraction assessing mitral regurgitation severity in functional mitral regurgitation. **A)** TTE of excentric mitral regurgitation with restricted posterior leaflet motion consistent with a moderate mitral regurgitation with an estimated effective regurgitant orifice area of 0.3 cm^2. **B)** CMR short-axis cine images in diastole [upper middle] and systole [upper right], showing thinned and akinetic contractility of inferior and inferolateral basal and middle left ventricle segments suggesting an ischemic mitral regurgitation with prior myocardial infarction. **C)** Volumetric cardiac magnetic resonance assessment of mitral regurgitation severity denoting a slightly dilated LV (LVEDV 184 mL, LVESV 105 mL), with an LVEF of 43% and left ventricle stroke volume of 79 mL. Aortic stroke volume by the phase-contrast image in ascending aorta (bottom middle) was 37 mL. The regurgitant volume was measured in 42 mL, and according to guidelines, it is consistent with moderate mitral regurgitation. Nevertheless, when assessing regurgitant fraction value is 53% confirming a severe mitral regurgitation in the specific context of left ventricle volumes, LVEF, and stroke volume in our patient. **D)** The late-gadolinium enhancement images showed non-ischemic cardiomyopathy with the global subepicardial distribution.

CMR = cardiac magnetic resonance, LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, LVEF = left ventricular ejection fraction.

support a volumetric quantification to define MR severity, supporting the RF as the most reliable parameter to define severity, especially in the setting of LV dilation and dysfunction when RV may have several effects with different related volumes that can be precisely estimated by CMR imaging, such as end-diastolic volume, LVEF, stroke volume, and cardiac output in an individualized patient approach. Therefore, the LV total systolic stroke volume and RV are relevant in patients and can be related to different cardiac outputs. In this context, the RF becomes the most relevant parameter of estimation in FMR, where most have LV dilatation and systolic dysfunction and different cardiac stroke volumes where a lower RV than 60 mL could represent a RF higher than 50% *(Figure 5)*.

In functional MR, CMR can assess for ischemia, regional wall motion abnormalities, and myocardial viability. The amount of scar by late-gadolinium enhancement could be relevant in this context in patients' prognoses beyond the MR severity. The relationship between FMR severity and LV scar has been examined in a study of patients with ischemic cardiomyopathy. They used RF to assess MR severity instead of effective regurgitant orifice area alone, and both parameters were well correlated in the study. Additionally, the investigators found that although one might suppose that increasing scar burden would also worsen MR, both were not well correlated. However, the prognosis did worsen with both increasing MR and increasing scar. Most importantly, the combination of scar and MR severity worked in tandem to dramatically affect prognosis, with a 4-year survival of only 50% in patients with significant scar burden and the most severe MR (regurgitant fraction > 35%).[31]

Most patients treated with MitraClip® had an ischemic MR in MITRA-FR or COAPT, and scar burden was not measured, but it is certainly reasonable to guess that it might have had an impact. It could be that patients with the most considerable scar burden have such sick hearts that they cannot benefit from interventions. It may be that only muscle rather than scar can participate in the beneficial effects of correcting MR. This hypothesis is supported by examining the subgroup of patients who underwent mitral surgery; the patients with the highest scar burden had the worst outcomes. Perhaps the ischemic patients in MITRA-FR had a more considerable scar burden, accounting for larger ventricles and the lack of benefit after MitraClip®. Nonetheless, those data suggest that scar burden alone cannot explain the different outcomes of the two studies but might be an essential factor, and scar burden is itself a risk factor in secondary MR and might modulate the interaction between MR severity and recovery post-MitraClip®.[32]

CMR imaging is currently well recognized and recommended in international valve disease guidelines. However, it is a cardiac imaging technique with several limitations. It has a relatively long scan time compared with echocardiography. Generally, it is more expensive and has less availability. Correct electrocardiographic gatting is always necessary, and arrhythmias can deteriorate the image quality and interpretation. A breath-hold apnea period is also necessary and cannot be done in unstable conditions.[33] Another relevant limitation of CMR against echocardiography is its lower temporal resolution (typically 25-45 ms, 10-fold lower than Doppler echocardiography). Thus, it may underestimate peak values in high-velocity jets and lead to the worst detail imaging of mitral valve involvement in specific cases.[34] Transesophageal echocardiography, especially by three-dimensional technique, has an essential role in intraprocedural MitraClip® intervention, allowing the assessment for correct device position and residual MR. Compared with CMR allows the determination of immediate post-procedure ventricular systolic function and pulmonary artery systolic pressure and helps determine complications.[35]

CONCLUSIONS

Functional MR is a complex condition with the involvement of the LV and the MV in different degrees, and characterization of each scenario would be useful to determine the best individualized therapy. Echocardiography is always the first-line modality for determining the etiology of MR and severity, but CMR allows integrated and precise information about LV volumes, LVEF, and accurate volumetric assessment to clearly define a severe MR quantitatively. The RF is

the most reliable volumetric method to define severe MR in FMR. Moreover, scar burden by late-gadolinium enhancement helps to determine the etiology of the underlying cardiomyopathy but also defines patients with the worst outcomes in the follow-up even after the intervention of the MV. Randomized clinical trials with the integration of CMR data in this context are necessary to study a generalized indication in the assessment of functional mitral regurgitation in a multimodality approach.

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REVIEW

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The U wave: an ignored wave filled with information

Onda U: una onda olvidada llena de información

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Keywords:
Electrocardiogram, U-wave, inverted, prominent, ischemia.

Palabras clave:
Eletrocardiograma, onda U, invertido, prominente, isquemia.

ABSTRACT

The U wave was first described over more than 100 years. However, numerous hypothesis about its origin and clinical significance still exist. It corresponds to the sixth wave of the electrocardiogram (ECG), and its visibility depends, among others, on the heart rate, but it may be absent in 50-75% of cases. Its origin is a cause of debate; there are four crucial hypotheses about its genesis: 1) repolarization of purkinje fibers, 2) repolarization of papillary muscles, 3) M cells theory, and 4) mechanoelectrical theory. Variants of the U wave are prominent and inverted. The inverted U wave is associated with hypertension, coronary heart disease or valvular disease. The prominent U wave is related to bradycardia, hypokalemia, hypothermia, long QT syndrome or with the use of some medication like class Ia and III antiarrhythmics.

RESUMEN

La onda U se describió por primera vez hace más de 100 años. Sin embargo, aún existen numerosas hipótesis sobre su origen e importancia clínica. Corresponde a la sexta onda del Electrocardiograma (ECG), su visibilidad depende, entre otras cosas, de la frecuencia cardíaca, pero puede estar ausente en el 50-75% de los casos. Su origen es motivo de debate; existen cuatro hipótesis cruciales sobre su génesis: 1) repolarización de las fibras de Purkinje, 2) repolarización de los músculos papilares, 3) teoría de las células M, y 4) teoría mecanoeléctrica. Las variantes de la onda U son: prominente e invertida. La onda U invertida se asocia con hipertensión, enfermedad coronaria o enfermedad valvular. La onda U prominente está relacionada con bradicardia, hipocalemia, hipotermia, síndrome de QT largo o con el uso de algunos medicamentos como los antiarrítmicos de clase Ia y III.

INTRODUCTION

More than 100 years ago, Willem Einthoven described the first five waves of the electrocardiogram (ECG) using a capillary electrometer, but it was some years later with the invention of the string galvanometer when he identified the sixth deflection of the ECG, the one following the T wave and he named it the U wave.[1] Nevertheless, there was neither a definition nor description of its normal characteristics,[2] and it was believed that the U wave represented currents generated by late repolarization of some areas of the ventricular myocardium.[3,4]

Despite its longstanding description, there are no unified criteria nor definition, and there are still lots of uncleared hypotheses about its origin. We know so far that the presence of a U wave can be a normal or pathological finding that can be associated with arterial hypertension, valvular disease, ischemic coronary disease if it is an inverted U wave. In the case of a prominent U wave, it is associated with hypokalemia, hypothermia, long QT syndrome and some antiarrhythmics. In this article, we will review these findings and their possible pathological significance.[5]

MORPHOLOGY AND NORMAL CHARACTERISTICS

The U wave corresponds to the fourth phase of the action potential. It happens during

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the protodiastolic period of the cardiac cycle and matches the second or third cardiac sounds.[6]

The U wave is not constantly seen, and it is absent in 50-75% of cases.[6] Its visibility on the ECG depends on the heart rate, and it is evident in 90% of cases with heart rates below 65 bpm (beats per minute), and its rarely seen with rates over 95 bpm.[5,7,8] It is also more evident under some special conditions like hypokalemia, advanced age, and medications such as class Ia antiarrhythmics and amiodarone.[8]

Surawicsz meticulously described its typical features, and after, were widely reproduced.[5,9] The U wave begins after the end of the T wave and before the P wave of the following cardiac cycle;[6,7,10] it is usually better visualized in leads V2 and V3,[6-8] and in normal conditions, has the same polarity as the T wave.[11]

The standard duration of the U wave in adults is around 170 ± 30 ms, and its amplitude is in average 11% of T wave's amplitude (ranges from 3 to 24%); the morphology is usually monophasic positive or negative deflection, but it may be biphasic, and it has an asymmetric shape with a rapid ascending limb and a slower descending limb.[5,6,8]

The T-U junction is situated at or close to the isoelectric baseline. However, it may slightly deviate; with heart rates between 50-100 bpm, the distance from the end of T wave to the apex of U wave is between 90 to 110 ms, and from the end of T wave to the end of the U wave 160 to 230 ms.[5,6]

Accurate measurement of the QT interval is crucial, when the T and the U waves are easily identifiable the separation of them is not difficult, the end of the T wave is evident. The confusion appears when the T wave is notched, because its second peak can be mistaken with the U wave; to differentiate them, another lead where the T wave is not notched, or a lead without U wave could be useful. It is helpful to know that the distance between T wave peaks is usually less than 150 ms, in contrast to the distance between the first T peak and the U wave peak that is more than 150 ms. Another important concept is the QT + U or Q (T+U) interval. It describes the fusion of these segments in the ECG and mostly occurs in the circumstances when QT measures more than 100 ms, so the T wave masks the U wave.[5,12]

THE HYPOTHESIS OF THE ORIGIN

The genesis of the U wave is not clear yet; four major theories that try to explain it.

1. Repolarization of intraventricular conduction system

Hoffman and Cranefield first described the theory of repolarization of Purkinje fibers, and it was based on the fact that the action potential of these fibers is the longest of all the heart fibers.[13] Later on, Watanabe found a close relationship between the U wave and Purkinje repolarization in a series of experiments with canines and canine Purkinje fibers from ventricular muscle tissue under conditions known to accentuate the U wave as hypokalemia, hypothermia, administration of quinidine, and bradycardia.[14] However, there are many arguments against this theory, like the ones listed by Surawicz. He believed

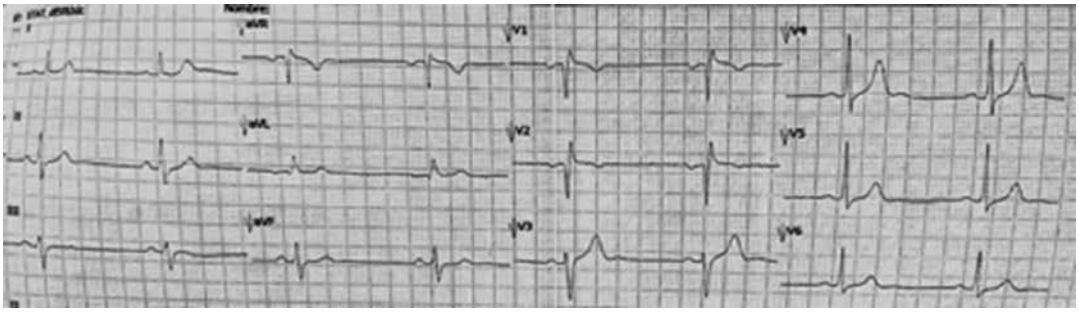

Figure 1: Normal U waves in leads V3 and V4 in a patient with sinus bradycardia.

