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Summary

EDITORIAL

2022 Dr. Pedro Cossio Foundation Award

Premio Fundación Dr. Pedro Cossio 2022

DR. JORGE LERMAN[MTSAC]

At last everything has returned to the long-awaited normality!

Although it is true that the prodigies of technology allowed our virtual congresses to be carried out successfully for two years, finally the 48th Argentine Congress of Cardiology could be enjoyed between October 20 and 22, 2022 with all our senses and in person.

The Scientific Committee of the Congress selected 4 works as candidates to obtain the Cossio Award corresponding to this year and the following work was the winner:

Effect of influenza vaccination in patients with cardiovascular disease: An updated meta-analysis of randomized controlled clinical trials. Authors: Lucrecia M. Burgos, Ezequiel J. Zaidel, Álvaro Sosa Liprandi, Adrián Baranchuk.

Influenza is an acute viral disease that predominates in autumn-winter, which according to estimates by the US Center for Disease Control affects 3 to 11% of the population each season, depending on age, comorbidities and the socio-cultural-economic condition of the population groups. (1) Although these proportions are estimates, there is no doubt that they represent a serious public health problem. Cardiovascular patients are one of the most vulnerable groups affected according to the incidence of complications or mortality. Several types and subtypes of influenza viruses have been identified, but one of the most common is influenza type A (influenza A) H1N1 based on encoding proteins present on its surface (H = hemagglutinin, N = neuraminidase).

During the 20th and 21st centuries, various influenza epidemics and pandemics occurred on the planet, but one of the most recent and resonant was that of the years 2009-2010. It affected the 5 continents and it is estimated that there were more than 1 600 000 affected and more than 19 000 registered deaths during the first 12 months. (2) Already in 2004, the well-remembered Enrique Gurfinkel and his collaborators had shown, in a pioneering work, a very significant reduction of cardiovascular death and coronary events in acute coronary patients who received the anti-influenza vaccine (AIV) randomly compared with a control group after 1-year follow-up. (3) But since the aforementioned pandemic, the World Health Organization and the main societies of cardiology in the US and Europe recommend annual vaccination against influenza in patients with cardiovascular disease, due to the afore-mentioned vulnerability, and because compelling benefits are achieved. The most recent recommendation was published in 2021 by the Inter-American Society of Cardiology through the authors of the work we are commenting on. (4) The 2009-2010 pandemic led to universal awareness about the usefulness of AIV with health and government campaigns to generalize its application in risk groups, but the ideal objectives have not yet been achieved, particularly in deprived population groups. (5)

Professionals from Instituto Cardiovascular de Buenos Aires, Sanatorio Güemes, and the Kingston Health Science Center in Ontario, Canada, carried out a meticulous systematic search of all the studies published in Pubmed, the Cochrane Library, and Clinical Trial Registries in relation to AIV in patients with heart failure (HF) or cardiovascular disease (CVD). (6) They also manually reviewed the reference list of all recent publications and presentations at international cardiovascular congresses by referencing keywords related to this topic, to ensure complete capture of relevant articles. This thorough search initially identified a total of 957 studies. Duplications were eliminated, the risk of bias was assessed and the existence of heterogeneity in the different works was quantified. From this extensive list, they selected those randomized clinical trials that compared the results of AIV vs. placebo or vs. no intervention, in patients with HF or CVD, and strict inclusion and exclusion criteria were applied. They followed the successive steps of the PRISMA protocol flowchart to analyze systematic reviews and finally selected 6 trials totaling 9316 patients for definitive analysis. The primary endpoint was all-cause mortality (ACM) and secondary endpoints were cardiovascular mortality (CM), myocardial infarction (MI), and major adverse cardiovascular events (MACE) among vaccinated and unvaccinated patients. After a mean follow-up of 16±9.7

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Jury's president

months, AIV was associated with a 33% reduction in ACM compared with control: RR 0.67 (95% CI 0.47 to 0.95) (p=0.03). It also reduced CM by 36% (p=0.02), MACE by 31% (p=0.007), and a non-significant trend of MI reduction of 18%.

This work has the enormous merit of the strict methodology used. It was a broad and meticulous search of all the available information, which was subjected to a detailed inclusion and exclusion process following a pre-established protocol, which concluded with the analysis of 6 publications. It is the most complete and updated meta-analysis existing, since it also included two studies published in the last year. Despite the overwhelming evidence available, the influenza vaccination rate in cardiovascular patients is far from ideal. A multicenter study demonstrated a wide variability of prescription (or acceptance) in patients with heart failure: between 70 and 80% in Europe, 52% in North America, and 2.6% in Asia. (7) In our setting there is also marked underutilization: 46% according to a study carried out in a high complex center. (8) Various barriers may be related to this behavior: among others, the lack of doctors' conviction, patients' myths and beliefs, economic limitations or the lack of provision by the public or private medical coverage systems. The results shown in this study should represent a stimulus for primary care physicians, clinicians, and cardiologists to extend the indication of influenza vaccination to cardiovascular patients and other high-risk groups.

The other candidate works to obtain the Cossío Award were:

Cardiogenic shock classification (SCAI) to predict in-hospital and long-term mortality in acute heart failure. Authors: Lucrecia M. Burgos, Rocío Baro Vila, Franco Ballari, Ana Spaccavento, Bianca M. Ricciardi, María L. Talavera, Fernando Botto, Mirta Diez

Cardiogenic shock (CS) is one of the most dramatic situations faced by the staff of an emergency room, intensive care or coronary care unit. Despite the number of highly efficient pharmacological and instrumental resources that have been incorporated in recent decades, mortality continues to be very high. On the other hand, the heterogeneity of patients with CS who attend the hospital at different stages of the disease is well known. They cover a wide spectrum of hemodynamic disorders ranging from isolated hypoperfusion that is reversed with initial therapies, to refractory shock with multiple organ failure and hemodynamic collapse. This implies the selection of different treatment modalities, from pharmacological to highly complex invasive ones, which will directly impact on clinical results and prognosis. Acknowledging the aforementioned heterogeneity of the groups of patients with CS, a multidisciplinary group led by the Society for Cardiovascular Angiography and Interventions (SCAI) recently designed a classification scheme for CS, with an adequate clinical basis for rapid evaluation at the patient's bedside. The purpose was to provide a simple and pragmatic tool to be used without delay in clinical practice in this group of patients. (9) This classification considers five stages, was widely validated in multiple publications and applied in practice. As a summary, stage A ("At risk") includes patients without signs or symptoms of CS, but who are at risk of developing it, for example, those with large acute myocardial infarction, previous acute infarction and/or symptoms of heart failure. Stage B ("Beginning") consists of patients who have clinical evidence of hypotension or tachycardia, but without hypoperfusion. Stage C ("Classic") comprises patients with hypoperfusion requiring an initial set of interventions (inotropes, vasopressors, mechanical support or extracorporeal membrane oxygenation, ECMO). Stage D ("Deteriorating") involves patients who have failed to stabilize despite intense initial efforts and require further escalation. Stage E ("Extremis") includes patients with circulatory collapse, often in refractory cardiac arrest with ongoing cardiopulmonary resuscitation or being supported by multiple simultaneous acute interventions, including ECMO.

This retrospective cohort analysis conducted at Instituto Cardiovascular de Buenos Aires aimed to validate the SCAI scheme in acute heart failure (AHF) and establish its in-hospital and long-term prognosis. A total of 856 consecutive patients with AHF admitted between 2015 and 2020 were included. Mean age was 74.7±13 years and 63.7% were male. The most frequent cause was coronary heart disease (35.6%), followed by valvular heart disease (27.5%). Median left ventricular ejection fraction (LVEF) was 42% (29-58), and 45.7% had LVEF <40%. The proportion of patients with shock, in SCAI stages A to E, was 39.8%, 39.4%, 14.1%, 4.1%, and 2.6%, respectively. Patients with more severe stages were younger; more frequently had reduced LVEF, were in functional class III-IV, and had had previous hospitalizations for AHF. There was a gradual increase of in-hospital mortality in each SCAI stage: A 0.6%, B 2.7%, C 21.5%, D 54.3%, and E 90.6% (Log Rank p <0.0001). After a follow-up of 16.8 months, mortality was: A 24.9%, B 24%, C 49.6%, D 62.9% and E 95.5% (Log Rank p <0.0001). After multivariate adjustment, each stage of SCAI shock remained associated with increased mortality (all with p <0.001 compared with stage A). But there was no difference between stages A and B for adjusted mortality (p = 0.1).

This work provides two important contributions: the applicability of the SCAI scheme in AHF and its remote prognosis. The limitation is that it was performed in a high complex center, and it is therefore difficult to reproduce these results in hospitals lacking advanced resources. There is no doubt that patients with CS or AHF in the severe stages of the SCAI scheme should be transferred in the short term to tertiary care centers with a 24/7 cardiac catheterization service and a specialized coronary care unit with mechanical circulatory support. Of course, that transfer will be conditioned

by the possibilities presented by the patient's situation and the resources available for transportation. One possible reason that would explain the paradox of the younger age of the cases in stages D and E that was observed in the work we are commenting on, is that in the selection of candidates to be referred to a reference center with the capacity for mechanical circulatory support and transplantation, they are usually younger and without comorbidities.