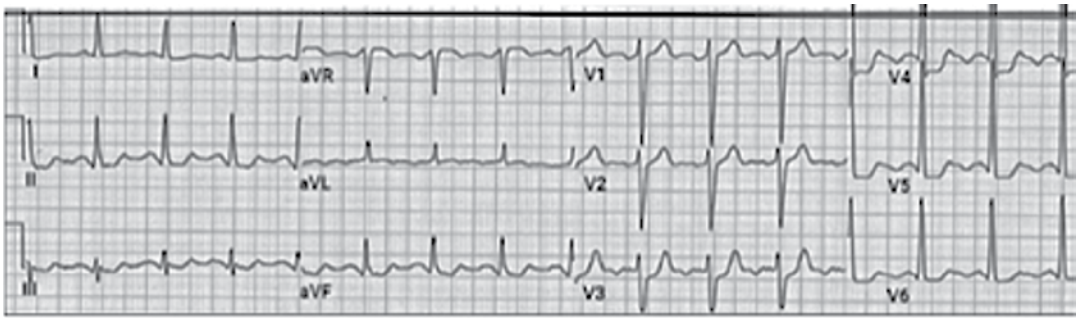

Figure 2: Inverted U waves in leads V3-V6 and aVL.

the difference in action potential duration, primarily of the functional refractory periods between the His-Purkinje system and the ventricular muscle in humans, do not explain the duration of U wave, and that the small mass of the conducting system tissue might fail to produce the deflection. Other arguments are the existence of U wave in amphibia, even though they do not have Purkinje fibers;[3,11] and that the configuration of the U wave is not concordant with the repolarization pattern of Purkinje fibers, among others.[5,6]

2. Repolarization of papillary muscles

Furbetta, Bufalari, and Santucci considered that the U wave corresponded to the repolarization of papillary muscles and the structures connected to them embryologically and functionally, primarily because of the results they obtained in experiments with dogs, where they found that the voltage of the U was highest indirect leads from points of the ventricular surface near the origin of these muscles.[2,15]

They also described the «papillary muscles syndrome» resulting from cardiovascular diseases that specifically affect the papillary muscles with perfusion disruption, strain, or metabolism disturbances. The electrocardiographic signs group every alteration on the U wave and de T-U segment and are arranged in 3 possible patterns: left, right and biventricular papillary muscle syndrome.[15] Nonetheless, arguments like the one posed by Surawicz, exposing that the differences between action potential durations of these structures are not sufficiently large to explain the typical duration of U wave, also go against this theory.[5]

3. M cells theory

The M cells were first described in a dog´s myocardium by Antzelevitch and Sicouri. They are a subpopulation of cells in the deep subepicardial to the mid myocardial portion of the ventricular wall with different electrophysiologic characteristics of those of the cardiac muscle and the conducting system.[4,16] The M cells' theory was based on the fact that their action potentials are distinctly more prolonged than those of other myocardial cells. They fulfilled some of the points that contradicted other theories, among these is that the repolarization is long enough, at least at slow rates, to match the timing of the U wave, and that the mass of M cells appeared to be substantial to cause a deflection on the electrocardiogram, occupying up to 40% of the left ventricular wall in dogs and 30% in humans. The main conflicting issue with this hypothesis is that it meets all the requirements at marked slow heart rates; these cells are more likely to prolong the T-wave rather than create distinct U waves.[3,9,16,17]

4. Mechanoelectrical theory

This theory is based on the electrical manifestations of ventricular stretch, which could be explained by mechanosensitive ion channels, transducing mechanical stimuli on electrical changes, creating after-potentials and influencing repolarization timing.[5]

It states that the U wave genesis is due to stretch-induced delayed after depolarization caused by the ventricular wall's distension during rapid ventricular filling.[2,16,18,19] Surawicz

Table 1: Most common conditions associated with changes in the U wave.

Negative U waves
Cardiac disease
• Coronary artery disease
• Hypertension
• Valvular disease
• Primary cardiomyopathy
• Left ventricular enlargement
• Congenital heart disease
Other conditions
• Hyperthyroidism
Normal
• 7% of the population has negative U waves without heart disease
Prominent U waves
Rhythms
• Bradycardia
• Complete heart block
• Congenital long QT syndrome
Cardiac disease
• Early repolarization
• Mitral valve prolapse
• Left ventricular enlargement
• Cardiomyopathy
• Circumflex-related myocardial infarction
Physical
• Hypothermia
• Forced inspiration
• After exercise
• Central nervous system/cerebral events
Electrolytes
• Hypokalemia
• Hypomagnesemia
• Hypocalcemia
Medications
• Class III antiarrhythmics
• Class IA antiarrhythmics
• Epinephrine
• Digitalis
• Phenothiazines

specified that the U wave's appearance coincides with the isovolumic interval from the closure of the semilunar valves to the opening of the atrioventricular valves and the early diastolic interval.[5,19]

This explanation was supported mainly by the timing of the U wave coincident with the time of ventricular relaxation.[20] However, it was questioned because, with the advent of intracellular recording, it was noticed that, in general, normal cardiac cells did not generate after depolarizations, so they cannot explain the U wave that appears under normal conditions (> 40% of adults).[3,4] However, in the model of Di Bernardo et al., it was considered that after-potentials could explain U waves in normal subjects. They also affirmed that delaying repolarization in different regions of the heart cannot explain the U wave. Although they found that after-potentials' presence does explain some of its characteristics, like the polarity, and that abnormal after-potential timing corresponds with abnormal U wave inversion *(Figure 1)*.[9]

Next, we explain the most common conditions associated with changes in the U wave *(Table 1)*.

INVERTED U WAVES

Since the middle of the last century, it has been spoken about the importance of the inversion of the U wave and negative U wave. The U wave has typically the same polarity as the T wave, and it is clear that the U wave inversion with an upright T wave has pathological significance.[21]

Few studies have been published on the prevalence and prognosis of negative U wave. Holkeri et al. investigated the prevalence and prognostic significance of negative U-waves and other U-wave morphologies in a large general population sample with a follow-up of approximately 25 years. Primary endpoints were all-cause mortality, cardiac mortality, and sudden cardiac death, and secondary endpoint was hospitalization due to cardiac causes. 60.6% of the subjects had normal U-waves, 3.5% presented with negative U-waves (amplitude greater than or equal to 0.05 mV), and 15.4% with minor negative (less than 0.05 mV) or discordant U-waves. They found that negative U-waves are often associated with older age and cardiovascular risk factors and that, in general, it is a marker of poor prognosis.

Table 2: Types of inverted U waves and its relationship with coronary artery disease.

Presentations	Characteristics	Relationship with coronary artery disease (%)
Discordance type I	Negative T wave with positive U wave	64
Discordance type II	Positive T wave with negative U wave	46
Concordant	Negative U and T waves	88

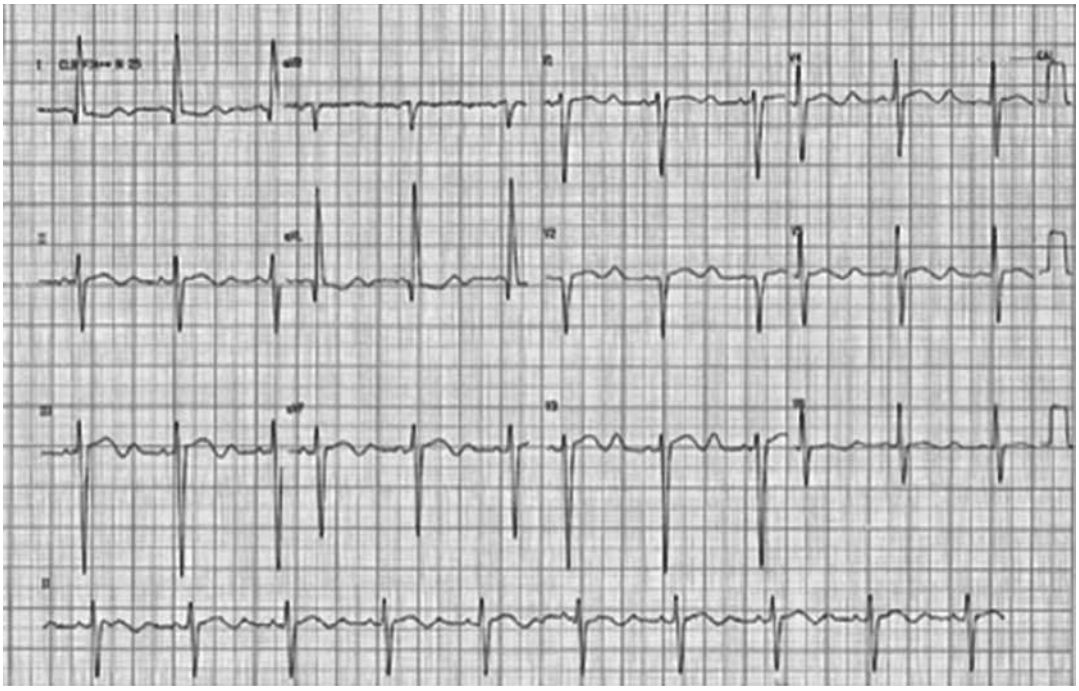

Figure 3: Prominent U waves are seen in a patient with hypokalemia.

In men, this association is independent of cardiovascular risk factors, whereas women did not show a significant association to any of the endpoints.[22]

The most accepted pathophysiological mechanism to explain the appearance of inverted U wave is related to prolonged ventricular diastole conditions. This is explained because prolonged stretching generates a delay in the activation of the channels that are activated by stretching, which generates a post potential and consequently a delayed post depolarization that is represented with the inverted U wave in the electrocardiogram.[9]

There is no consensus on defining a significant inverted U wave, but most studies and articles report that U wave inversion was considered significant if there was a negative deflection of more than 0.05 mV within the TP segment.[6]

An inverted U-wave is associated with abnormalities in 93% of cases. The main causes of negative U waves are coronary heart disease, hypertension, valvular disease, congenital heart disease, hyperthyroidism and left ventricular hypertrophy.[6]

Usually, hypertension and coronary heart disease are the two most common diagnoses in which inverted U waves are found. The negative U wave is a transitory event lasting from minutes to months according to its cause and therapy. This transitory behavior proves the

negative U wave to be a functional and not a structural change.[23]

In coronary heart disease, inverted U waves have been described in 2 scenarios: epicardial coronary disease and vasospastic angina (Prinzmetal angina) *(Figure 2)*.

Epicardial coronary disease[7]

During acute ischemia, an abnormal relaxation pattern occurs. QT is prolonged, but mechanical systole shortens, explaining that the U wave is produced during diastole. This discrepancy can vary during the acute scenario, which explains that the inverted U wave can appear and disappear during acute ischemia.[24]

The inverted U wave's clinical significance is that it may be the only finding of ischemia and can precede the appearance of typical ST-segment and/or T wave changes.

The inverted U wave helps locate the culprit's vessel and usually indicates extensive ischemia or stunning. The U wave's inversion should suggest that the culprit vessel for myocardial ischemia is the anterior descending artery.[7] In 20% of patients with an anterior wall infarction, an inverted U wave can be found, mainly in small infarctions, with less elevation of the ST-segment, better collateral circulation and a greater amount of stunned viable myocardium.[6]

U wave inversion after exercise or exercise-induced inversion of the U wave is highly predictive of significant coronary artery disease and, more specifically, of disease of the proximal left anterior descending coronary artery.[6] However, during a myocardial stress test, the appearance of an inverted U wave has been associated with a lower likelihood of having extensive myocardial necrosis or complications when an acute occlusion occurs. This pattern probably indicates the presence of collateral circulation.[25]

Studies have shown that with the correction of the ischemia generated by a vessel occlusion, either by coronary arteriography or surgical revascularization, pathological changes in the U wave revert.[26]

It is important to establish the relationship between the T wave and the U wave; both waves can have the same polarity (concordant) or have different polarities (discordant). Below in *Table 2* are the different presentations.[8]

Vasospastic angina (Prinzmetal angina)

The U wave appears during the time of vasospasm. It has been found that during treatment with drugs to decrease vasospasm, such as calcium channel blockers, the U wave disappears. In this type of angina, the inversion of the U wave does not locate the compromised vessel.[6,27]

Arterial hypertension explains 40% of the causes of U waves. The appearance of U wave is related to poor blood pressure control.[23] It has also been associated with poorly controlled hypertension leading to left ventricular hypertrophy. Therefore, the presence of an inverted U wave is an indirect sign of left ventricular hypertrophy. Usually more evident in leads V5 and V6.[6]

The inversion of the U wave in the left precordial leads is associated with aortic and mitral regurgitation because of left ventricular volume overload and left ventricular growth. The inversion of the U wave in the right precordial leads is associated with right chambers growth.[6]

PROMINENT U WAVES

They are several definitions in the literature concerning the prominent U waves; some of them will be explained below:

1. The U wave reaches an amplitude of 0.1 to 0.2 mV in lead V3, recalling that the U wave's usual mean amplitude is 0.33 mm.[12]
2. U wave with an amplitude generally less than one-fourth of the preceding T wave height.[10]
3. U wave that reaches an amplitude of 1.5 mm or more; however, there may be normal U waves of up to 2 mm (0.2 mV) in the lead II, V2, V3 and V4.[6]

It is important to accentuate that the U wave voltage is inversely proportional to heart rate and that a prominent U wave may also be referred to in the literature as elevation of the U wave, tall U wave or high U wave.[6]

U waves are essential to distinguish from bimodal or notched T waves, in which the second T wave apex is called T2; the latter must be at a distance from the first one (T1) < 150 ms; the T1-U interval is > 150 ms.[6]

Several pathologies have been associated with the development of prominent U waves, as a follow are mentioned:

When the heart rate is ≤ 65 bpm, U waves are found in 90% of cases;[6] in bradycardia, the U wave is best observed or can appear as afterdepolarizations,[4] it becomes more difficult to find in tachyarrhythmias as the other waves overlap the U wave.[12]

In the early repolarization variant, bradycardia is commonly found, and U waves are usual and best observed in lead V3.[6]

In long QT syndrome, prominent U waves may represent early afterdepolarizations produced in Purkinje fibers and/or the ventricular muscle.[4] The combination of a long QTU syndrome and «torsade de pointes» is the development of the fatal arrhythmia, which is usually preceded by bradycardia or pauses, in which the prominent U can be seen. This pattern is also called «pause-dependent long QT syndrome».[4] A channelopathy affecting inward rectifier potassium I (K1) channels (Andersen-Tawil syndrome) presents with prominent U waves, QT prolongation, and ventricular tachycardia.[6]

Hypokalemia can present prominent afterdepolarization potentials or unequal prolongation of the M cell action potential,[17] producing prominent U waves in the surface ECG;[9] others consider that the U wave is unchanged. The wave that really changes is the T wave, as it fades to a small size making the U wave is more noticeable,[19] or that in hypokalemia, the U wave is a consequence of the slowed phase 3 of the action potential, giving rise to small opposing voltage gradients that extend across producing a low amplitude bifid T wave.[6,10]

It is important to recall that hypokalemia can be found in familial periodic paralysis syndrome, alkalosis or more common in prolonged episodes of diarrhea or vomiting, especially if are treated with intravenous infusions with low electrolyte count, and diabetic coma treated with high doses of insulin.[18]

Other electrolyte alterations, such as hypomagnesemia (< 1.8 mmol/L) and hypocalcemia, can present prominent and alternant U wave with ventricular irritability.[6]

Hypothermia creates a marked increase in the difference in the action potential duration of Purkinje fibers, and ventricular muscle fibers the phase 2 was greatly prolonged with low temperature (32 ºC) and even more with lower heart rates (60 bpm) and the duration of phase 3 is also markedly increased by lowering the potassium concentration.[14]

When using epinephrine, an early appearance of a prominent U wave is seen. It starts on the T wave's descending branch; this can be explained by the related hypokalemia the medication produces because of an increase in potassium permeability; this can be prevented by administering potassium previously or concomitantly with epinephrine.[2]

Other medications such as digitalis can increase the voltage of the U wave, with no change in its polarity, explained by an inhibition of reabsorption of potassium during diastole; this effect can be magnified by the fact that digitalis lower heart rate, and as explained above, bradycardia is an environment that facilitates the identification of the U wave.[18]

All medications that increase the amplitude of the negative after-potentials increase ventricular excitability, thus generating U waves.[18] They can be classified as class III antiarrhythmics (amiodarone, dofetilide, sotalol) and class IA antiarrhythmics (quinidine, disopyramide and procainamide).[6] Quinidine increases the amplitude of the U wave by disproportionate prolongation of the M cell action potential[2,17] also discreetly prolongs the QRS complex and the QTc interval with torsade de pointes tendency and depressed, widened, notched, and inverted T wave. Phenothiazines have similar electrocardiographic effects as quinidine.[6]

Myocardial infarction can also present elevation of U waves, and this is usually seen in the acute phase when the ST-segment is elevated. In the last phase, when the ST-segment decreases, the U wave remains upright or, in the minority of cases, becomes inverted.[2] This finding is seen in posterior myocardial infarction due to circumflex occlusion in the 6-24 hours period since the onset of symptoms.[6]

Endocranial hypertension due to alterations of the central nervous system can present with augmented T and U waves; as both are increased, the T/U ratio does not change.[6]

Prominent U waves can be found in the after-exercise context, explained by the appearance of afterdepolarization potentials.[18]

Other situations such as forced inspiration, mitral valve prolapse, acquired complete atrioventricular block, left ventricular enlargement, and hypertrophic cardiomyopathy with solitary hypertrophy of papillary muscle can course with prominent U waves.[6]

It is believed that the severity of the underlying cause of the U wave is correlated with the type of U wave generated in the surface ECG, and as the alteration regress, the U wave may disappear or, by the contrary, may progress if the underlying cause persist *(Figure 3)*.[15]

CONCLUSIONS

Even though the U wave may be forgotten and there are still many gaps in its understanding. Today we have more information that allows us to identify when it occurs under normal circumstances or when its characteristics guide us to identify possible abnormalities, recognizing it as a valuable tool to support the diagnosis of specific pathologic conditions. The U wave must continue to be the subject of investigations and reports to continue enriching the associations and relationships with diseases and conditions of humans.

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Review

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The role of microRNAs in the development of heart failure

El rol de los microRNAs en el desarrollo de la insuficiencia cardiaca

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Keywords:
MicroRNA, Heart failure, cardiac hypertrophy.

Palabras clave:
MicroRNA, insuficiencia cardiaca, hipertrofia cardiaca.

ABSTRACT

MicroRNAs are single-stranded RNA of 22 nucleotides of length. Since their description in 1993, microRNAs have gained importance due to their ability to modify the expression of other genes at a post-transcriptional level. MicroRNAs are involved in regulating cardiac hypertrophy by acting as stimulators or inhibitors of some pathways related to the cell cycle. In this review, the most relevant ones will be discussed. MicroRNA-1 is a muscle tissue-specific microRNA, is considered an anti-hypertrophic microRNA. MicroRNA-133a, expressed in cardiac muscle, is characterized by its anti-hypertrophic effect. This microRNA modifies some pathways such as calcium, cell growth and development. MicroR-185 plays an anti-hypertrophic role and has three major targets during the process: sodium/calcium transporter, nuclear factor activating T cells, and Ca2+/Calmodulin-dependent protein kinase II. MicroRNA-378, expressed in cardiac myocytes, acts as a repressor of cardiac hypertrophy. On the other hand, microRNA-155 promotes cardiac hypertrophy through calcium signaling pathways and inflammation pathways. MicroRNA-200c is considered pro-hypertrophic and is thought to inhibit the action of myosin light chain kinase. It is even possible that the concentration microRNAs give us more information about the prognosis or diagnosis of cardiac diseases in the future.

RESUMEN

Los microRNAs son RNA monocatenarios de 22 nucleótidos de longitud. Desde su descripción en 1993, los microRNAs han ganado importancia debido a su capacidad para modificar la expresión de otros genes a nivel postranscripcional. Los microRNAs están involucrados en la regulación de la hipertrofia cardíaca al actuar como estimuladores o inhibidores de algunas vías relacionadas con el ciclo celular, en esta revisión se discutirán los más relevantes. El microRNA-1, un microRNAs específico de tejido muscular se considera un microRNA antihipertrófico. El microRNA-133a, expresado en el músculo cardiaco se caracteriza por su efecto antihipertrófico, este microRNA modifica algunas vías relacionadas con el calcio, el crecimiento y desarrollo celular. MicroR-185 desempeña una función antihipertrófica y tiene tres objetivos principales durante el proceso: el transportador de sodio/calcio, las células T que activan el factor nuclear y la proteína cinasa II dependiente de Ca2+/Calmodulina. El microRNA-378, expresado en miocitos cardiacos, actúa como represor de la hipertrofia cardíaca. Por otro lado, el microRNA-155 promueve la hipertrofia cardiaca a través de vías de señalización de calcio y vías de inflamación. El microRNA-200c se considera prohipertrófico y se cree que puede inhibir la acción de la cinasa de cadena ligera de miosina. Es posible que la concentración de los microRNAs nos dé más información sobre el pronóstico o diagnóstico de enfermedades cardíacas en el futuro.

INTRODUCTION

MicroRNAs are defined as single-stranded RNA with approximately 22 nucleotides in length. Since its description in 1993, the microRNAs have gained importance due to their ability to modify the expression of other genes at a post-transcriptional level.[1,2] The microRNAs can be found attached to other intracellular or extracellular structures that prevent them from being degraded by RNases. Although between 95-99% of circulating microRNAs are attached to protein complexes, others may be encapsulated in microvesicles, apoptotic bodies, and High-density lipoprotein cholesterol (HDL-C).[3] MicroRNAs are involved

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in regulating cardiac hypertrophy by acting as stimulators or inhibitors of some pathways related to the cell cycle *(Figure 1)*.[4] In addition, it has been described that microRNAs levels may be altered in other pathophysiological mechanisms in the heart, such as remodeling, apoptosis or hypoxia, which is why they have been suggested as diagnostic or prognostic markers for heart failure.[4] The importance of the study of microRNAs is based on the discovery of new therapeutic targets that may be able to help in the treatment of heart diseases (among others) from a molecular level; initially, the knowledge of microRNAs help to understand the principles of regulation of the genetic material involved in heart diseases, especially in heart failure and how its modification or intervention could possibly replace the currently used drugs representing greater effectiveness; although this is a scenario that will occur in the future, molecular medicine has begun to move towards this type of treatment. In addition, at present, the detection of the presence of microRNAs as disease markers can help detect the development of heart failure or the risk of developing many years before any symptoms appear, this will help patients with higher risk may have a closer follow-up. Understanding the way in which microRNAs interact, in turn allows a greater understanding of pathologies. Currently, dozens of alterations in microRNA have been described in patients with heart failure; in this review, the most relevant ones will be discussed.

MicroRNA-1

MicroRNA-1 is a muscle tissue-specific microRNA abundantly expressed in the heart, and together with other microRNAs, has a significant role in the development of embryonic stem cells and cardiomyocyte progenitor cells.[5] MicroRNA-1 is considered an anti-hypertrophic microRNA because an increase in its expression is associated with less cardiac hypertrophy.[4] Some studies have shown that microRNA-1 is even important for cardiogenesis. In 2007 were described alterations in cardiogenesis in mice whose concentration of microRNA-1 had been altered *(Figure 2)*.[6]

MicroRNA-1 has an important role in regulating cardiac hypertrophy by inhibiting some pro-hypertrophic pathways such as the calcium signaling pathway. The calcium signaling pathway is a pro-hypertrophy pathway that increases intracellular calcium; by increasing intracellular calcium in the cardiomyocyte, the

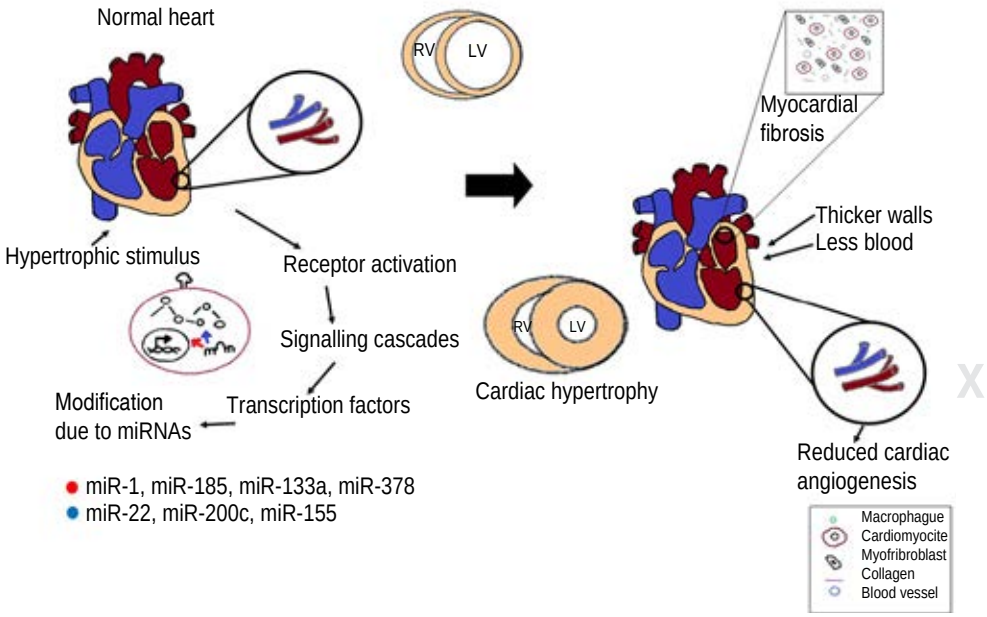

Figure 1:

A hypertrophic stimulus activates its corresponding receptor leading to a complex signaling cascade activating hypertrophic genes, like some physiological changes.
RV = right ventricle,
LV = left ventricle.

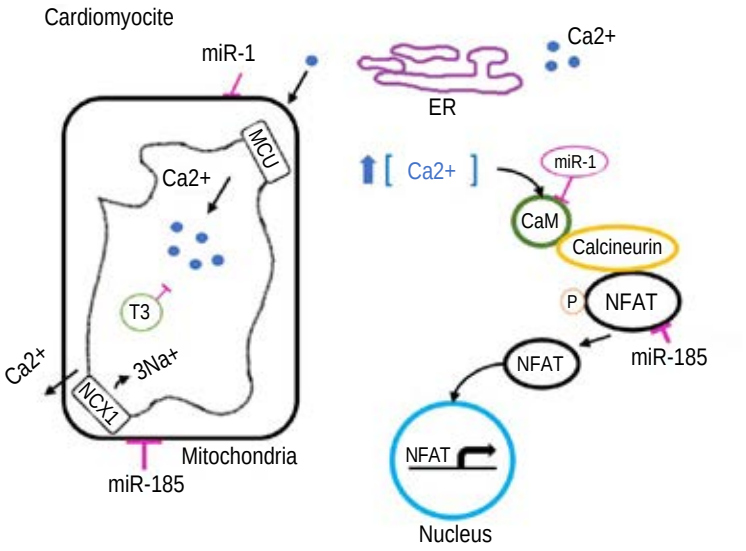

Figure 2: MicroRNA-1 downregulates the expression of crassulacean acid metabolism and directly regulates mitochondrial calcium uniporter expression during development; T3 enhances the expression level of microRNA-1, suppressor of mitochondrial calcium uniporter. MicroRNA-185 targets the sodium-calcium exchanger and nuclear factor of activated T cells 3.
MCU = mitochondrial calcium uniporter, CaM = calmodulin.

calcineurin-NFAT (Nuclear Factor of Activated T cells) pathway is activated, which causes dephosphorylation of NFAT, which leads to its translocation in the nucleus. Once inside the nucleus, the expression of NFAT increases the transcription of pro-hypertrophic genes (genes involved in the hypertrophic response). The action of microRNA-1 in the cardiomyocyte inhibits the calcineurin-NFAT pathway, which will result in the inhibition of the transcription of pro-hypertrophic genes.[7,8]

On the other hand, some authors have pointed out that this is not the only way by which microRNA-1 could regulate the entry of calcium into the cardiomyocyte. MicroRNA-1 may inhibit the mitochondrial calcium uniport, a subunit of the mitochondrial calcium uniport pore complex. This complex is responsible for introducing calcium from the intracellular space into the cardiomyocyte.[9] Some studies have indicated that in biopsies of patients with cardiac hypertrophy, microRNA-1 is decreased while this complex is increased, suggesting that microRNA-1 can regulate the expression of this complex and, therefore, inhibit cardiac hypertrophy.[10]

Another way microRNA-1 could be involved with cardiac hypertrophy is by its relationship with the thyroid hormone T-3. A study conducted in 2017 demonstrated that overexpression of microRNA-1 reduces the expression of histone deacetlyase-4 (HDAC4), which attenuates thyroid hormone-induced cardiac hypertrophy.[11]

Insulin-like growth factor-1 (IGF-1) is a hormone that has been reported to induce cardiac hypertrophy and could be another target of microRNA-1. A 2009 study demonstrated that microRNA-1 is negatively correlated with IGF-1 because both IGF-1 and its receptor are targets of microRNA-1. Furthermore, it was shown that the transduction cascade regulates the expression of microRNA-1 and that microRNA-1 is inversely related to cardiac mass and myocardial thickness, suggesting that the interaction between IGF-1 and microRNA-1 has important repercussions on the myocardium.[12]

Although several studies correlate microRNA-1 with cardiac hypertrophy, there are still no sufficiently valid clinical studies to determine the usefulness of microRNA-1 in the context of heart failure. The relationship of microRNA-1 with heart failure is still under investigation. However, it is also important to mention that clinical studies suggest that microRNA-1 could be used as a marker for heart failure in the future. In 2011, a study showed that microRNA-1, along with other microRNAs, was elevated in patients with the acute coronary syndrome, proposing that microRNA-1 could be used to diagnose acute heart failure due to acute coronary syndrome[13] *(Table 1)*.