Presence of subclinical atheromatosis before 45 years of age. Analysis of a cohort study in Argentina. Authors: Gustavo A. Giunta, Lorena Helman, Pablo D. Cutine, Maria Florencia Aguiló, Daniel Antokoletz, Daniel Pirola, Maria Isabel Rodriguez Acuña, Laura Brandani

The ultrasound examination of the vascular bed (carotid arteries, aorta and femoral or iliac arteries) is a very valuable tool to diagnose subclinical atherosclerosis (ATS). It is particularly useful for the appropriate reclassification of persons at intermediate cardiovascular risk, as suggested by the main cardiovascular prevention guidelines with class IIb recommendation and level of evidence B. (10) Compared with other postulated methods (coronary calcium assessment) vascular ultrasound has the great advantage of its practicality, versatility, less sophisticated technology and lower cost.

This cross-sectional study of Fundación Favaloro analyzed 1788 patients between 18 and 45 years of age who spontaneously attended a cardiovascular prevention program between January 2017 and December 2018. Mean age was 30.1±8.6 years and 49.3% were women. Cases with clinical cardiovascular coronary, cerebrovascular or peripheral disease history were excluded from the study. Atherosclerosis was defined as the presence of atheromatous plaques evaluated by ultrasound at the level of the carotid arterial tree. These plaques were characterized by a focal protrusion towards the arterial lumen of ≥0.5 mm width, as more than 50 % increase of the adjacent intima-media thickness (IMT) or as a diffuse IMT increase of >1.5 mm measured between the media-adventitia and the intima-lumen. Its presence was considered as a binary variable: absence (No) and presence (Yes). Atherosclerosis was detected in 3.1% of cases. It was more prevalent in men and as expected, it was associated with age (<30 years=0.6%; 30 to <40 years=1.8% and ≥40 years=11.7%), hypertension (9% vs. 3%, p<0.01), total cholesterol (212.9±38.4 mg/dL vs. 182.5±35.8 mg/dL p<0.0001) and triglycerides (150±92 mg/dL vs. 105.3±65.3 mg/ dL, p <0.0001). HDL-cholesterol (HDL-C) was lower in patients with ATS (49.2±11mg/dL vs. 54.7±13.6 mg/dL p <0.0001) and the use of statins was higher in those with ATS (3.6% vs. 0.7%, p <0.05). Patients with ATS had a non-significant increase of the metabolic index (20% vs.10%; p=NS), but the prevalence of ATS was associated with the increase in the number of components present (p <0.005). The Framingham score evidenced a greater proportion of ATS patients at high or moderate risk, but 83.6% of subjects with ATS belonged to the lower risk category and 10.9% to that of moderate risk. The calculation of the vascular age among those over 40 years revealed an increase of 4.8 years in the absence of ATS and of 7.7 years in its presence (p<0.005).

There are few studies in our setting indicating that in young individuals, apparently healthy from a cardiovascular point of view, atherosclerotic lesions may be present, especially when there are risk factors, though this is infrequent. This work reflects this situation, demonstrating an exponential increase with age and its association with cardiovascular risk factors. The atherosclerotic vascular disease and its clinical consequences are generated by the interaction of LDL-C plasma concentration in the presence of an inflammatory state, but essentially as a function of time during which the endothelium was exposed to the deleterious effect of LDL-C. Consequently, it is important to detect at an early stage the existence of hypercholesterolemia and premature vascular lesions, with the purpose of aborting the damage that would ensue at the mid- or long-term. In the case of this study, it should be taken into account that its conclusions apply to a highly selected population, consisting of individuals who voluntarily attended a prevention program to know their health status, and cannot be directly extrapolated to the general population. Moreover, only the carotid territory was explored, excluding the iliofemoral and aortic territories. Recently, the examination of multiple vascular territories by ultrasound and computed tomography has demonstrated an increase of the diagnostic and predictive value. (11)

The cardiovascular exercise test contributes to an accurate risk assessment in patients with low-risk pulmonary hypertension. Authors: Ignacio Martín Bluro, Leandro Barbagelata, María Lorena Coronel, Luciano Melatini, Graciela Svetliza, Norberto Vulcano, Andrés Nicolás Atamañuk, Walter Mauricio Masson Juarez

Pulmonary hypertension is defined as mean arterial pressure of 20 to 25 mmHg or more (according to different criteria). It is a condition produced by numerous etiologies and it is formed by groups of diverse severity and prognosis. (12) According to its severity, patients can be classified into 3 risk groups: low (<5% estimated mortality risk at 1 year), intermediate (5-10% estimated mortality risk at 1 year) and high risk (>10% estimated mortality risk at 1 year). The following variables are recommended to define these groups: 1) functional capacity (FC) defined by the World Health Organization (WHO), 2) the 6-minute walk test (6MWT) and 3) oxygen consumption (VO_2) in a cardiopulmonary exercise test (CPET). (13)

Researchers from Hospital Italiano de Buenos Aires, the Cardiology Institute of Corrientes, the Southern Pneumonology Institute of Bahía Blanca and Hospital Juan A. Fernández of Buenos Aires carried out a cross-sectional multicenter study including 18 patients over 18 years old with pulmonary arterial

hypertension (PAH). Sixteen were women (89%), median age was 43.5 years and median time from diagnosis to evaluation was 4.7 years. In half of the cases (n=9) the etiology of PAH was considered idiopathic, in 6 cases associated with connective tissue disease, in 2 cases secondary to human immunodeficiency virus (HIV) and in 1 case to porto-pulmonary hypertension. The inclusion criteria involved belonging to a low-risk stratum according to the simplified risk evaluation of the French registry: 1) FC I-II, 2) NT-proBNP <300 pg./mL and 3) 6-minute walk test >440 meters. (14) Two patients (11%) were receiving a vasodilator drug, 12 (67%) 2 drugs and 4 (22%) 3 drugs. They all performed CPET on a treadmill following the Bruce or modified Bruce protocol, and the gas exchange was continuously analyzed. The recorded variables included heart rate, blood pressure, peripheral oxygen saturation (SpO_2), oxygen consumption (VO_2), rate of carbon dioxide production (VCO_2) and minute ventilation (VE). The respiratory quotient (RQ) or the respiratory exchange ratio (VCO_2/VO_2) were used as maximum exercise indicator. A RQ >1.1 was considered as maximum exertion. Peak $VO_2$was defined as average VO_2 during the last minute of exercise and was expressed in mL/min/kg, and was additionally reported as percentage of the predicted value (according to prespecified tables which consider sex, age and body surface area). Functional capacity was defined as normal when the VO_2 as percentage of predicted VO_2 was ≥85%. The three variables considered in risk evaluation were: peak VO_2, the percentage of the predicted value and the VE/VCO_2 slope. The proportion of patients presenting these abnormal parameters (peak VO_2 ≤15 ml/min/kg, the percentage of predicted value ≤65% and VE/VCO_2 slope ≥36) was examined. Despite all patients were considered at low risk when they entered the study, peak VO_2 was below the predicted 85% in all of them. Only one patient (6%) did not present any of the 3 high-risk variables, 8 (44%) presented one variable, 7 (39%) presented 2 and 2 (11%) presented the 3 variables. Therefore, 94% of PAH patients considered a priori as low risk, presented some high-risk factor when analyzed with the CPET. A message to consider with these results is the great accuracy presented by an objective, measurable and reproducible technique such as CPET instead of subjective estimations as FC. Moreover, CPET would be a potentially useful tool to identify "high-risk from low-risk"; in other words, to establish an "absolute low risk". However, these should be considered preliminary conclusions due to the low number of patients included and the sample heterogeneity. Finally, more extensive studies with a long-term follow-up should establish the prognosis and survival of the patients studied with the present protocol, to confirm its clinical utility.

The Jury of the 2022 Dr. Pedro Cossio Award was completed with the Argentine Society of Cardiology former presidents Dr Carlos Barrero and Dr. Carlos Tajer, to whom I thank their knowledgeable and responsible participation.

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ORIGINAL ARTICLE

Effect of Influenza Vaccination in Patients with Cardiovascular Disease: An Updated Meta-Analysis of Randomized Controlled Trials

Efecto de la vacunación contra la influenza en pacientes con enfermedad cardiovascular: un metaanálisis actualizado de ensayos clínicos controlados aleatorizados

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ABSTRACT

Background: Influenza is a major cause of morbidity and mortality in patients with cardiovascular disease (CVD). The aim of this updated systematic review and meta-analysis was to evaluate the effect of influenza vaccination (IV) on morbidity and morbidity in adult patients with CVD.
Methods: We conducted a systematic review and meta-analysis (PubMed, Cochrane Library, International Clinical Trials Registry Platform, and manual search of conference presentations) of randomized clinical trials published up to April 2022 analyzing whether IV reduced all-cause mortality in adult patients with CVD, including heart failure (HF) and coronary artery disease (CAD), compared with patients who were not vaccinated.
Results: A total of six clinical trials comprising 9316 patients were analyzed. Five trials included CAD patients, and one trial included HF patients. Mean follow-up was 16 ± 9.7 months. Influenza vaccine was associated with a reduction of mortality compared to controls: relative risk (RR) 0.67, 95% confidence interval (95% CI), 0.47-0.95; p = 0.03; I^2 = 53%, and with reduction of cardiovascular death compared to controls: RR 0.64; 95% CI 0.44-0.94; p = 0.02; I^2 = 54%. There was a non-statistically significant reduction in myocardial infarction compared to control: RR 0.82, 95% CI 0.60-1.12; p = 0.57; I^2 = 0%.
Conclusion: In this meta-analysis of six randomized controlled clinical trials, IV was associated with a 33% and 36% relative risk reduction of all-cause mortality and cardiovascular death, respectively, in patients with CVD. We sought to promote consensus about the persistent benefits of influenza vaccination in patients with CVD by including two new clinical trials in CAD and HF, confirming the association of vaccination with risk reduction in subjects with CVD.