MicroRNA-133a

MicroRNA-133a is a microRNA that, like microRNA-1, is expressed in cardiac muscle and is characterized by its anti-hypertrophic effect, while microRNA-133b is specifically expressed in skeletal muscle microRNA-133a modifies some pathways such as calcium, cell growth and development.[14] Both microRNA-1 and microRNA-133a *in vitro* are deregulated during cardiac differentiation of cardiac progenitor cells (PCs), but only the expression of microRNA-133a increases under oxidative stress.[15] A study presented in 2010 quantified the serum

concentrations of various microRNAs in patients with ST-segment elevation myocardial infarction against a control group. The results showed that on day 0, microRNA-133a, microRNA-133b, microRNA-1 and microRNA-499-5p had a significant increase in serum concentration compared to the control groups.[16] On the other hand, a study in 2007 intentionally looked for a relationship between microRNA-133 and heart failure; they found a decrease in the expression of both microRNA-133 and microRNA-1 in mice and humans with cardiac hypertrophy, *in vitro* they found that the expression of microRNA-133a and microRNA-1 inhibited the development of cardiac hypertrophy. Also, *in vivo*, the infusion of antagomir (an agent that causes inhibition of microRNA-133) increased the possibility of cardiac hypertrophy *(Figure 3)*.[17]

Table 1: Differences among the microRNAs described.

microRNA	Type	Targets	Up-/down-regulated
microRNA-1	Cardiac	IGF-1R/IGF1/MCU	Downregulated
microRNA-133a	Cardiac	Gq/PKCd	Downregulated
microRNA-22	Cardiac	Sirt1/Hdac4	Upregulated
microRNA-155	Circulating	Jarid 2/AT1R/SOCS1	Upregulated
microRNA-200c	Epitelial	MLCK	Upregulated
microRNA-185	Circulating	Nfatc3/Ncx1/Camk2d	Downregulated
microRNA-378	Cardiac	Grb2/IGF1R/Mapk1	Downregulated

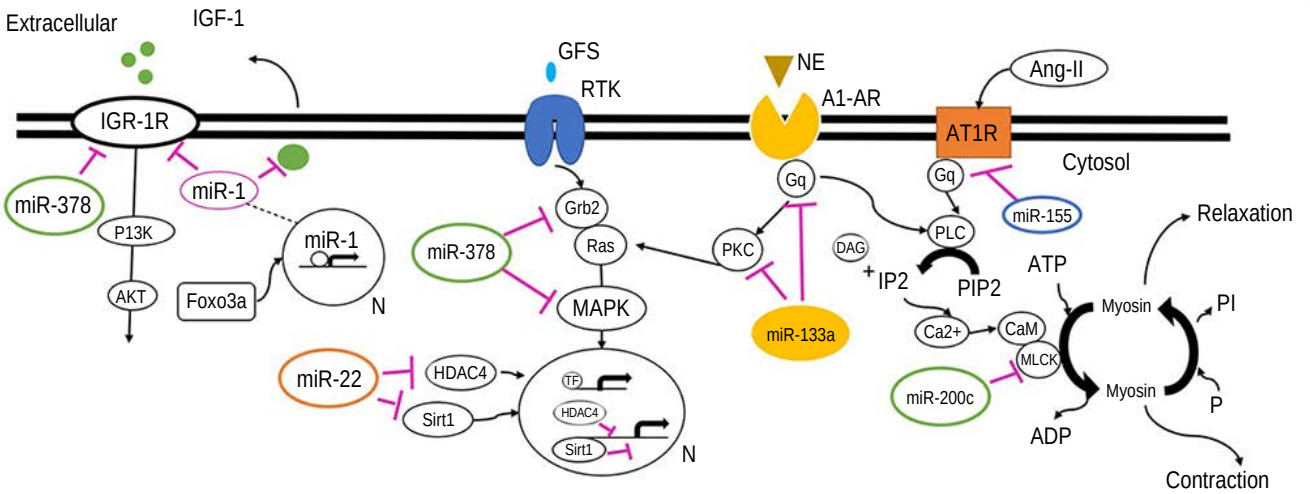

Figure 3: MicroRNA-133a attenuates cardiomyocyte hypertrophy by inhibiting protein kinase C and Gq. Alfa 1-adrenoceptor couples to G protein due to its activation by NE, resulting in the activation of phospholipase C, which activates calcium signaling pathways and the PKC-MAPK pathway (protein kinase C-mitogen-activated protein kinase pathway), increasing the expression of hypertrophic transcription factors. MicroRNA-155 attenuates Angiotensin II-induced hypertrophy through downregulating Angiotensin II type 1 receptor and its downstream Ca2+ signaling. MicroRNA-200c promotes cardiac hypertrophy by directly targeting myosin light chain kinase. MicroRNA-378 targets GRB2, thus repressing the activity of GRB2-RAS signaling. It represses mitogen-activated protein kinase, signaling by targeting mitogen-activated protein kinase 1. Both MicroRNA-378 and microRNA-1 repress insulin-like growth factor 1 receptor, but microRNA-1 also targets IGF-1 protein. The activation state of the IGF-1 signal reciprocally regulates microRNA-1 expression through the forkhead box (FOXO3a) transcription factor. MicroRNA-22 targets two histone deacetylases, sirtuin-1 and histone deacetylase 4, implying that microRNA-22 plays a role in epigenetic regulation of gene expression during cardiac hypertrophy.

The action of microRNA-133 is mainly due to the inhibition of the Gq protein and protein kinase C pathways. By binding norepinephrine to the α1 adrenergic receptors, the receptors are coupled to the G proteins, which results in the activation of phospholipase C when phospholipase C is activated, the degradation of phosphatidylinositol 4,5 bisphosphate into inositol 1,4,5 triphosphate and diacylglycerol is catalyzed, which activates calcium signaling pathways and protein kinase C pathways, resulting in transcription of hypertrophic transcription factors. By blocking the Gq protein and protein kinase C pathways, the entire cascade secondary to these is inhibited, which is why microRNA-133 has an anti-hypertrophic effect.[18]

In-vitro, the exposure of cardiomyocytes to high glucose levels produces hypertrophic changes and reduces the expression of microRNA-133a. Likewise, the levels of microRNA-133 decreased in mice after two months of having induced diabetes.[19]

MicroRNA-133 may seem like a good candidate for diagnosis or prognosis in terms of heart failure. However, until today there is no clinical study with sufficient evidence to determine the clinical use of this particular microRNA *(Table 1)*.

MicroRNA-155

MicroRNA-155, contrary to microRNA-1 and microRNA-133, is a microRNA that promotes cardiac hypertrophy through calcium signaling pathways and inflammation pathways. MicroRNA-155 may be expressed in some macrophages.[20] These macrophages expressing microRNA-155 are thought to promote cardiac hypertrophy through two pathways: the Janus kinase signal transducer (JAK) pathway and the activator of transcription 3 (STAT3) pathway; also can inhibit suppressor macrophages of cytokine-1 signaling (SOCS1), which stimulates phosphorylation of STAT3, as STAT3 is phosphorylated in macrophages, pro-hypertrophic signaling of the paracrine type is carried out in cardiomyocytes.[4]

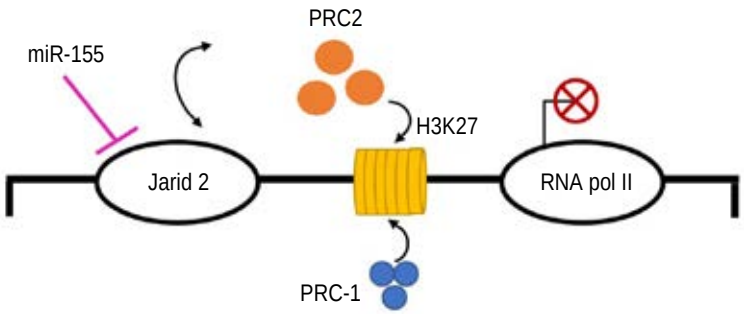

Figure 4: MicroRNA-155 inhibits Jumonji and AT-Rich interaction domain containing 2, which recruits polycomb repressive complex 2 and with polycomb repressive complex 1 repress transcription by catalyzing the histone H3K27, inhibiting RNA polymerase II.

However, this is not the only way in which microRNA-155 could induce cardiac hypertrophy. A study in 2014 suggested that microRNA-155 can induce cardiac hypertrophy by inhibiting the expression of Jarid2, a transcriptional regulator of cardiac development, since it is linked to cell proliferation.[4]

Another proposed mechanism by which microRNA-155 can induce cardiac hypertrophy is through angiotensin II. A study suggested this in 2016 after noting an increase in angiotensin I receptor levels, intracellular calcium and calcineurin beta in cardiomyocytes with microRNA-155 inhibitors and subsequently treated with angiotensin II. Since some of the microRNA-155 inhibitors do not decrease hypertrophy, it has been suggested that the inhibition of microRNA-155 and the activation of calcium pathway signaling may induce myocardial cell apoptosis, which could reduce the levels of markers of cardiac hypertrophy.[21] It has been observed that the CYTOR gene (Cytoskeleton Regulator RNA), a non-coding RNA chain that is over-expressed in cancer cells, is up-regulated in cardiac and hypertrophic cardiomyocytes; they also deduced that knock-down of this gene increases angiotensin II levels in the cardiac hypertrophy *(Figures 4 and 5) (Table 1)*.[22]

Other microRNAs

In 2009 evaluated the myocardial expression of various microRNAs in patients with heart failure before and after treatment with ventricular assist devices. Their study reported that 71.4 % of microRNAs were regular after treatment, suggesting that microRNAs could be used as a

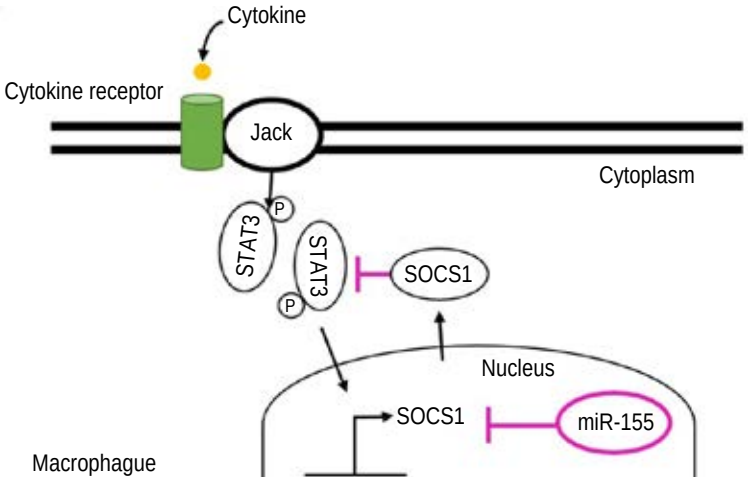

Figure 5: MicroRNA-155 silences suppressor of cytokine signaling 1, a negative regulator of the Janus kinase/signal transductor and activator of transcription signaling pathway.

marker of recovery after treatment.[23] Like this study, many authors have described alterations in plasma concentrations or tissue expressions in many diseases. However, in many cases, little is known about how microRNAs interact in the course of some diseases. In this section, we will discuss some microRNAs in which has been described that they play a secondary role in heart failure.

MicroRNA-22 is a microRNA expressed mainly in cardiac muscle and skeletal muscle and is stimulated during cardiac hypertrophy and myocyte differentiation. This microRNA is essential for cardiac development and morphogenesis.[24] MiR-22 is considered a pro-hypertrophic microRNA; some authors have suggested that microRNA-22 could inhibit sirtuin 1 (SIRT1) and histone deacetylase 4 (HDAC4), which are considered protective for cardiac hypertrophy.[4,25] It has also been observed that the overexpression of microRNA-22 in neonatal rat cardiomyocytes increased cell size and induced hypertrophic markers, while the elimination of microRNA-22 attenuated hypertrophy induced by phenylephrine, isoprenaline or angiotensin II *(Figure 3 and Table 1)*.[26]

Another microRNA that has been associated with cardiac hypertrophy is microRNA-200c. MicroRNA-200c is a microRNA considered pro-hypertrophic. MicroRNA-200c is thought to be able to inhibit the action of myosin light chain kinase (MLCK). These two molecules have been shown to maintain a negative correlation in their concentrations. It means that overexpression of microRNA-200c reduces MLCK concentrations, and overexpression of microRNA-200c significantly increases the production of reactive oxygen species and apoptosis *(Figure 3 and Table 1)*.[4,27]

MicroRNA-185 is also a regulator of cardiac hypertrophy, and it plays an anti-hypertrophic role in the heart and has three major targets during the process such as Ncx1 (sodium/calcium transporter), Nfatc3 (nuclear factor activating T cells), and Camk2d (Ca2 +/Calmodulin-dependent protein kinase II) *(Figure 2 and Table 1)*.[25,28]

MicroRNA-378 is expressed in cardiac myocytes and not in cardiac fibroblasts, and it acts as a repressor of cardiac hypertrophy since it represses the pro-hypertrophic signal through the mitogen-activated protein kinase (MLCK) pathway when targeting MAPK1, to insulin-like growth factor receptor 1 (IGF1r), to Growth factor receptor-bound protein 2 (GRB2), and the Ras 1 kinase suppressor (Ksr1).[25,29] The overexpression of microRNA-378 blocks the activity of Ras, stimulated by phenylephrine and also prevents the activation of two signaling pathways, phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT) and Raf1-mitogen-activated protein kinase kinase-1 (MEK1)-Extracellular signal-regulated protein kinase-1(ERK1)/2 *(Figure 3 and Table 1)*.[25,30]

CONCLUSION

MicroRNAs have become a research objective in recent decades not only regarding heart failure but for a wide range of pathologies because the pathways in which they can intervene are increasingly known. However, in order to become more useful in the clinic, it is important to know not only their function but also to know how they interact with other molecules, how they behave in circulation and in tissues, or to know if plasma concentrations are related to expressions at the tissue level. It is even possible that the concentration of one but of several microRNAs give us more information about the prognosis or diagnosis in

the future. MicroRNAs must be thought of not only at the individual level but as a large group of molecules that modify normal molecular pathways in response to disease.

As there are various pathophysiological mechanisms in the heart, there is a wide variety of microRNAs that alter their plasma or tissue levels. However, few will have clinical use in the future. It is because, at the moment, many of the alterations in the concentration or expression of the microRNAs have not reached a greater sensitivity or specificity to the traditional markers of heart failure. It is necessary to continue with microRNA research to give them a clear clinical utility and superior to current diagnostic and prognostic methods.

For the moment, it would be pertinent to carry out multicenter studies with a great variety of individuals since many of the studies that were presented above have been carried out in Anglo-Saxon countries, and few have been carried out in developing countries. Due to the genetic variants that could exist between populations, the studies could be adapted to the context in Mexico. For this, both private initiatives and public institutions have resources for microRNA research to benefit the population.

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REVIEW

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Deductive analysis of the electrocardiogram to determine the site of origin of premature ventricular beats/contractions

Análisis deductivo del electrocardiograma para definir el sitio de origen de las extrasístoles ventriculares

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Keywords:
Electrocardiogram, ventricular premature contractions, site of origin, electrocardiogram analysis, ventricular arrhythmia location.

Palabras clave:
Electrocardiograma, extrasístoles ventriculares, sitio de origen, análisis del electrocardiograma, localización de arritmia ventricular.

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ABSTRACT

Premature ventricular contractions (PVC's) have become a therapeutic target, especially when the arrhythmia burden is higher than 10% of the recorded beats. Knowing their point of origin can help to optimize the different treatment strategies, especially the invasive ones. Deductive electrocardiogram (ECG) analysis is a rational methodology that assesses the activation vector and morphologies of the PVC's thus allowing a quite precise definition of the arrhythmia originating focus. Knowledge of the different cardiac structures within the chest and the heart itself as well as between them facilitates the comprehension of the vectors and morphologies on the twelve-lead ECG and gives valuable information to complete the patient's clinical picture. Here we present the main ways to analyze the PVC's ECG from the classical concepts, and we include diagnostic parameters to identify their point of origin.

RESUMEN

Las extrasístoles ventriculares se han convertido en objeto de tratamiento, especialmente si la carga de arritmia es mayor al 10% de los latidos en un día. Conocer el sitio de origen de las mismas permite optimizar la planeación de las estrategias de tratamiento, especialmente las invasivas. El análisis deductivo del electrocardiograma (ECG) es una forma racional de analizar los vectores de activación y las morfologías de las extrasístoles, gracias a la cual se puede definir de manera bastante precisa el foco de origen de la arritmia. Conocer la posición de las estructuras cardiacas en el tórax y en el propio corazón, así como las relaciones entre ellas, facilita la comprensión de los vectores y morfologías de los complejos en el ECG de doce derivadas y es una información valiosa para completar el panorama clínico del enfermo. En este trabajo se presentan las principales formas de analizar el ECG de las extrasístoles ventriculares a partir de los conceptos clásicos y se incluyen parámetros de diagnóstico para definir su origen.

INTRODUCTION

Premature ventricular contractions (PVC's) are common arrhythmias that have to be evaluated in the complete clinical context of the patient. Their presence is related to higher mortality risk in the presence of cardiac disease, and possibly so among subjects with a structurally normal heart. The risk of sudden cardiac death in each of them might be different, but in any case, higher than in the general population. Patients with PVC's also have a high risk to develop a «tachycardiomyopathy» or an arrhythmia-induced cardiomyopathy that will cause heart failure (HF). Development of HF will depend on the arrhythmia burden, the patient's co-morbidities, use of medications, metabolic or electrolyte disorders, presence of channelopathies and family history as main factors.[1-4]

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The present work is intended to help the clinician determine the approximate anatomical origin of the PVC's since that knowledge might help to define therapeutic plans that currently consider ablation procedures earlier in the treatment process because of its increasing success rates.[5]

It is important for the clinician to be able to determine the site of origin of PVC's for several reasons, even if the treatment is intended to be done by an electrophysiology service. It is known that the right ventricle's PVC's, especially the ones originating from the outflow tract, usually have a benign course and they usually appear in structurally normal hearts, while the PVC's arising from the left ventricle might be related to structural heart disease and thus, usually have a worse prognosis.[6] A higher arrhythmia burden induces tachycardiomyopathy or at least ventricular dysfunction. Nonetheless, that risk is higher when the PVC's come from the tricuspid annulus, even when compared against the ones that originated from the papillary muscles or the left bundle branch fascicles.[7,8] The ventricular function deterioration is independent of the presence or absence of baseline heart disease.[9-13]

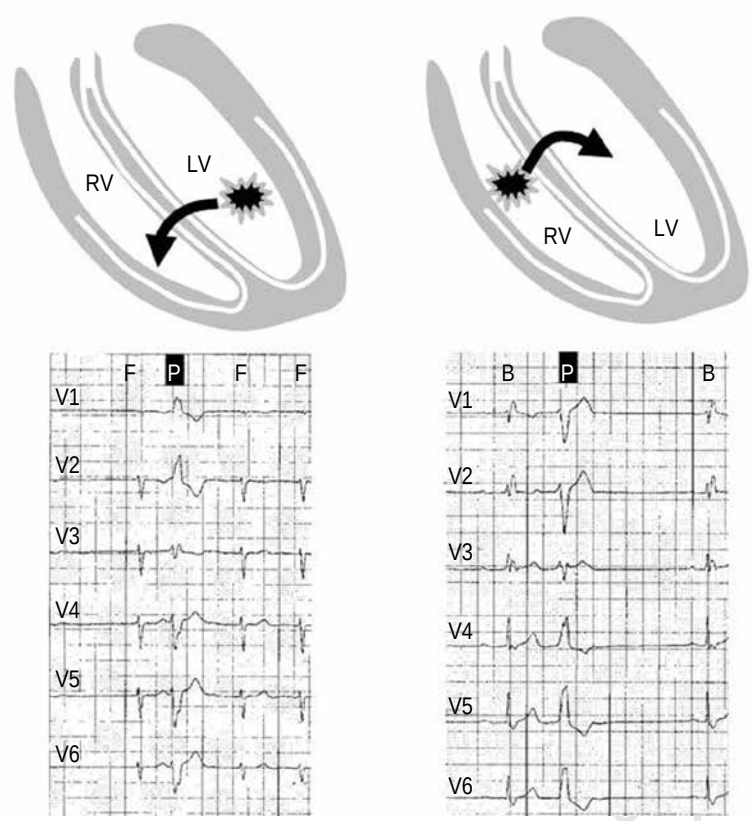


Figure 1: When a PVC is originated in the ventricular myocardium, the action potential induces a «cell-to-cell» depolarization pattern similar to the one seen when there is a bundle branch block. That «jump» from one ventricle to the other induces a left bundle branch block (LBBB) when the PVC comes from the right ventricle, and if generated in the left ventricular, it will show a RBBB pattern as a general rule, but with exceptions mentioned in the text.

Arrhythmia units are still scarce in Mexico, that is why specialized evaluation is usually delayed, and the clinician will be prompted to make appropriate and timely therapeutic decisions. Review all of them is out of reach of the present work, even though it has to be taken into account that the presence of structural heart disease – ischemia scars, hypertrophic cardiomyopathy or dysplasia, among others – restrict the choice of antiarrhythmic drugs, that have frequent side or toxic effects. Some fascicular PVC's will respond to verapamil, that can be used as a «bridging» therapy while waiting for ablation. Propafenone might also be used in subjects without structural heart disease. It must be considered that the PVC might arise from the lesion site - ischemia scar, for instance – or maybe originated from a random independent focus or as a pro-arrhythmic effect of drugs. In these circumstances, the definition of the origin site allows optimizing ischemia treatment, for example, while a more definitive therapy is defined and implemented.

The 12-lead electrocardiogram (ECG) has some limitations to define a precise anatomic location, however it allows locating the PVC's origin to a certain region, frequently in the vicinity of a specific intra-cardiac structure, even though it might also originate from a random point in the myocardium.

With this information, the prognostic significance of the PVC's can be more precise, and the planning for an invasive therapeutic strategy will be more efficient.[14]

The Mexican Electrocardiography School has used the deductive analysis technique since its origins.[15] Putting together the depolarization axis in the frontal and horizontal plane information, along with the morphological analysis of the ECG waves and their duration and other data, allowing to define the PVC's

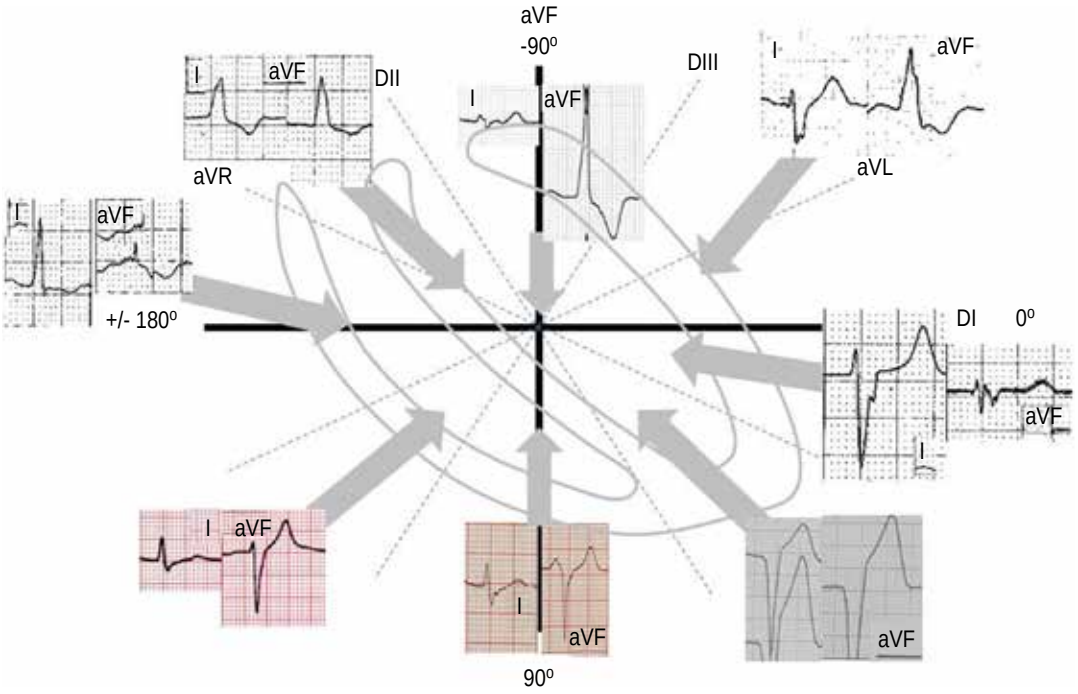


Figure 2: The main ventricular depolarization axis in the frontal plane allows to approximately determine the site of origin of a PVC to a superior or inferior focus and left or right of the originating ventricle. An important issue is that the main depolarization vector is directed away from its originating point. Thus, if a PVC shows a left inferior axis, its origin is an upper right location. In the image, the ECG recording is located in the approximate origin point and the arrow points in the ventricle's main vector's depolarization direction.

origin with enough accuracy and it is a familiar tool for many of us.

The present simplified review is intended to facilitate a better comprehension of the ECG criteria useful to establish the origin point of PVC's.

PREMATURE VENTRICULAR CONTRACTION'S MORPHOLOGY

The PVC's morphology is determined by its site of origin. Usually, the depolarization focus is located within the myocardium, away from the specialized conduction system. That focus generates a stimulus that has to cross the myocardium and induce ventricular contraction. As in the bundle branch blocks, when the PVC is originated in the left ventricle (LV), the PVC adopts a Right bundle branch block (RBBB) morphology and vice versa, when the PVC has a left bundle branch block (LBBB) morphology, its origin is usually in the right ventricle (RV), exception made in some cases of PVC's from the aortic cusps, that might show an LBBB pattern too.[16-18] This phenomenon is explained by the myocardial activation sequence. When the action potential initiated by the automatic focus of the PVC crosses the myocardium, it has to make a «jump» from one ventricle to the other, an action that implies a delay in the depolarization of the ventricular myocardium *(Figure 1)*. When there are polymorphic PVC's, the patient's clinical context must be known and included in the analysis. Some patients with extensive scarred tissue might have a single generation focus within the myocardium, with several «exit» points, or present with different generation foci distributed through the fibrotic area. Cardiac magnetic resonance imaging (MRI) studies in subjects undergoing ventricular tachycardia (VT) ablation have shown that polymorphic PVC's or PVC's with right bundle branch block

morphology are frequently related to a larger amount of fibrotic tissue.[19]

DEPOLARIZATION AXES

The depolarization axes in the frontal and horizontal plane allow a more precise identification of the ventricular ectopic focus.