Keywords: Influenza - Influenza Vaccines - Cardiovascular Diseases/Mortality - Myocardial Infarction

RESUMEN

Introducción: La influenza es una causa importante de morbilidad y mortalidad en pacientes con enfermedades cardiovasculares (ECV). El objetivo de esta revisión sistemática actualizada y metaanálisis fue evaluar los efectos de la vacunación contra la influenza (VI) sobre la mortalidad y morbilidad en pacientes adultos con ECV.
Métodos: Se realizó una revisión sistemática y un metaanálisis (PubMed, Cochrane Library, International Clinical Trials Registry Platform, y búsqueda manual en presentaciones en congresos de la especialidad), de ensayos clínicos aleatorizados publicados hasta abril de 2022 que investigaron si la VI reduce la mortalidad por todas las causas en pacientes adultos con ECV, incluyendo insuficiencia cardíaca (IC) y enfermedad de las arterias coronarias (EAC), en comparación con pacientes que no fueron vacunados.
Resultados: Se analizaron un total de seis ensayos clínicos, que incluyeron 9316 pacientes. Cinco ensayos incluyeron pacientes con EAC, y uno con IC. El seguimiento medio fue de 16 ± 9,7 meses. La VI se asoció con una reducción de la mortalidad en comparación con el control, cociente de riesgos (RR) 0,67, intervalo de confianza del 95% (IC95%) 0,47-0,95; , p = 0,03; I^2 = 53%; y con una reducción de la mortalidad cardiovascular en comparación con el control, RR 0,64; IC95% 0,44-0,94; p = 0,02; I^2 = 54%. El uso de la VI se asoció con una reducción no estadísticamente significativa de infarto de miocardio en comparación con el control, RR 0,82; IC95% 0,60-1,12; p = 0,57; I^2 = 0%.
Conclusión: En este metaanálisis de seis ensayos controlados aleatorizados, la VI se asoció con una reducción del riesgo relativo del 33% y del 36% de la mortalidad por todas las causas y cardiovascular, respectivamente, en pacientes con ECV. Intentamos promover un consenso con respecto a los beneficios persistentes de la vacuna contra la influenza en pacientes con ECV, incluyendo dos nuevos ensayos clínicos en EAC e IC, donde se confirma la asociación de la vacunación con la reducción de riesgo en sujetos con ECV.

Palabras clave: Gripe Humana - Vacunas contra la Influenza - Enfermedades Cardiovasculares/Mortalidad - Infarto del Miocardio

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INTRODUCTION

Although influenza is primarily considered a viral infection usually limited to the respiratory system, several cardiovascular complications have been described. (1) Cardiovascular disease (CVD) and influenza have been associated for a long time due to an overlap in the peak incidence of each disease in the winter months. (2) Epidemiological studies observed an increase in cardiovascular (CV) mortality during influenza outbreaks, indicating that CV complications of influenza, including exacerbation of heart failure (HF), acute ischemic heart disease, and, less often, other CV manifestations (stroke, cardiac arrhythmias, venous thromboembolism, or myocarditis), are important contributors to morbidity and mortality during influenza virus infection. (3)

The connection between heart disease and influenza is complex: it can occur via the inflammation-thrombosis pathway, direct effects of the virus on the myocardium, or exacerbation of pre-existing CV disease. (4) The mechanisms postulated to explain the increased risk of vascular events include precipitating plaque rupture, endothelial dysfunction, triggering of other latent infections contributing to plaque rupture, triggering of the procoagulant pathway, tachycardia and vasodilation associated with fever, and infection-related metabolic disorders, including elevated triglyceride and blood glucose levels. (5,6)

Influenza vaccination (IV) is a well-established strategy for reducing influenza-related morbidity and mortality patients with CVD. (7,8) Based on observational studies and randomized clinical trials, vaccination has been associated with significant reductions in all-cause mortality and major adverse cardiovascular events. (9-12)

Currently, the World Health Organization, the Centers for Disease Control and Prevention, the American Heart Association/American College of Cardiology, and the European Society of Cardiology recommend annual influenza vaccination for patients with established CVD. (13-15) In 2021, the Inter-American Society of Cardiology published a consensus statement on IV and CVD, (16) citing the most recent meta-analysis with 4 randomized clinical trials that showed that IV was associated with a reduction in cardiovascular events, (17) and another meta-analysis based on observational data from HF patients, which had consistent findings. (18)

Because two new clinical trials have been recently published in the last two years, we decided to perform an updated meta-analysis of randomized clinical trials on the impact of IV on CV mortality and outcomes in patients with CVD.

OBJECTIVE

Our primary objective was to perform a systematic review and meta-analysis of randomized clinical trials to evaluate the effect of IV on mortality in patients with CVD. The secondary objective was to evaluate the effect of IV on CV mortality, myocardial infarction, and major adverse cardiovascular events (MACE) in patients with HF and coronary artery disease (CAD).

METHODS

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist was used to perform and report this systematic review. (19)

Search method for identification of studies

A systematic search was conducted to identify articles published up to April 2022 in MEDLINE (PubMed database), the Cochrane Library, and the International Clinical Trials Registry Platform. We searched the following keywords or MESH terms in the title or abstract: "influenza," "influenza vaccine," "vaccine," "myocardial infarction," "coronary artery disease," "acute coronary syndrome," "heart failure," and "congestive heart disease".

We performed manual searches checking the reference list of all the relevant publications to ensure complete collection of relevant articles, and we also reviewed recent presentations at international cardiovascular congresses.

Selection of relevant studies for inclusion

Two reviewers (LMB, EJZ) independently screened titles and abstracts to identify potentially relevant articles. Any discrepancy in the data collected was resolved via discussion. Full-text articles were included in this review if they met all the following inclusion criteria: (1) randomized clinical trials comparing influenza vaccination with placebo or no intervention when data on one of the outcomes were reported; (2) articles providing data on the effectiveness of influenza vaccination in patients with HF or CAD compared with an unvaccinated control group; (3) influenza vaccination was administered within one year after study enrollment; (4) articles published in English or Spanish language.

We excluded duplicates, studies that included patients with different doses of influenza vaccination but without an unvaccinated arm, and all nonrandomized controlled trials.

Type of participants

Participants >18 years with established CVD; HF or (CAD stable or unstable angina and ST-segment elevation or non-ST-elevation myocardial infarction) were included in the study.

Outcome measures

The primary outcome measure was all-cause mortality, while the secondary outcome measure was CV mortality, myocardial infarction, and major adverse cardiovascular events (MACE) among vaccinated and unvaccinated patients with HF and CAD.

Data collection and management

Two reviewers independently extracted data and all disagreements were resolved by discussion or arbitration. The following data were systematically extracted:

- Trial characteristics: design, duration, region, scope, year of publication.
- Intervention: type and method of vaccination, control intervention.
- Participants: number of participants, inclusion and exclusion criteria, total number and number in comparison groups, baseline characteristics (age, sex, cardiovascular

risk factors, cardiovascular medication).
- Results: primary and secondary outcomes according to trial, myocardial infarction or reinfarction, unstable angina, cardiovascular death, and related outcomes.

Any discrepancy in data extraction was resolved via discussion with another author (ASL).

Subgroup analysis
A subgroup analysis was performed to compare the effects of vaccination on mortality in patients with HF and CAD.

Bias assessment
Bias was independently assessed by two investigators. We assessed evidence of bias of randomized controlled trials with the Cochrane risk of bias tool, (20,21) with evaluation of the following criteria: random sequence generation (adequate method), allocation concealment, blinding of participants and personnel, management of incomplete outcome data, loss to follow-up or withdrawal from the study, intention-to-treat analysis, selective reporting, similarity in baseline characteristics, any other observed biases.

Measures of treatment effect
All outcome measures were dichotomous results and were presented as risk ratios (RR) at the last follow-up reported.

Heterogeneity assessment
Heterogeneity between trials was quantified with the I^2 statistics, which is independent of the number of studies in a meta-analysis, and with the chi-square test, with significance levels set at a value of $p = 0.1$. An I^2 value > 50% meant significant heterogeneity between studies. (22)

Data synthesis
Based on heterogeneity test, the pooled RR was calculated using fixed effects model when there was no heterogeneity and random effects model in case of heterogeneity.

Statistical analysis
All outcome measures were dichotomous results and were presented as risk ratios (RR) and 95% confidence intervals (95% CI) at the last follow-up reported.

Two-tailed p value < 0.05 was considered statistically significant.

Publication bias was estimated in case there were more than 10 studies by visual assessment in the funnel plot. Egger's regression test was used to examine the asymmetry of the funnel plot. (23)

The selection process was carried out using the Reference Manager Rayyan QCRI. (24) All data extracted from the included studies were entered into Review Manager (RevMan 5.3).

Ethical considerations
This review does not contain any direct interaction with human participants.

RESULTS
Search results
A total of 957 studies were identified through literature search; 527 studies were selected and 486 were excluded after an initial screening of titles and abstracts. The remaining 41 publications were reviewed in full text and evaluated according to the inclusion criteria. Finally, 6 trials were selected for the quantitative analysis. (25-30)

The search and selection process is represented in a PRISMA flow diagram (Figure 1).

Characteristics the studies included
A total of six clinical trials comprising 9316 patients were analyzed. Five trials included CAD patients (FLUVACS, FLUCAD, IVCAD, IAMI and Phrommintikul et al.), and the IVVE trial included HF patients. Mean follow-up was 16 ± 9.7 months. Table 1 summarizes the main general characteristics of the trials. A description of each study included in the meta-analysis can be found in Table 1 of the supplementary material.

Risk of bias in included studies
Risk of bias across studies is shown in Figure 1 of the supplementary material, and risk of bias within studies is shown in Figure 2 of the supplementary material.

Effects of influenza vaccination
Primary outcome measure: All-cause mortality.

Influenza vaccine was associated with lower mortality compared to control: RR 0.67, 95% CI 0.47-0.95; $p = 0.03$; $I^2 = 53\%$ (Figure 2)..

Secondary outcome measure: Cardiovascular death, myocardial infarction and MACE

Influenza vaccine was associated with lower cardiovascular death compared to control: RR 0.64, 95% CI 0.44-0.94; $p = 0.02$; $I^2 = 54\%$ (Figure 3), and with reduction of MACE: RR 0.69, 95% CI 0-53-0.90; $p = 0.007$; $I^2 = 68\%$ (Figure 4). There was a non-statistically significant reduction in myocardial infarction compared to control: RR 0.82, 95% CI 0.60-1.12; $p = 0.57$; $I^2 = 0\%$ (Figure 5).

Subgroup analysis

A subanalysis of overall mortality was performed comparing IV vs. control, stratified by history of CAD and HF. This effect was not consistent between the two study populations: in HF, RR 0.91 (95% CI 0.80-1.02; $p = 0.1$) and in CAD RR 0.56 (95% CI 0.41-0.76; $p = 0.0002$), p for interaction = 0.004. (Figure 3 of the supplementary material).

DISCUSSION
In this updated meta-analysis of controlled clinical trials including 9316 patients with CAD or HF, IV was associated with a significant reduction in all-cause mortality, cardiovascular death, and MACE. Vaccinated patients presented a non-significant reduction in the incidence of acute myocardial infarction.

The information about the association of influenza and CVD is conclusive, but its mechanisms are still under study. Yet, the inflammation-thrombosis model seems to be the most widely accepted one. Other fac-

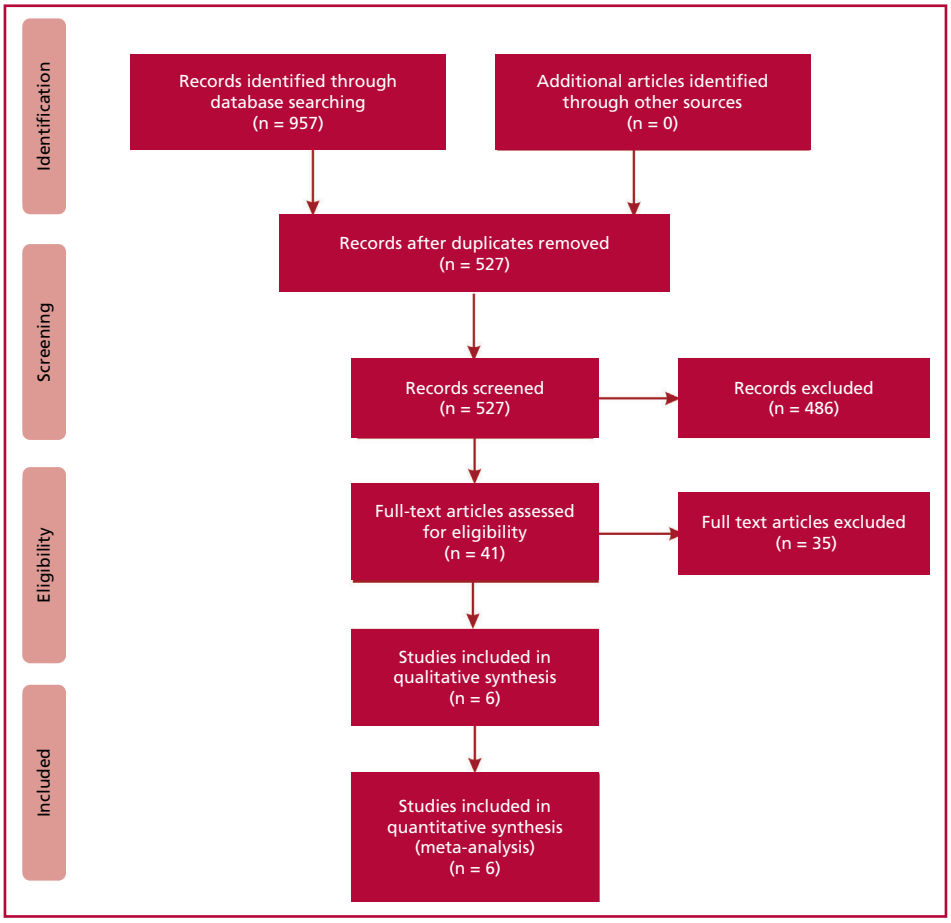

Fig. 1. PRISMA flow diagram for the selection procedure for elegible studies.

tors, such as increased metabolic demand due to the adrenergic surges and hyperdynamic CV response, and hypoxia secondary to pulmonary infection also seem to play an important role. (31,32)

Since the pioneering study conducted in Argentina by Gurfinkel et al. was published in 2004 (25) and then incorporated as the main and only evidence in the CDC guidelines in the United States in 2009, (33) IV has been gradually established as a prevention strategy for CV events.

Some recognized limitations to broaden the use of IV include uncertainty about external validity, reproducibility in different regions, climates, and high and low resource countries, and the safe use in the setting of an acute event or its efficacy in subjects with HF. These factors led to the development of the new clinical trials evaluated here.

In addition, although the recommendation for IV is not new, it is still sub-optimally accepted. In the United States, only 50% of patients with CAD received IV, with important disparities according to socioeconomic determinants. (34) Similarly, one third of those hospitalized for HF did not receive IV. (35)

We compared the results of our meta-analysis with those of previous publications. A Cochrane review published in 2015 of four secondary prevention trials included 1682 patients with CVD and reported reduction in CV mortality (RR 0.45; 95% CI, 0.26- 0.76), but not in AMI. (36) More recently, in 2021 a meta-analysis of these four randomized trials and 12 observational studies including more than 237 000 patients with CVD, reported that influenza vaccination was associated with significant reductions in the risk of all-cause mortality, CV mortality, and MACE at a median follow-up of 20 months. (17)

We believe that the main findings of this meta-analysis are confirming that the benefit of reducing all-cause mortality and cardiovascular death and the trend towards a reduction in the risk of myocardial infarction remains after including new randomized clinical trials involving more than 7000 subjects. The benefit in reducing events is also maintained when two populations that were not previously evaluated are included in the meta-analysis: subjects with a recent coronary event (IAMI trial) and subjects with heart failure (IVVE trial).

As for the IAMI study, (29) the indication of IV in subjects with coronary artery disease was supported by different clinical trials and previous meta-analyses; however, the authors proposed the strategy of indicating IV during hospitalization due to an acute coronary event, demonstrating the safety and efficacy of this

Table 1. Characteristics of the studies included in the meta-analysis.

Studies	Patients	Age, mean (SD)	Men, %	Follow-up, months	Control therapy	N° in the control cohort	N° in the intervention group	Region
FLUVACS 2004 (25)	ACS (66%) or stable CAD and planned PCI (34%)	65 (NR)	79.4%	12	Without treatment	147	145	Argentina
FLUCAD 2008 (26)	56% with stable CAD, 24% with PCI for ACS, 20% with PCI for stable angina	60 (10)	72.5%	12	Placebo	333	325	Poland
IVCAD 2009 (27)	Hospitalized patients and outpatients with recent ACS or stable CAD	55 (9)	66%	12	Placebo	131	135	Iran
Phrommintikul et al., 2011 (28)	47%, 36% STEMI, 16% with unstable angina	66 (9)	56%	12	Without treatment	218	221	Thailand
IAMI 2021 (29)	Hospitalized patients and outpatients with recent ACS (STEMI 54.4%, NSTEMI 45.3%) or high-risk stable CAD (0.3%) Symptomatic NYHA	59,9 (11,2)	81.8%	12	Placebo	1260	1272	Sweden, Denmark, Norway, Latvia, United Kingdom, Czechia, Bangladesh, Australia
IVVE 2022 (30)	functional class II-IV heart failure	57 (NR)	49%	36	Placebo	2569	2560	India, China, Africa

ACS: acute coronary syndrome; CAD: coronary artery disease; NR: not reported; NSTEMI: non-ST-segment elevation myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SD: standard deviation; STEMI: ST-segment elevation myocardial infarction.