The depolarization axis can be determined using DI and aVF *(Figure 2)* in the usual way for the frontal plane, which shows four 90º main quadrants (upper left 0 to -90º, upper right -90º to -180º, and so on with the lower left and lower right), and V1 and V6 for the horizontal one *(Figure 3)*. This way, one can locate the quadrant of origin of the PVC from the main depolarization vector in a right-to-left, superior-inferior and anterior-posterior direction.

The main depolarization axis can be determined in the same way that the atrial or ventricular depolarization vector direction is defined, but it is important to remember that the main vector is directed away from its source. Thus, if a PVC depolarization vector has a right-inferior axis, its source is most likely the left superior quadrant. If it is positive in V1, it comes from the posterior segments,[20] but it comes from the anterior region if V1 is negative. If the vector is positive in V6, it comes from the right, and if it is negative in V6, it comes from the left. The work by Asirvatham demonstrates that V1 is useful to differentiate between PVC's arising from the right ventricle outflow tract or, in a more general way, from any of both outflow tracts. If the main QRS deflection is negative in V1 and the transition zone is delayed (V4), the origin is usually anterior –right ventricle (RV)–.[20,21] The presence of positive deflections with earlier transition zones (V2) suggests a posterior origin, possibly related to the aortic cusps.[20]

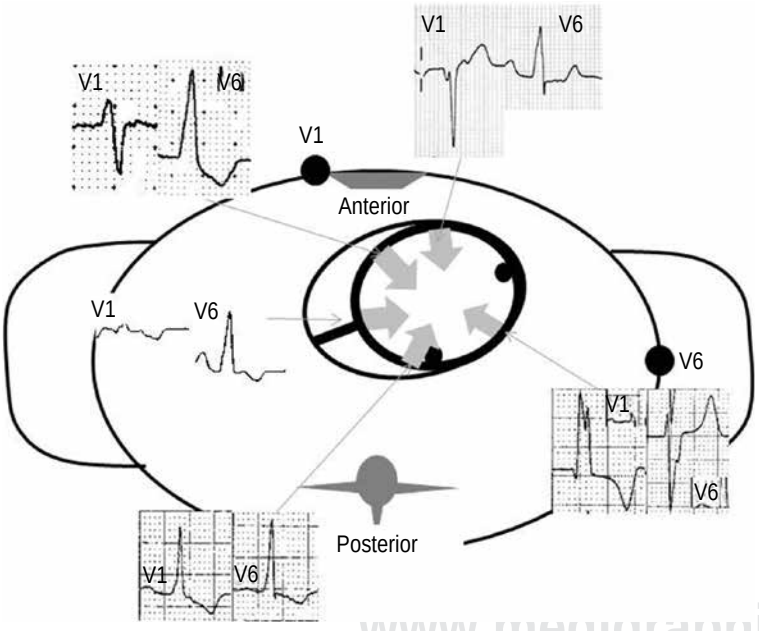


Figure 3: The horizontal plane's depolarization axis allows the definition of an approximate origin point for the PVC in the anterior-posterior and lateral-medial dimensions. Again, the main depolarization vector is directed away from its origin point. If a PVC has a positive vector in V1 and negative in V6, its origin is most likely left postero-lateral or left lateral. In the image, the ECG record is located in the approximate origin site. The volume arrow points in the main depolarization vector's direction. The thin arrow points to its vector.

At this point, morphological information must be added. For instance, if the PVC has an LBBB pattern, the PVC is originated in the right ventricle, although it has to be kept in mind that PVC's from the right aortic cups might also show an LBBB pattern. If the depolarization axis is directed towards the left inferior quadrant, The PVC is most likely originated in the right superior segment of the right ventricle. If the QRS is negative in V1 and positive in V6, its origin is located in the anterior and superior segment of the right ventricle. The structure located in that position is the right ventricular outflow tract. If the main depolarization vector of the PVC's QRS is directed in a right superior direction, with an RBBB morphology, positive in V1 and negative n V6, the PVC is arising from the posterior mid-apical segments of the left ventricle. A structure that might originate that PVC is the postero-medial papillary muscle *(Figures 4 and 5, Table 1)*.[22]

Further on, we will review specific features from specific locations since there are regions where structures are superimposed, and the precise differentiation of a focal origin is more complex.

EPICARDIUM OR ENDOCARDIUM?

Most ventricular arrhythmias arise from the endocardium; nonetheless, ablation

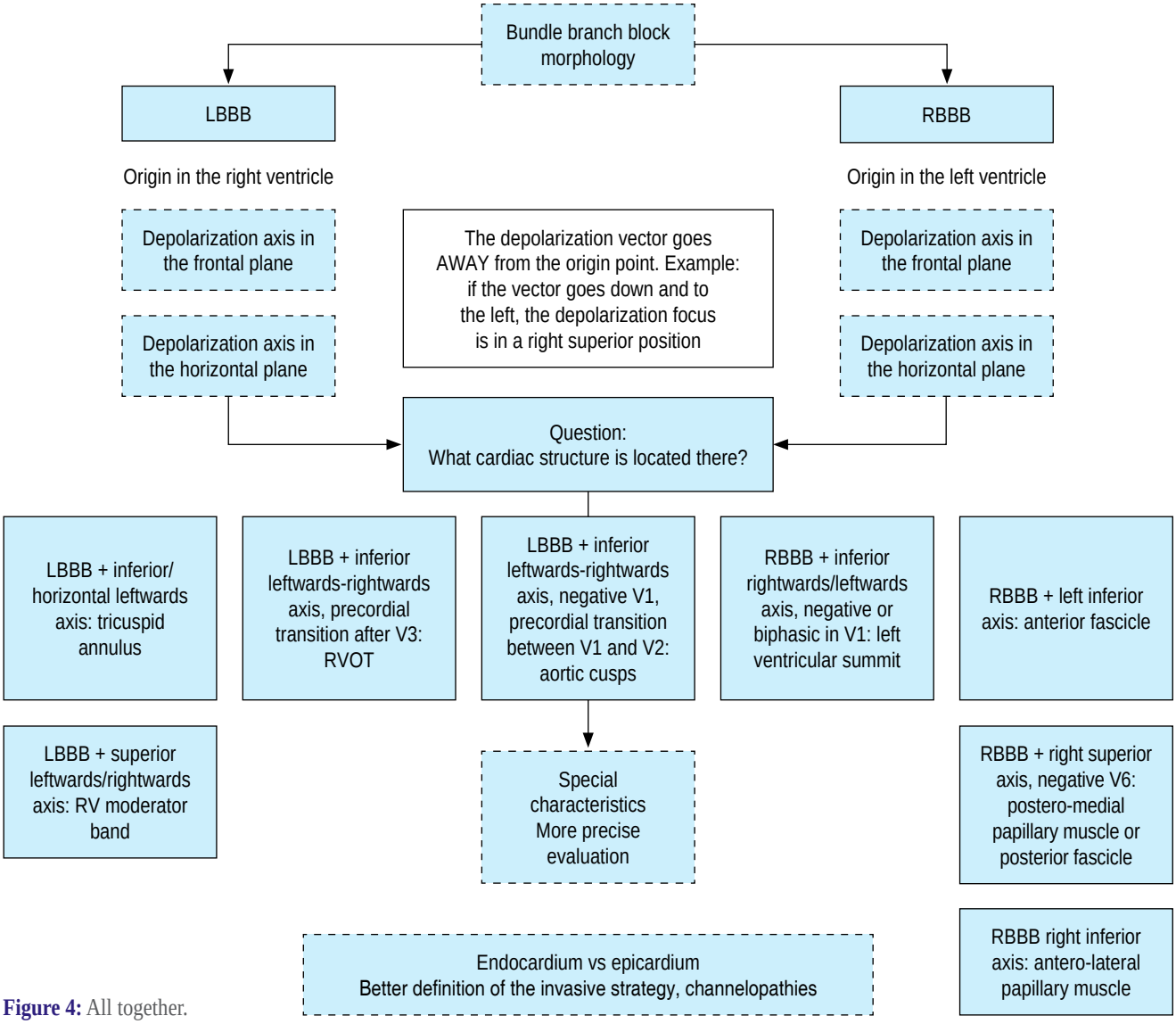


Figure 4: All together.

studies have demonstrated that a certain number of them come from the epicardium.[23,24] The main heart disease has to be considered too; for example, among people with arrhythmogenic right ventricular cardiomyopathy or a dilated cardiomyopathy, an epicardiac origin is more frequent than in patients with idiopathic arrhythmias or ischemic heart disease.[25] Brugada syndrome, a complex channelopathy, can be treated with ablation of the right ventricular epicardium, even in the absence of PVC's from that area.

Another element to consider is the morphology of the scar itself – which can be defined using MRI – in ischemic heart disease subjects. In them, an automatic focus might have different «exit» points through different myocardium channels, thus mandating extensive ablation to isolate the whole scarred tissue. The different exit points might show different ECG patterns.

The ECG of the epicardiac arrhythmias usually shows an initially slow depolarization pattern until it reaches the His-Purkinje system. It manifests as a pseudo-delta wave that lasts

more than 34 ms in the precordial leads, an intrinsecoid deflection in V2 longer than 85 ms (measured from the start of the QRS complex to the R wave peak) as well as other criteria listed in *Table 2* and illustrated in *Figure 6*.[24]

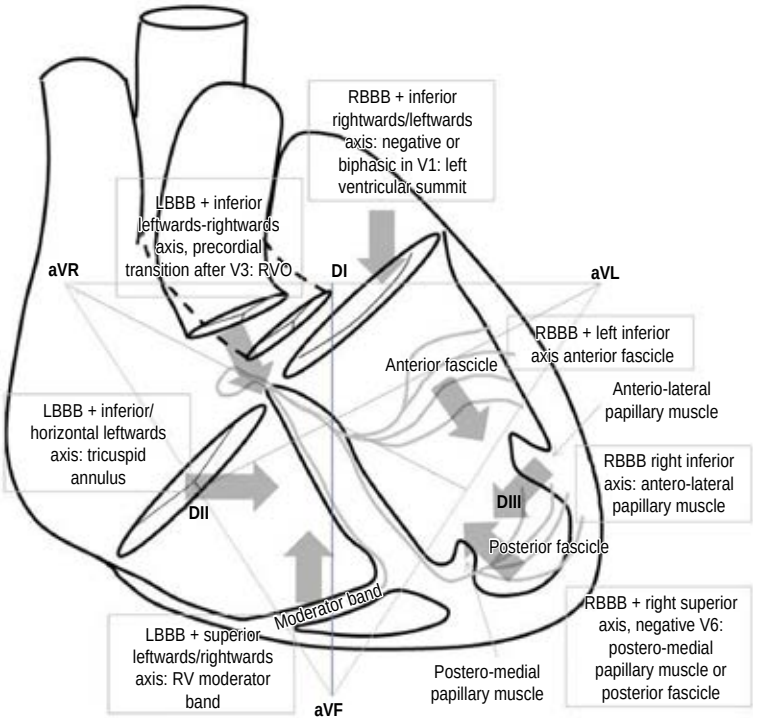


Figure 5: All together: main depolarization vectors from the main intra-ventricular structures.

SPECIFIC ORIGIN FOCI

Outflow tracts or superior ventricular foci

Both ventricles outflow tracts have a complex superposition, in a way that different kinds of ventricular arrhythmias might have similar ECG features *(Figure 7)*.[25] To avoid unnecessary complications, we have decided to suppress anatomic discussions. From an ECG standpoint, it is important to know the location of the anatomical structures adequately, but the

Table 2: Main electrocardiographic features of the epicardiac ventricular arrhythmias.

Epicardiac ventricular arrhythmia features
Pseudo-delta wave > 34 ms
Intrinsecoid deflexion in V2 > 85 ms
Shorter RS complex > 121 ms
Maximum deflexion index in precordial leads > 0.55 (onset to QRS peak/total QRS duration)
Q wave in DI (antero-lateral epicardiac ventricular arrhythmia)
Q wave in inferior leads (inferior epicardiac ventricular arrhythmia)

Modified from: Boas R et al.[14]

Table 1: Getting things together.