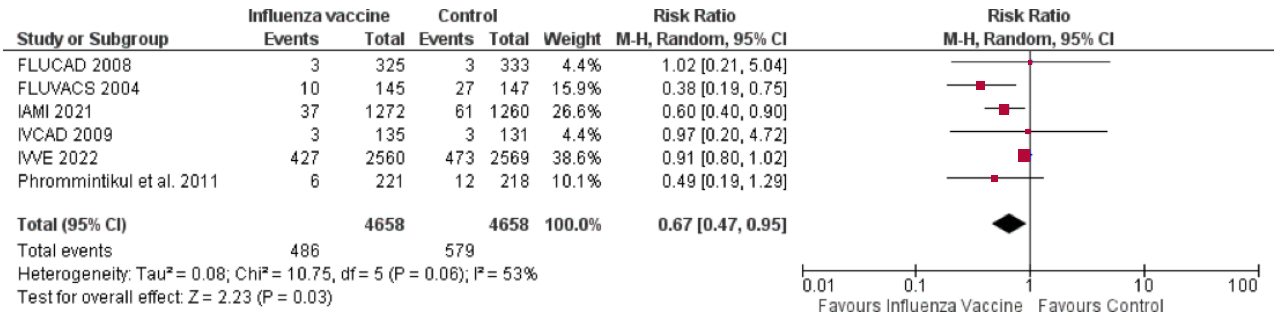

Fig. 2. Forest plot of the effect of influenza vaccine versus placebo on all-cause mortality

strategy. The indication of vaccination during hospitalization is a well-known strategy to increase adherence to vaccination, and in a previous study we have evaluated that this strategy was associated with a higher effective vaccination rate compared to office-based prescription. (37) Therefore, a possible key strategy to increase adherence would be to include influenza vaccination as part of the acute coronary syndrome discharge checklist. Checklists provide evidence-based prescribing of pharmacotherapies, (38) and adding the vaccine is key to establishing vaccination as part of standard-of-care therapy.

Our meta-analysis showed a trend towards a reduction in myocardial infarction in subjects receiving IV. The clinical trials included showed the same trend in this outcome. Possibly, one of the limitations to definitely confirm the association is the number of subjects evaluated in the clinical trials.

One of the main limitations in producing evidence about the usefulness of IV in subjects with HF was the overlap with other formal indications, mainly age: three quarters of subjects with HF have an indication for IV only because they 65 years old or greater, and at the other extreme, only 3-6% of subjects with HF are < 50 years. (39) The IVVE is the most recently presented study that is part of this meta-analysis, (30) in which the investigators included more than 5129 patients with HF with particular features: the

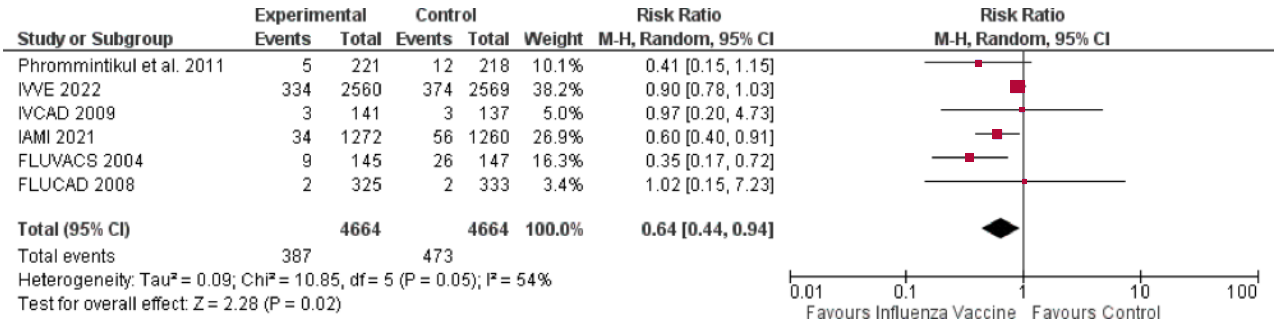

Fig. 3. Forest plot of the effect of influenza vaccine versus placebo on cardiovascular death.

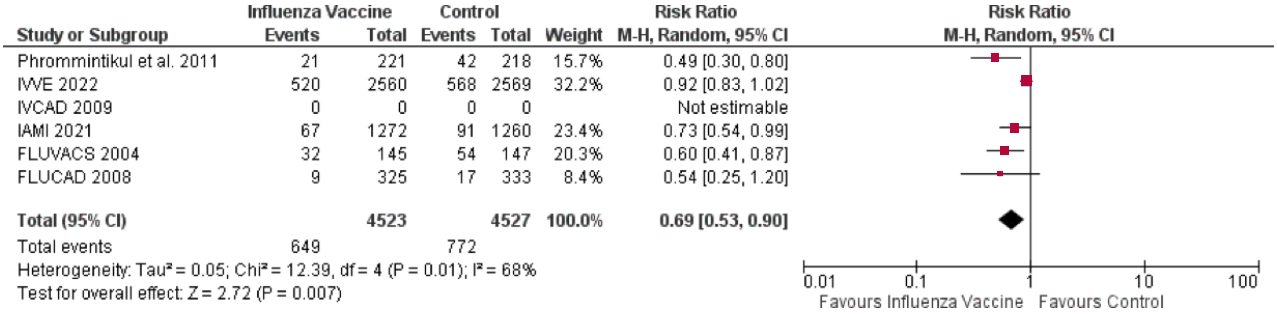

Fig. 4. Forest plot of the effect of influenza vaccine versus placebo on MACE.

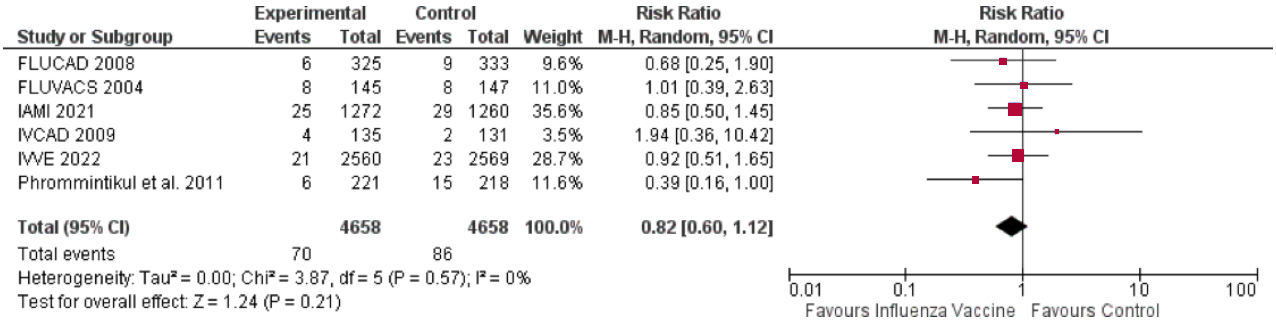

Fig. 5. Forest plot of the effect of influenza vaccine versus placebo on myocardial infarction.

average age was 57 years, and the patients came from low- and middle-income countries in Asia and Africa. The authors of the IVVE study reported a reduction in outcomes as all-cause mortality, cardiovascular death, and MACE during periods of peak circulation of influenza, and a trend towards a reduction in events throughout the duration of the study. Rather than a neutral result, this finding reinforces the pathophysiological association and strengthens the indication for IV in this population. When the overall results of this study were included in our meta-analysis, the benefits in reducing events had the same direction and magnitude of effect.

The characteristics mentioned above could explain the differences found in the stratified analysis of subgroups according to baseline CV disease. However, through this meta-analysis we cannot distinguish how many of the subjects recruited for CAD had concomitant HF and vice versa, or whether the benefit is greater or not in subjects with both clinical conditions.

To become aware of the magnitude of the findings on the effectiveness of IV in reducing events in patients with CVD, the results can be compared with those of traditional pharmacological treatments such as statins, beta-blockers and angiotensin-converting enzyme inhibitors (ACE inhibitors). (40) Cardiovascular death decreased with each treatment in the meta-analyses of the main trials: RR was 24% for statins, (41) 23% for beta-blockers, (42) and 16% for ACE inhibitors. (43) Similarly, smoking cessation reduces the

risk of CVD by 39%. (44)

The strengths of this review are the extensive systematic review of the literature performed and the inclusion of only randomized clinical trials with low risk of bias. We found low heterogeneity in the primary and secondary outcomes analyzed, probably due to the similar trial design, population included, and definition of outcomes.

However, this review has limitations. We could not assess publication bias due to the low number of studies included in the meta-analysis. The COVID-19 pandemic had an impact on recruitment, follow-up, and influenza circulation, which affected the last two large randomized clinical trials; however, the benefit in reducing major events was sustained. Few clinical trials have been included, and there is great variability in the number of subjects included and in their baseline characteristics. Nevertheless, the reduction in events was in the same direction, although with a significant difference in the magnitude of the effect. Finally, the data from the IVVE study have not been published yet in an indexed journal at the time this analysis was completed and come from the presentation at a scientific congress; therefore, the results could be modified or have a different interpretation than the one we have used for this analysis.

CONCLUSION

In this updated meta-analysis of six randomized controlled clinical trials, influenza vaccination was associated with a 33% and 36% relative risk reduction of all-cause mortality and cardiovascular death, respectively, in patients with CVD.

Over the past few decades, considerable evidence has accumulated about the cardioprotective effects of influenza vaccination in patients with established cardiovascular disease.

We sought to promote consensus based on the highest level of evidence about the persistent benefits of influenza vaccination in patients with CVD by including two new clinical trials in CAD and HF, confirming the association of vaccination with risk reduction in subjects with CVD. The present meta-analysis may help health care workers to strongly recommend influenza vaccination for secondary prevention of cardiovascular events.

Conflicts of interest

None declared.

(See authors conflicts of interest forms in the website/ Supplementary material)

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SUPPLEMENTARY MATERIAL

Supplementary material Table 1. Characteristics of the studies

FLUCAD 2008	Methods	Setting: Poland; single-center; hospitalized patients within 1 week of the coronary artery intervention before hospital discharge; outpatients vaccinated during visits to the cardiologist office. Design: individually randomized, double-blind, parallel groups.
	Participants	N:658 (325/352) completed in the intervention group and 333/333 in the control group. Patients between 30 to 80 years with coronary artery disease confirmed by angiography with ≥ 50% stenosis of 1 epicardial coronary artery. Age: Intervention group: 58.8 years (range 35 to 80); control: 58.1 years (range 32 to 80) Sex (% men): Intervention group: 71.1%; control: 73.9%.
	Interventions	Intervention group (n = 325): intramuscular single inactivated subunit influenza vaccine containing 0.5 mL dose (15 mg) hemagglutinin of each of the following strains: A/NewCaledonia/20/99 (H1N1), A/Christchurch/28/03 (H3N2), B/Jiangsu/10/03. Control group (n = 333): placebo containing all vaccine compounds except viral antigens.
	Results	Primary outcome: cardiovascular death within 12 months after vaccination Secondary outcomes: major adverse cardiac events (MACE) which was the composite of cardiovascular death, acute myocardial infarction (or coronary revascularization) and coronary ischemic event defined as a combination of MACE or hospitalization for myocardial ischaemia (MACE or hospitalization for myocardial ischemia) at 12 months), coronary revascularization, hospitalization for myocardial ischemia, myocardial infarction, adverse events.
	Notes	The study was financed by the Grant of Polish Ministry of Education and Science No. 2P05B 01627. Solvay Pharmaceuticals B.V. provided influenza vaccine and placebo vaccine.
FLUVACS 2004	Methods	Setting: Argentina; 6 centers Design: individually randomized, parallel groups
	Participants	N: 301 (292/301 /200 completed the study). Inclusion criteria: > 21 years; 2 groups: (1) patients with or without ST-segment elevation myocardial infarction (MI) within the previous 72 hours; (2) patients undergoing percutaneous coronary intervention (PCI).
	Interventions	Intervention group (n = 100 MI, 51 PCI): single intramuscular vaccination containing 0.5 ml of A/Moscow/10/99-like virus, A/New Caledonia/20/99 (H1N1)-like virus, and AB/Sichuan/379/99-like virus. Control group (100 MI, 50 PCI): saline.
	Results	Primary outcome: cardiovascular death. Secondary outcomes: composite double or triple outcome measure of cardiovascular death, non-fatal myocardial infarction, and re-hospitalization for severe recurrent ischemia.
	Notes	

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IAMI 2021	Methods	Investigator-initiated, randomized, double-blind trial. 30 centers in 8 countries (Sweden, Denmark, Norway, Latvia, United Kingdom, Czechia, Bangladesh, and Australia) from October 2016 to February 2020.
	Participants	Patients with recent MI or PCI were randomly assigned in a 1:1 ratio to receive either influenza vaccine (n = 1272) or placebo with saline (n = 1260). The trial was stopped early because of the COVID-19 pandemic on March 1, 2020 Inclusion criteria: Age ≥ 18 years. ST-segment–elevation myocardial infarction (STEMI) or non–ST-segment–elevation myocardial infarction (NSTEMI) and had completed coronary angiography or PCI. Patients with stable coronary artery disease if they were ≥75 years, and had additional risk factors Mean age of patients: 60 years. Percentage of women: 18.2%. Other outstanding features/characteristics: 35.5% current smokers. 54.5 % with STEMI, 45.2% with NSTEMI, 0.3% with stable CAD, 74.3% treated with PCI.
	Interventions	Influenza vaccine content was consistent with World Health Organization recommendations according to season and hemisphere; trivalent inactivated vaccine (Vaxigrip) in the 2016 Northern Hemisphere season and quadrivalent inactivated vaccine (Vaxigrip Tetra or FluQuadri) in the following seasons (Table I in the Data Supplement). Influenza vaccine was provided by Sanofi Pasteur, which had no role in the design or conduct of the study or in preparation or review of the article. Placebo was sterile 0.9% normal saline solution.
	Results	The primary end point was the composite of all-cause death, MI, or stent thrombosis at 12 months after randomization, assessed during a telephone interview with participants or relatives. The 3 components of the primary composite end point plus cardiovascular death, all at 12 months, were considered key secondary efficacy end points. Secondary exploratory end points included unplanned revascularization; stroke, or transient ischemic attack; the composite of cardiovascular death, MI, or stent thrombosis; and hospitalization for heart failure or for arrhythmia.
	Notes	
IVCAD 2009	Methods	Setting: Iran; medical center, inpatient and outpatient care. Design: individually randomized, parallel groups
	Participants	N: 278 (135/141 completed follow-up in the intervention group and 131/137 in the control group). Inclusion criteria: adults ≥ 25 years with stable angina and coronary artery stenosis confirmed by coronary angiography or acute, evolving or recent myocardial infarction (after recovery from the acute phase) Age: intervention group: 54.9 ± 9.0 years; control group: 54.5 ± 9.2 years. Sex (% men): intervention group: 66%, control group: 67%.
	Interventions	Intervention group (n = 141): 0.5-mL intramuscular dose of the trivalent anti-influenza vaccine (Influvac, Solvay Pharma). The vaccine contained 15 g hemagglutinin of each of the three strains, namely Solomon Islands/3/2006 (H1N1), Wisconsin/67/2005 (H3N2), and Malaysia/2506/2004 (B) according to the World Health Organization guidelines for the anti-influenza vaccination campaign of 2007–2008. Control group (n = 137): 0.5-mL intramuscular dose of placebo.
	Results	Primary outcome: acute coronary syndrome (including myocardial infarction and unstable angina), coronary revascularization, cardiovascular death. Secondary outcomes: number of influenza episodes, physiological variables, adverse events.
	Notes	

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IVVE 2022	Methods	Setting: countries in China (14%), India (23%), and Africa (40%) Design: randomized controlled trial.
	Participants	Patients >18 years with clinical diagnosis of heart failure and NYHA functional class II, III and IV. Mean age of patients: 57 years. Percentage of women: 51%. Percentage with diabetes: 23%. NYHA class II: 69%, III 26%, IV 4%. Left ventricular function: ≤ 30%: 32%, 31-39%: 24%. Previous myocardial infarction (MI): 2 1%.
	Interventions	Inactivated influenza vaccine 0.5 ml intramuscularly (n = 2560) or matching placebo (n = 2569).
	Results	Primary outcome: composite outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and heart failure hospitalizations. Secondary outcomes: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, heart failure hospitalizations, all-cause hospitalizations, or all-cause mortality.
	Notes	Funding: Joint Global Health Trials Scheme of the UK Department for International Development, Medical Research Council, National Institute for Health Research, and the Wellcome Trust. Sanofi Pasteur provided influenza vaccine for the trial.
Phrommintikul et al. 2011	Methods	Setting: Thailand; Department of Internal Medicine, no details provided. Design: individually randomized, parallel groups. Dates and follow-up: recruitment from November 2007 to October 2008; 12-month follow-up.
	Participants	N: 442 (220/221 completed the trial in the intervention group and 217/218 in the control group). Inclusion criteria: patients > 50 years admitted with acute coronary syndrome within 8 weeks. Age: intervention group: 65 ± 9 years; control group: 67 ± 9 years. Sex (men%): intervention group: 61%; control group: 52%.
	Interventions	Intervention group (n = 221): Single-dose intramuscular injection of 0.5 mL of split, inactivated influenza vaccine (no further data provided). Control group (n = 218): absence of intervention.
	Results	Primary outcomes: cardiovascular outcomes (myocardial infarction, unstable angina, hospitalization for acute coronary syndrome, heart failure or stroke, cardiovascular death). Secondary outcomes: not reported.
	Notes	

COVID-19: coronavirus disease-2019, MACE: major adverse cardiovascular event, MI: myocardial infarction, PCI: percutaneous coronary intervention.

Supplementary material

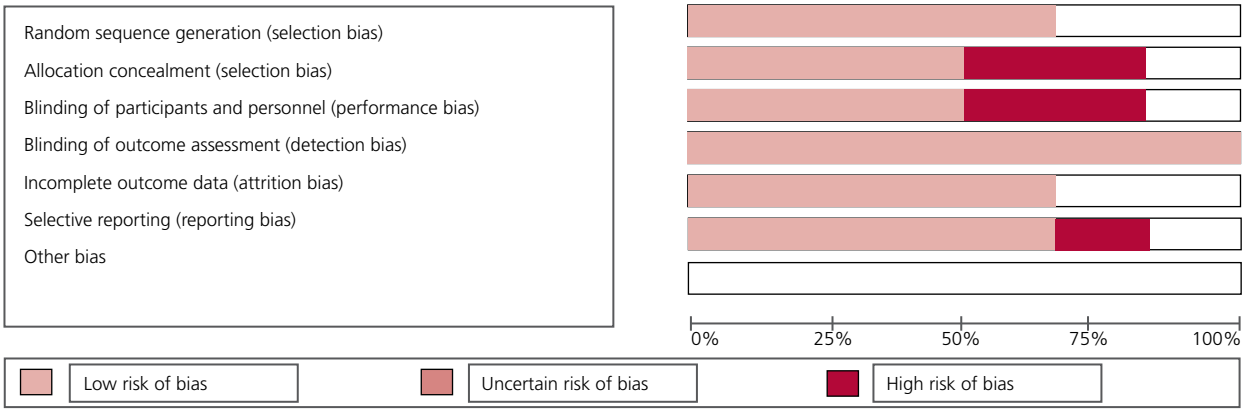

Fig. 1. Element of risk of bias in all the studies included.