Depolarization vector main direction	Bundle branch block	Possible origin
Inferior or horizontal leftward axis, with a postero-anterior direction	Left bundle branch	Tricuspid annulus
Inferior axis with a leftward, center or rightwards precordial leads transition after V3	Left bundle branch	Right ventricular outflow tract
Inferior axis with a leftward, center or rightwards axis, precordial leads transition prior to V3	Left bundle branch	Aortic cusps
Superior vertical, right of leftwards axis	Left bundle branch	Moderator band
Inferior or horizontal axis with a right wards deviation, negative V6	Right bundle branch	Mitral annulus
Inferior left axis, monophasic S pattern V1	Right bundle branch	Left ventricular summit
Superior right axis, negative V6	Right bundle branch	Posterior fascicle or posterior-medial papillary muscle
Inferior right axis	Right bundle branch	Antero-lateral papillary muscle
Inferior left axis	Right bundle branch	Anterior fascicle

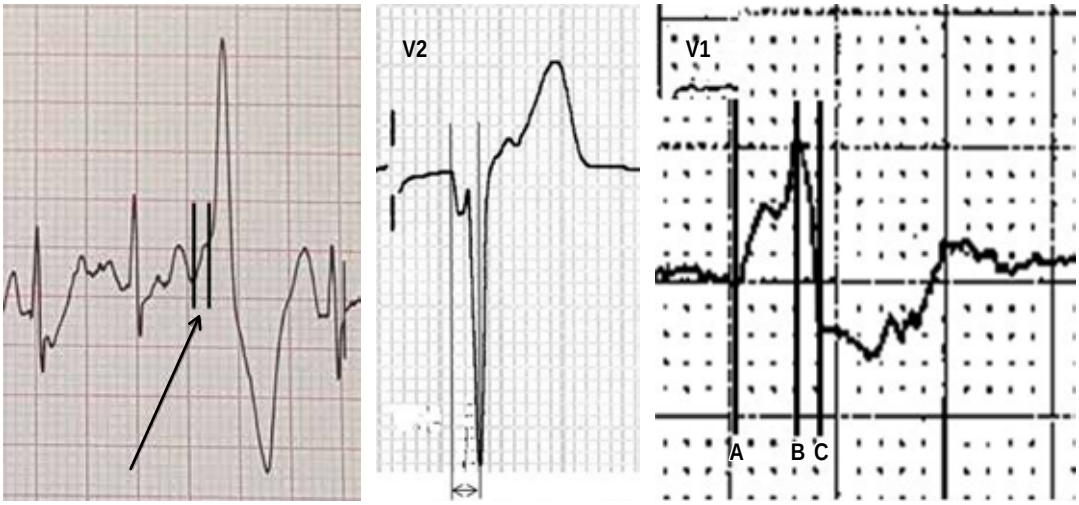


Figure 6:

Ventricular epicardiac arrhythmia features.

anatomic discussion about the existence or not of a left outflow tract might only be confusing in this work.

Right ventricular outflow tract (RVOT)

This structure is located in the superior region of the precordium, in the center of the chest. The RVOT surrounds the left ventricular outflow tract and crosses it in the anterior portion, so that the pulmonary valve is located in front and to the left of the aortic valve.[25] The RVOT is the site of origin of 70 to 80% of the idiopathic arrhythmias of the outflow tracts. The PVC's originating from that point will show an LBBB pattern and an inferior axis in the frontal plane that might slightly deviate right or left. The RVOT can be conceptualized as a semi-circle structure with two opposed crests. The anterior or free wall, and the posterior or septal wall have posterior (right) and anterior (left) extensions. Thus, the RV free wall is located behind the sternum, but both outflow tracts are superimposed. A transition at V3 or later (V4, V5, V6) suggests that the origin is the RVOT. Since the RVOT is an anterior structure inside the thorax, the horizontal axis will be posterior (negative V1, usually with a QS morphology).[25] If the ventricular depolarization axis goes leftwards (positive DI), the origin focus might be in the posterior RVOT, whereas if the axis deviates to the right (negative DI), the focus is usually more anterior *(Figure 7)*.[25,26] Arrhythmias from the septal wall of the RVOT usually show an earlier transition (V3-V4). It is rather unusual that RVOT PVC's have a transition before V2.

Left superior foci

The left superior foci, also known as the «left ventricle outflow tract» (LVOT), can be located in structures such as the aortic cusps (aortic valve sinuses), the mitro-aortic continuity, the superior basal septum or the left ventricle's summit.[26]

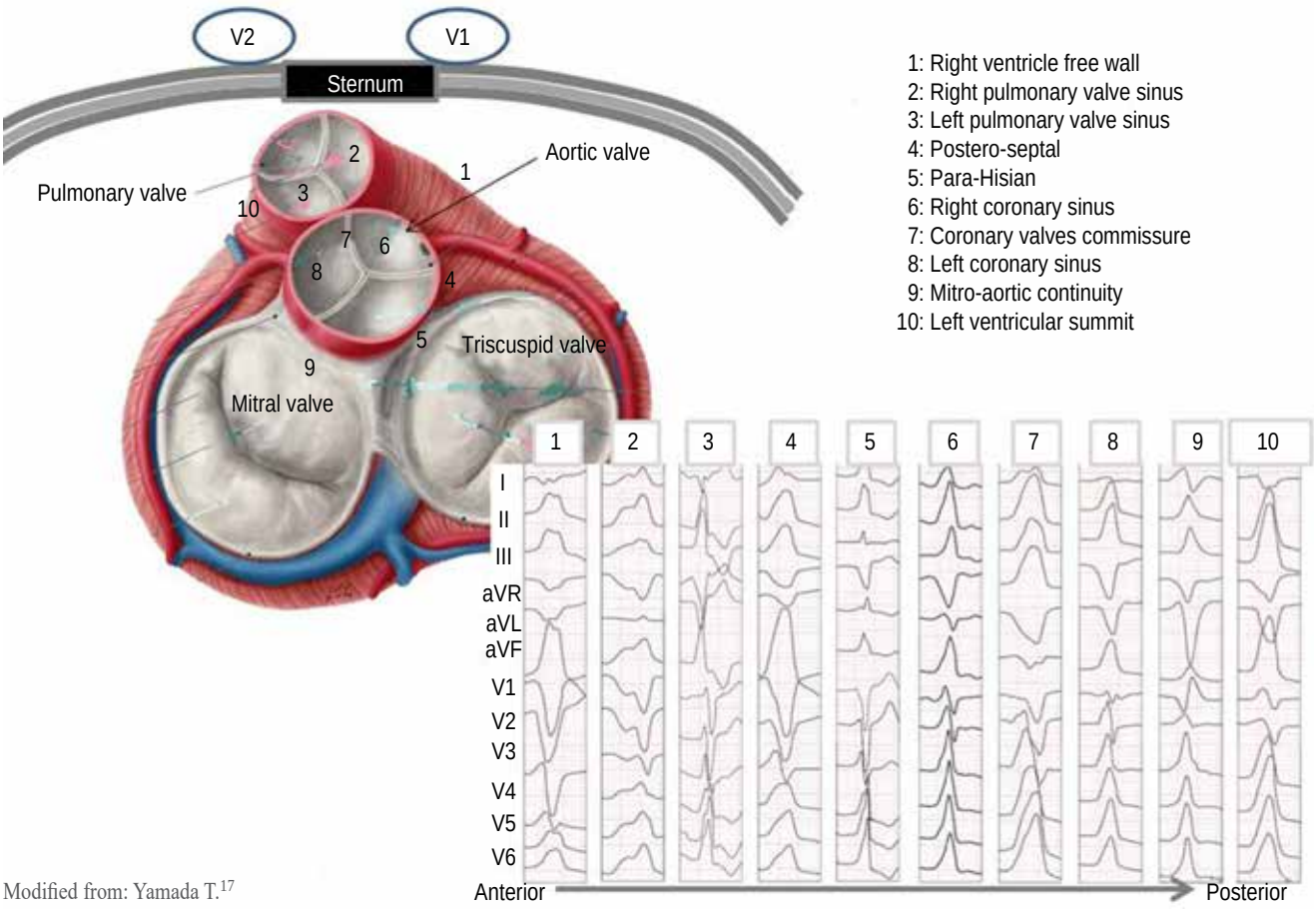
Those structures are responsible for 15 to 25% of the idiopathic ventricular tachycardias.[26,27] The LVOT is an elliptical opening in the left ventricle in which the mitral valve has a posterior and leftwards position when compared to the aortic valve position, which is almost in the centerline of the chest. Both valves share a fibrous band that is the «mitro-aortic continuity» and comprises the anterior leaflet of the mitral valve and the left and non-coronary leaflets of the aortic valve *(Figure 7)*.[25]

Aortic cusps

Premature ventricular contractions might originate from the myocardial tissue within the inter-leaflet commissure and in the base of the aortic sinuses. Despite this possible source of confusion, especially when considering the different approaches for arrhythmia ablation, the term «aortic cusps» is widely accepted as an origin focus for PVC's.

Premature ventricular contractions generated there have an inferior axis that can go right or leftwards and show an LBBB block pattern in 80% of cases. Some ECG characteristics are common to the LVOT and RVOT arrhythmias because of the vicinity of the posterior RVOT to the aorta. The PVC's from the aortic cusps usually have a larger R wave - usually 50% larger than the sinus rhythm QRS –, absence of S wave in V5-V6, and an earlier transition in the precordial leads, when compared with the nearby sites of the RVOT.[24,28] The PVC's from the right coronary sinus might show an rS pattern, with a wide «r» and transition in V3. The QRS complex shows less amplitude in DII and DIII with higher positivity in DII because that sinus is located in a more inferior and rightwards position when compared to the left coronary sinus. The higher the sinus, usually the higher the QRS amplitude.

The left coronary sinus shows an earlier transition, between V1 and V2, with a



Modified from: Yamada T.[17]

Figure 7: Schematic view of the intra-thoracic location of the main structures in the outflow tracts or both ventricles' upper portions. The main depolarization axis will be determined by the anatomic location of the originating structure, its relations with close structures and then, to the position of the surface ECG electrodes (precordial leads) and its relative exit point.

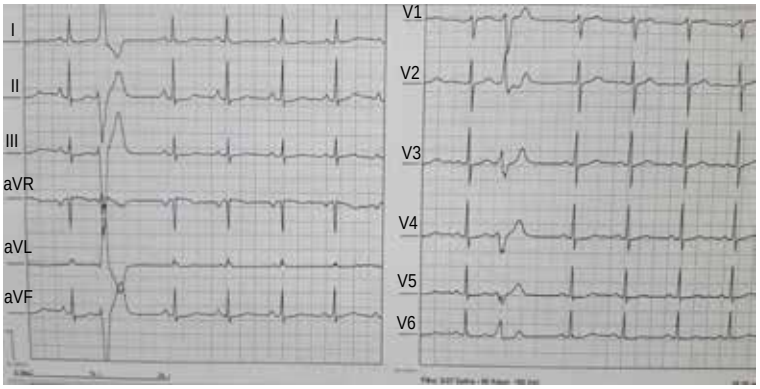


Figure 8: Shows a PVC with LBBB morphology (V1, V6), left superior axis (positive DI and aVL, negative aVF). The PVC's intrinsecoid deflexion is 100 ms. There is a QRS slurring in the precordial leads, with a transition area in V5-V6. The QRS goes from 160 to 180 ms in different leads.

wider R wave (longer than 120 ms in V2) and a higher voltage *(Figure 7)*. This sinus is located in the left lateral and posterior position; thus, the R wave is usually negative in DI and positive in DII, DIII, with a more positive DIII.

Some relatively common idiopathic PVC's originate in the commissure between both coronary sinuses. They show a slurred QS complex in V1, and the transition is in V3.

Mitro-aortic continuity

This region has some Purkinje-like conduction fibers or tissue. The ventricular arrhythmias that arise from here present as monophasic R waves in all the precordial leads, with a RBBB pattern or they might show a qR pattern in V1.[24,29] Others have found that an early R/S wave transition (V2) and an R wave in V3 are frequently seen in PVC's from the anterior mitral-aortic continuity, while the same transition pattern but displaying high R waves in V1 and V3 suggest a middle mitro-aortic continuity origin.[30,31]

Left ventricle summit

This region is the highest portion of the epicardium of the left ventricle and is the origin of up to 12% of the outflow tracts arrhythmias.[32,33] It is the area between the left anterior descending artery, the circumflex artery and an imaginary arch depicted between both vessels at the level of the first septal branch of the anterior descending artery. The PVC's from this point have an RBBB morphology with the left inferior axis, unless the originating focus is displaced towards the anterior interventricular vein, in which case the PVC might have a LBBB morphology owing to the proximity to the interventricular septum. In the precordial leads and the horizontal plane, there is a monophasic R wave pattern similar to the one found in the PVC's from the mitro-aortic continuity. The PVC's that come from the «inaccessible» area of the LV summit show a LBBB with high voltage in DII and DIII and an absence of the s wave in V5 and V6. As in most epicardiac arrhythmias, PVC's usually have a pseudo-delta wave or an initial slurring of the QRS complex *(Figure 7)*.[24,33] Some cases show a «Rupture» pattern, manifested by an LBBB (QS) in the anterior precordial leads, with a less negative V2 and a more negative QS in V3, suggesting that in that specific area, the originating foci might be intra-myocardial rather than epi or endocardiac.[34,35]

Para-Hisian arrhyhmias

These might represent up to 3% of the idiopathic ventricular tachycardias. They show an LBBB morphology with a narrower QRS complex, inferior axis and an early transition, even if V1 frequently displays a QS pattern. The depolarization vector usually follows the normal depolarization direction. Because of its posterior origin, to the right and slightly below the mitral annulus, R waves can be identified in aVL and DI.

Right ventricle's inferior foci

Moderator band

The RV moderator band is a potentially arrhythmogenic structure because it contains a His' right bundle branch fascicle. Owing to its size and insertions, it is a complex element when approaching it for ablation.[36]

Premature Ventricular Contractions arising from it show a LBBB with a superior leftwards

frontal depolarization axis. The PVC's QRS lasts for 135 to 165 ms, somehow narrow, but with a 100 ms intrinsecoid deflection in precordial leads that also show a relatively late transition (usually after V4). Nonetheless, it has to be kept in mind that the transition zone might change according to the exit point within the band itself *(Figure 8)*.[36,37]

Left ventricle's inferior foci

The PVC's that arise from the left ventricle's inferior foci show a RBBB and a superior rightward or leftward axis, according to the relative position of the exit point compared to the interventricular septum (IVS) *(Figure 9)*.