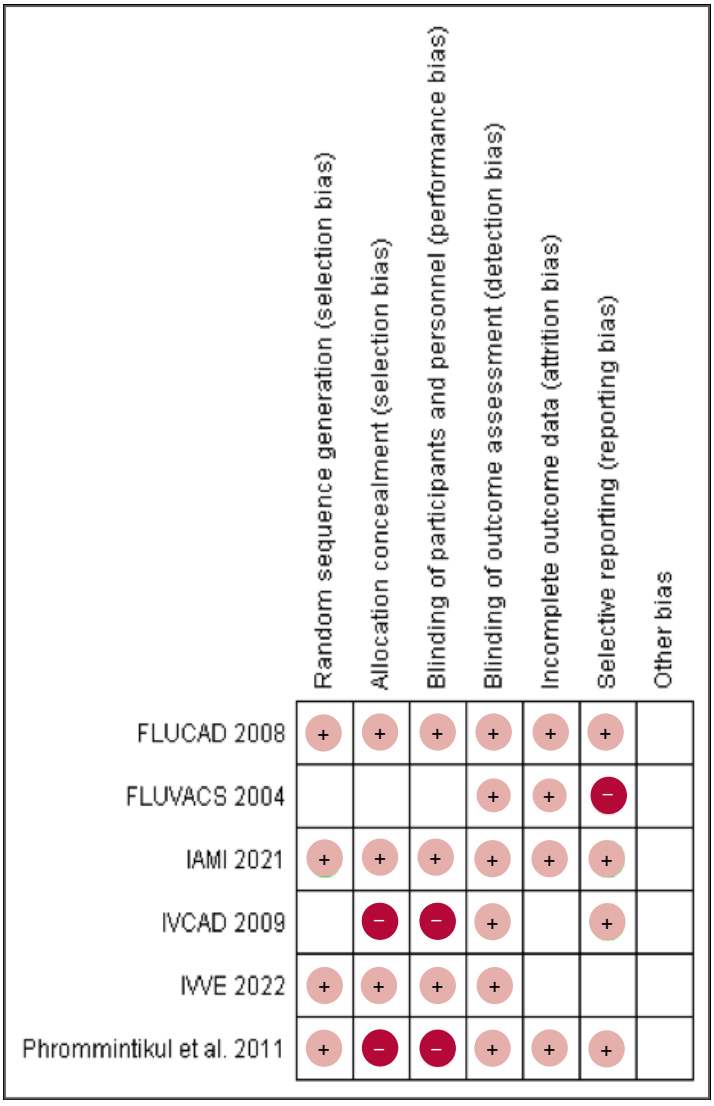

Fig. 2. Risk of bias for each study included.

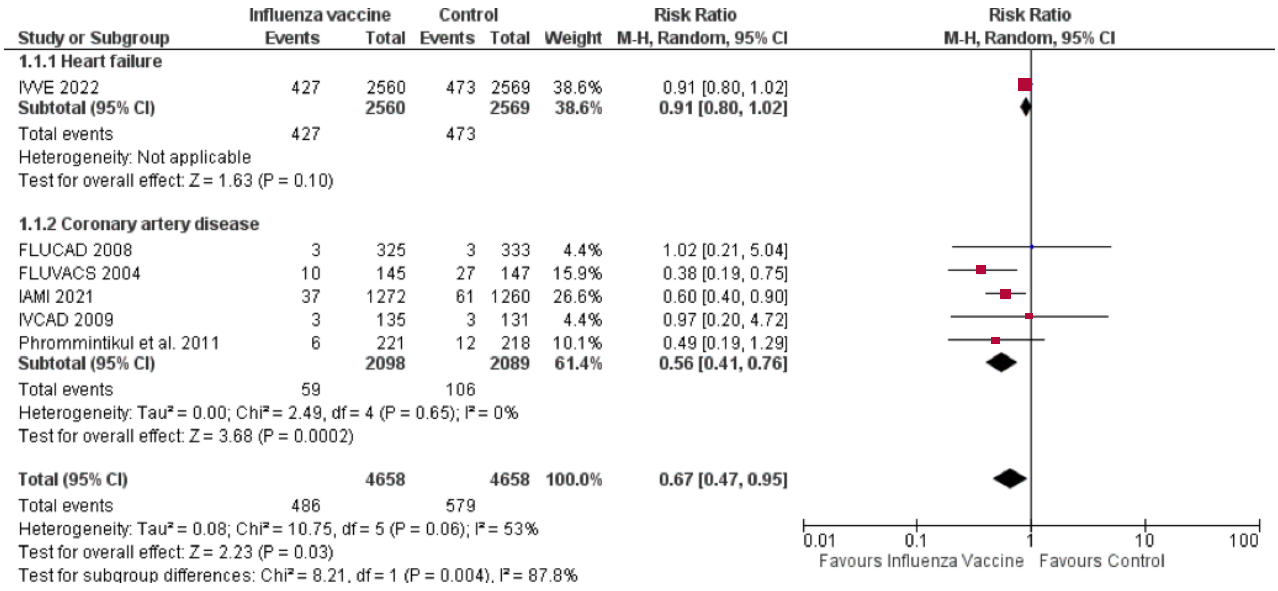

Fig. 3. Forest plot of the effect of influenza vaccination versus placebo on all-cause mortality in patients with heart failure and coronary artery disease.

ORIGINAL ARTICLE

Presence of Moderate or Severe Regurgitation after Transcatheter Aortic Valve Implant with the Cusp Overlap Strategy

Presencia de regurgitagión moderada o grave luego del implante percutáneo de la válvula aórtica con la estrategia de "Cusp Overlap"

CARLOS FAVA[1], GUSTAVO LEV[1], ANDRÉS RODRÍGUEZ, FRANCO ANDREOLI, SILVINA GÓMEZ, OSCAR MENDIZ[1]

ABSTRACT

Background: The aim of this study is to whether higher transcatheter aortic valve implantation (TAVI) with self-expandable valves using the right and left cusp overlap strategy (Cusp Overlap, COVL) is associated with a lower incidence of moderate or severe paravalvular regurgitation (PVR), compared with the conventional strategy (CON).
Methods: A total of 206 consecutive patients undergoing TAVI with self-expandable valves between August 2019 and May2022 were analyzed. The CON technique was used in the first 101 patients (49%) and COVL was used in 105 (51%).
The primary endpoint (PEP) was the presence of moderate or severe paravalvular regurgitation at 30 days.
Results: There were no clinical differences between the groups in terms of mean age, sex or comorbidities, except for a trend towards more patients with diabetes and previous percutaneous coronary intervention in the COVL group.
The STS score was greater in the COVL group (6.9 ± 2.2 vs. 5.8 ± 2.4 in the CON group; p = 0.01).
There was no difference in the PEP at 30 days with 2% incidence of moderate PVR in the CON group and 0.9% in the COVL group, and none of them presented severe PVR. There were no differences in mortality, myocardial infarction, coronary artery obstruction, stroke, major bleeding or vascular complications. The need for permanent pacemaker was lower with the COVL strategy (6.7% vs. 17.8%, p = 0.01) and a new left bundle branch block occurred in 5.7% vs. 12.9% (p = 0.07).
Conclusions: In this single-center series, the strategy of high transcatheter aortic valve implantation using the COVL strategy showed no difference in the presence of moderate or severe regurgitation compared with the conventional strategy, with no differences in complications, and was associated with a lower need for definitive pacemaker and with a trend towards lower incidence of left bundle branch block at 30 days.

Key words: Aortic Valve Insufficiency -Self Expandable Metallic Stents - Transcatheter Aortic Valve Replacement

RESUMEN

Introducción: Analizar si la estrategia del implante alto usando superposición de las cúspides derechas e izquierdas (Cusp Overlap, COVL) en el implante percutáneo de la válvula aórtica (TAVI) se relaciona con menor incidencia de regurgitación paravalvular (RPV) moderada o grave, comparada con la estrategia convencional (CON).
Material y métodos: Se analizaron 206 pacientes consecutivos que recibieron TAVI con válvulas autoexpandidles entre agosto de 2019 y mayo de 2022. Se utilizó una estrategia CON en 101 pacientes (49%) y COVL en 105 (51%).
El Punto Final Primario (PFP) fue la presencia de regurgitación paravalvular moderada y grave a 30 días.
Resultados: No hubo diferencia clínica entre los grupos en cuanto a la edad media, sexo ni comorbilidades; excepto una tendencia a más diabetes y angioplastia coronaria previa en el grupo COVL El STS score fue mayor en el grupo de COVL (6,9 ± 2,2 vs. 5,8 ± 2,4 en CON, p = 0,01).
A 30 días no hubo diferencia en el PFP (RPV moderada en 2% en CON, y 0,9% en COVL; ninguno presentó RPV grave). Tampoco hubo diferencia en mortalidad, infarto, oclusión coronaria, accidente cerebrovascular, sangrado mayor y complicación vascular. La necesidad de marcapasos definitivo fue menor con la estrategia de COVL (6,7% vs. 17,8%, p = 0,01) y un nuevo bloqueo de rama izquierda ocurrió en 5,7% vs. 12,9% (p = 0,07).
Conclusiones: En esta serie de un solo centro, la estrategia del implante alto de la válvula aórtica percutánea usando la técnica de COVL no demostró diferencia en la presencia de regurgitaciones moderadas o graves comparada con la estrategia convencional, sin presentar diferencia en las complicaciones, y se asoció a una menor necesidad de marcapasos definitivo y a una tendencia de menos bloqueos de rama izquierda a 30 días.