Fascicular arrhythmias

Arrhythmias coming from the anterior fascicle have a RBBB morphology and an inferior rightward axis, while the ones coming from the posterior fascicle will show a RBBB morphology with a leftwards superior axis in the frontal plane.[16] Ventricular tachycardia (VT's) arising from the fascicles usually has a re-entry mechanism. Thus they need a PVC to initiate and they can be verapamil sensitive.[38]

Papillary muscles

Papillary muscles (PM) can be the source of arrhythmias in structurally normal hearts as well as in diseased ones.

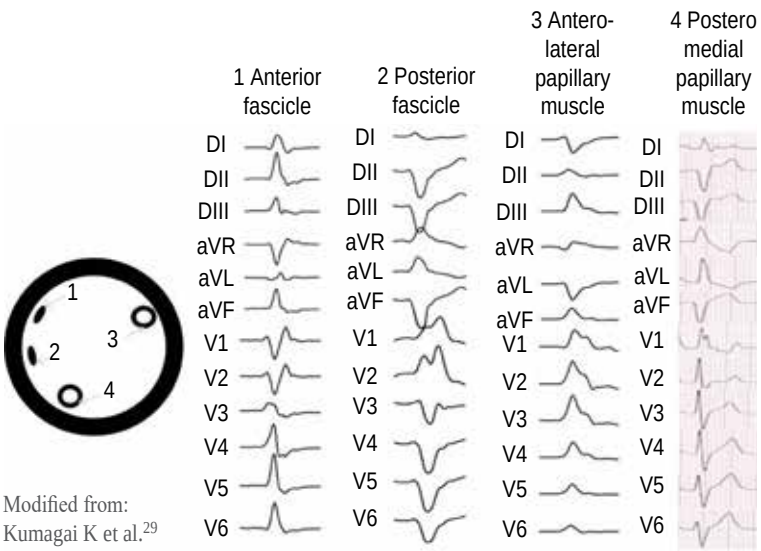
The PVC's originated in the antero-lateral PM usually have a RBBB morphology, a depolarization axis to the right and a transition area between V3 and V5. It is also frequent that they show a depolarization discordance in the inferior leads (positive DII with negative DIII).[39-41]

Arrhythmias from the postero-medial PM will also show a RBBB morphology, a superior axis in the frontal plane and transition between V3 and V5, without the discordance in the inferior leads.

Papillary muscle vs fascicular arrhythmias

Both PVC's show a resembling ECG pattern, but there are important differences.

The papillary muscle PVC's have a wider QRS complex (150 ± 15 ms vs 127 ± 11 ms), and they lack a rsR' activation pattern in V1. They also are monophasic (R or Rs) and they show a q wave in V1.[39,42] Fascicular arrhythmias usually have a q wave in DI or aVL (qR or qRs).



Modified from: Kumagai K et al.[29]

Figure 9: The left circle schematically shows the left ventricle with both fascicles and papillary muscles, numbered according to the ECG tracings. All PVC's have a RBBB morphology (V1), although the ones originating from the anterior fascicle are narrower. Main depolarization vectors are negative in DI in 3 and 4 (The papillary muscles) because those structures are more laterally located when considering the center line. Polarity in aVF is negative in 2, 3 and 4 because they are more inferior structures within the ventricle itself, and thus, they induce an «upwards» depolarization, while the anterior fascicle will do so in a cephalo-caudal direction.

CONCLUSIONS

Premature ventricular contractions might be associated with a higher risk or mortality in subjects with structural heart disease or even without it. They are capable of inducing tachycardiomyopathy, and that is the reason they have become a therapeutic target.

The deductive analysis of the ECG allows to define the approximate origin of the arrhythmia, and thus, to plan optimal treatment strategies in both conditions.

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( ) Both in English and Spanish; with a maximum of 250 words. Structured according to the order of information in the text: 1) Introduction, 2) objectives, 3) material and methods, 4) results and 5) conclusions.

( ) 3-5 Key words.

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Six or more authors

San-Luis R, Munayer J, Aldana T, et al. Venous connection total anomalous pulmonary. Five years of experience. Rev Mex Cardiol 1995; 6: 109-16.

Books

Myerowitz PD. Heart transplantation. New York: Futura Publishing; 1987: 20-31.

Book chapters

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Hidroclorotiazida

Información para prescribir (versión reducida)

1. Denominación distintiva: ROFUCAL®

2. Denominación genérica: Hidroclorotiazida

3. Forma farmacéutica y formulación: Tabletas

Cada tableta contiene:

Hidroclorotiazida ..... 12.5 mg o 25 mg

Excipiente cbp. ..... 1 tableta

4. Indicaciones terapéuticas: ROFUCAL® es un diurético de la familia de las tiazidas que está indicado en: Hipertensión arterial. Como monoterapia o combinado, para incrementar el efecto de otros antihipertensivos cuando se trata de formas más severas de hipertensión. En Edema, cuando está asociado a insuficiencia cardiaca congestiva, cirrosis hepática y en terapia con corticoesteroides y estrógenos. ROFUCAL® es útil también en el tratamiento de edemas relacionados con disfunción renal, como el síndrome nefrótico, la glomerulonefritis y la insuficiencia renal crónica. **5. Contraindicaciones:** el uso de ROFUCAL® está contraindicado en pacientes con anuria e hipersensibles al principio activo o componentes de la formulación, así como a otros fármacos derivados de las sulfonamidas. **6. Precauciones generales:** en pacientes que reciben tratamiento con dosis mayores de tiazidas, se pueden presentar casos de hiperuricemia o franca gota. Una diabetes latente puede hacerse manifiesta con el tratamiento a base de tiazidas. Los diuréticos pueden en dosis mayores precipitar una azoemia en pacientes con insuficiencia renal. **7. Restricciones de uso durante el embarazo y la lactancia:** no se recomienda su uso en embarazadas sanas o con edema pues se expone a la madre y al feto a un riesgo innecesario. Los diuréticos no previenen el desarrollo de toxemias del embarazo y no hay evidencia concluyente de que sean útiles en su tratamiento. Las tiazidas cruzan la barrera placentaria y aparecen en la sangre del cordón umbilical existiendo un riesgo de ictericia neonatal, trombocitopenia y otros posibles efectos adversos. **8. Reacciones secundarias y adversas:** Sistema gastrointestinal: Anorexia, irritación gástrica, náuseas, vómito, diarrea y muy ocasionalmente pancreatitis y sialoadenitis. Sistema Nervioso Central: Mareos, vértigo, parestesias y cefaleas. Hematológicos: Leucopenia, neutropenia/agranulocitosis, trombocitopenia, anemia aplásica y anemia hemolítica. Cardiovasculares: Hipotensión ortostática, vasculitis. Hipersensibilidad: Púrpura, fotosensibilidad, erupción cutánea, urticaria, fiebre y reacciones anafilácticas. Renales y urinarias: Disfunción renal y nefritis intersticial. Otros: Hiperglucemia, glucosuria, hiperuricemia, espasmo muscular, debilidad, inquietud, visión borrosa transitoria, calambres. **9. Interacciones medicamentosas y de otro género:** cuando se administran en forma conjunta otros fármacos puede ocurrir interacción con diuréticos tiazídicos como ROFUCAL®. **Alcohol, barbitúricos o narcóticos:** Puede haber aumento de la presión ortostática. **Aminas presoras:** Puede disminuir la respuesta a las aminas presoras, pero no lo suficiente como para no utilizarlas. **Anfotericina B, corticoesteroides o corticotropina:** Pueden intensificar el desequilibrio hidroelectrolítico, hipocalemia especialmente. **Anticoagulantes orales:** Pueden disminuir los efectos anticoagulantes. **Agentes antiinflamatorios no esteroideos:** Éstos pueden disminuir el efecto diurético. **Colestiramina y colestipol:** Retardan la absorción de ROFUCAL®. **Glucósidos digitálicos:** La hipopotasemia o la hipomagnesemia inducida por tiazidas favorece la aparición de arritmias cardiacas inducidas por digital. **Hipoglucemiantes orales e insulina:** Puede requerirse ajuste de la dosis de antidiabéticos. **Litio:** Los diuréticos disminuyen la depuración renal de litio y aumentan el riesgo de toxicidad. **Medicamentos para la gota:** La hidroclorotiazida puede aumentar el nivel de ácido úrico sérico. **Otros antihipertensivos:** Efecto aditivo o potencializante de sus efectos. **Sales de calcio:** Los diuréticos tiazídicos pueden incrementar los niveles séricos de calcio debido a la reducción de la excreción. **Probenecid o sulfinpirazona:** Se recomienda aumentar su dosis ya que la hidroclorotiazida puede tener efectos hiperuricémicos. **Relajantes no despolarizantes del músculo esquelético (ej. tubocurarina):** la hidroclorotiazida puede potenciar el efecto. **Ciclofosfamida, metotrexato:** Las tiazidas pueden reducir la excreción renal de los fármacos citotóxicos y potenciar su efecto mielosupresor. **10. Precauciones en relación con efectos de carcinogénesis, mutagénesis, teratogénesis y sobre la fertilidad:** estudios conducidos en animales no reportaron efectos carcinogénicos, mutagénicos así como tampoco alteraciones sobre la fertilidad a dosis terapéuticas. **11. Dosis y vía de administración:** ROFUCAL® se administra por vía oral. La dosis aplicada debe ser individual y acorde a la respuesta del paciente. ESQUEMA POSOLÓGICO DE ROFUCAL®. **Pacientes adultos con hipertensión arterial:** Inicio: 25 mg/día dosis única o repartida en varias tomas.*Ajustar la dosis según las cifras de tensión arterial. Máx: 50 mg diarios. **Pacientes adultos con edema:** 25 a 100 mg/día en una o dos tomas. Máx: 100 mg diarios.**

Premenstrual: 25-50 mg. Una o dos veces al día hasta el inicio de la menstruación.

*Algunos pacientes responden con una dosis inicial de 12.5 mg/día sola o combinada con otros antihipertensivos.

**Algunos pacientes responden al tratamiento intermitente (en días alternos o de tres a cinco días/semana).

Pacientes pediátricos con hipertensión arterial: Dosis pediátrica usual: 2.5 mg/kg/día en dos tomas. Lactantes <6 meses: hasta 3.5 mg/kg/día en dos tomas. Niños hasta 2 años: 12.5-37.5 mg/día en dos tomas. Niños 2-12 años: 37.5-100 mg/día en dos tomas. Muy pocos pacientes requieren de dosis altas sostenidas. **12. Manifestaciones y manejo de la sobredosificación o ingesta accidental:** además de la diuresis esperada, la sobredosis de ROFUCAL® puede producir grados variables de letargia, la cual puede progresar al coma en pocas horas con mínima depresión de las funciones respiratorias y cardiovasculares y sin evidencia de cambios en los electrolitos séricos o deshidratación. Además del lavado gástrico y del tratamiento de apoyo para el estupor o coma, puede ser necesario tratamiento de los efectos gastrointestinales. No se ha establecido claramente el grado en que la hidroclorotiazida es eliminada por hemodiálisis. Se debe mantener la hidratación y el equilibrio hidroelectrolítico, la respiración, las funciones cardiovascular y renal. **13. Presentaciones:** Caja de cartón con 15, 30 o 60 tabletas de 12.5 mg en envase de burbuja. Caja de cartón con 20 o 30 tabletas de 25 mg en envase de burbuja. **14. Leyendas de protección:** su venta requiere receta médica. No se deje al alcance de los niños. No se use durante el embarazo ni en mujeres en periodo de lactancia. Literatura exclusiva para médicos. Reporte las sospechas de reacción adversas al correo: farmacovigilancia@cofepris.gob.mx Para mayor información del producto o para reportar eventos adversos comuníquese al teléfono en la ciudad de México 4040-7671 0 LADA nacional sin costo al 01800-200-0170 o correo electrónico: farmacovigilancia@probiomed.com.mx **15. Nombre y domicilio del laboratorio:** PROBIOMED S.A. DE C.V. Yácatas No 307, Colonia Narvarte, Delegación Benito Juárez 03020 México, D.F. **16. Número de registro del medicamento ante la secretaría:** Reg. No. 74276 SSA IV.

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Cuida tu corazón.

Es el diurético de primera línea
y **piedra angular** del tratamiento antihipertensivo.[1]

Los **diuréticos tiazídicos** han demostrado que en **monoterapia** o **combinación**, **reducen** el **riesgo** de **cardiopatía**, enfermedad **vascular cerebral** e **infarto** de **miocardio**.[1]

Es **ideal** para usarse en **terapia combinada**, ya que tiene efecto **aditivo** o **potencializador** con otros antihipertensivos.[2,3]

Indicado en el **tratamiento** del **edema** asociado a **insuficiencia cardíaca congestiva** y/o **cirrosis hepática**.[2]

Dosis recomendadas:[2]

HTA*: 25 mg/día dosis única o repartida en varias tomas. **Dosis máxima:** 50 mg diarios.
Edema: 25 a 100 mg/día en una o dos tomas. **Dosis máxima:** 100 mg diarios.

***HTA:** Hipertensión Arterial.

Referencias: 1. Bell K, *et al.* Hypertension: the silent killer: Updated JNC-8 Guideline Recommendations (2015). Alabama Pharmacy Association; 1:1-8. **2.** Información para prescribir amplia. Rofucal®. **3.** Uchiwa, H., Kai, H., Iwamoto, Y., Anegawa, T., Kajimoto, H., ... Fukuda, K. (2017). Losartan/hydrochlorothiazide combination is safe and effective for morning hypertension in Very-Elderly patients. Clinical and Experimental Hypertension, 40(3), 267–273.

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