Palabras clave: Insuficiencia de la Válvula Aórtica - Stents Metálicos Autoexpandibles - Reemplazo de la Válvula Aórtica Transcatéter

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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has shown its benefit in high-risk or inoperable patients, (1,2) those at intermediate risk (3,4) and also in low-risk patients. (5,6)

According to different analyses, the presence of mild paravalvular regurgitation (PVR) occurs in 20% to 40% of the cases, (7) while moderate or severe PVR in about 3% to 12% (2) and has been associated with higher mortality rates. (8,9) Although the incidence of PVR has decreased with the learning curve of the operators and the new devices, it represents a complication that should be avoided or managed during the procedure.

Another issue with self-expandable valves is the need for implantation of a permanent pacemaker (PPM), with an incidence of about 17%-30% in large, randomized studies. (2-6)

To overcome these limitations, higher implant of percutaneous aortic valves using a view where the right and left cusps are overlapped (Cusp-overlap, COVL) is a technique developed to reduce contact with the membranous septum and conduction system and thereby reduce the need for PPM. (10)

This strategy has demonstrated a significant decrease in the need for PPM in some observational series, (11-13) but the impact on the incidence of perivalvular leaks leading to moderate or severe regurgitation has not been clearly evaluated.

METHODS

We analyzed 206 consecutive patients undergoing TAVI with self-expandable valves between August 2019 and May 2022. The conventional technique (CON) was used in the first 101 patients (49%) and the COVL strategy in the subsequent 105 (51%).

Patients with previous surgical bioprosthetic valves, prior PPM, bicuspid aortic valve or pure or predominant aortic regurgitation as indication of TAVI or implant of a balloon-expandable valve were excluded from the study.

The primary endpoint (PEP) was the presence of moderate or severe PVR at 30 days, defined according to the criteria of the VARC-3. (14) The incidence of the following events was also analyzed: all-cause mortality, acute myocardial infarction (MI), acute coronary artery obstruction due to TAVI, stroke, major bleeding (as defined by VARC), vascular complication, emergency cardiac surgery, reintervention, need for PPM implantation, and new-onset left bundle branch block (LBBB) persistent at 30 days.

Implant success (IS) was defined as adequate valve implant with a residual gradient <10 mm Hg at the end of the procedure in the absence of severe regurgitation, and clinical success (CS) as IS in the absence of death, acute MI, stroke, reintervention or urgent valve surgery.

All the patients were evaluated by the hospital "Valve Heart Team", with Doppler-echocardiography, coronary angiography with aortography, and a multi-slice contrast-enhanced computed tomography angiography with 3D reconstruction of the aortic valve, thoracic aorta, abdominal aorta, and subclavian, iliac and femoral arteries. An electrocardiogram (ECG) was recorded before TAVI, at 24 hours and at 30 days. Color Doppler-echocardiography was performed before TAVI, immediately after and at 30 days.

Anesthesia with conscious sedation was used, except for those in whom a percutaneous femoral access was not used and thus required general anesthesia. All patients received dual antiplatelet therapy with aspirin and clopidogrel; in those patients receiving oral anticoagulants for any other reason, only clopidogrel was indicated.

Anticoagulation with heparin 100 U/Kg was used during the procedure, with values controlled during its course.

In patients receiving implants with the CON strategy, the valve was positioned and implanted using the coplanar 3-cusp projection according to the computed tomography angiography and usually corrected by the left anterior oblique slightly cranial angiographic projection. The implantation was performed having as target an implant depth of approximately 2-4 mm below the aortic annulus under high stimulation frequency (120 bpm) with temporary pacing, at the operator's discretion.

In those undergoing the COVL strategy, the computed tomography angiography was previously analyzed in detail, identifying the projection where there was right and left cusp overlap, in opposition to the non-coronary cusp, and this was chosen as the projection for the implantation. In case of difficulties or differences, corrections were made according to the previous angiography.

When this was not feasible, positioning was performed using two pigtail or Amplatz AL2 catheters placed in the right and left sinuses, and then the angiographic projection showing cusp overlap was sought.

Usually, the COVL projection coincides with a caudally oriented right oblique projection.

The target was implantation approximately 2-3 mm below the aortic annulus with respect to the non-coronary sinus.

At the time of the final deployment, overstimulation with temporary pacemaker at 120 beats per minute was used to achieve system stability.

Both pre-dilation with a balloon diameter lower than that of the aortic annulus and post-dilation were performed according to the operator´s criterion.

All the patients were followed-up at 30 days with a face-to-face visit and analysis of PVR by Dopper-echocardiography performed 30 days after the implant.

Ethical considerations

The study was conducted following the recommendations of the Declaration of Helsinki and the International Conference of Good Clinical Practice. All patients signed an informed consent form before participating in the study. Their identity was preserved for the moment of the analysis.

Statistical analysis

Continuous variables are presented as mean and standard deviation and categorical variables as absolute value and percentage. The Student's t test was used to compare continuous variables and the chi-square test or Fisher's exact test was used for categorical variables. A p value < 0.05 was considered statistically significant.

RESULTS

The clinical characteristics of the populations were similar; age was 79.8 ± 7.9 years vs. 80.4 ± 6.9 years in the CON strategy vs. COVL strategy, and 48.5% were male vs. 55%. There was no difference in the prevalence of hypertension, previous MI, history of coronary artery surgery, percutaneous coronary intervention (PCI) before TAVI, chronic obstructive pul-

monary disease (COPD), renal function, and dialysis. Diabetes and PCI were slightly more common in the COVL group (20.8% vs. 32.3%, p = 0.06, and 31.7% vs. 44.8% p = 0.05, respectively).

The STS risk score was greater in the COVL group (5.8 ± 2.4 vs. 6.9 ± 2.2, p = 0.01).

There were no differences in the baseline ECG in terms of previous conduction disorders as atrioventricular (AV) block, right bundle branch block (RBBB), LBBB, or atrial fibrillation.

There was also no difference in left ventricular ejection fraction, mean trans-aortic gradient or aortic valve area.

Femoral access was used in all the p except for 2 p. in the COVL group who underwent subclavian access. Pre-dilation was greater in this group (87.6% vs. 57.4%, p<0.001) with no differences in the use of post-dilation. There was no difference in the use of percutaneous closure, which was done with any of the following devices: PROSTAR XL® (ABBOTT Vascular, Santa Clara, California) and Proglide® (ABBOTT Vascular, Santa Clara, California). (Table 1).

Self-expanding valves were implanted in all the patients. (Table 2)

There was no difference in the PEP at 30 days between both strategies (Figure 1), with 2% incidence of moderate PVR in the CON group and 0.9% in the COVL group, and there were no cases of severe PVR. There was no difference in mortality, acute MI, coronary obstruction, stroke, cardiac surgery, reoperation, vascular complication or major bleeding.

The COVL strategy resulted in a significant reduction in conduction disorders after implantation, with a lower need for PPM (6.7% vs. 17.8%; p = 0.01) and a trend towards less development of new LBBB (5.7% vs. 12.9%; p = 0.07). Of the patients requiring PPM, 6 were ≥ 80 years and only one patient presented normal sinus rhythm. One patient had previous atrial fibrillation, one presented first degree AV block, another had LBBB, and one had trifascicular block. (Table 3) (Figure 2)

DISCUSSION

In our series, TAVI with the COVL technique was not significantly associated with a difference in the presence of PVR compared with the conventional strategy,

Table 1. Characteristics of the population

	CON (101 p.)	COVL (105 p.)	*p* value
Age, years, (mean ± SD)	79.8±7.9	80.4±6.9	0.41
Men	49 (48.5)	58 (55.2)	0.33
Hypertension	90 (89.1)	98 (93.3)	0.20
Diabetes	21 (20.8)	34 (32.3)	0.06
Previous MI	23 (22.7)	18 (17.1)	0.31
Previous CABGS	19 (18.8)	16 (15.2)	0.42
Previous PCI	32 (31.7)	47 (44.5)	0.05
PCI before TAVI	22 (21.8)	30 (28.6)	0.18
COPD	19 (18.8)	13 (12.4)	0.22
Stroke	5 (4.9)	4 (3.8)	0.68
eGFR	60.1±19.3	61.8±20.1	0.44
Dialysis	3 (3)	4(3.8)	0.73
Mortality according to STS score	5.8±2.4	6.7±2.2	0.01
Atrial fibrillation	16 (15.8)	25 (23.8)	0.43
AV block	6 (5.9)	7 (6.7)	0.83
RBBB	10 (9.9)	9 (8.6)	0.73
LBBB	10 (9.9)	15 (14.3)	0.33
LVEF (%)	52.7±13.4	53.1±12.6	0.45
AVA	0.71±0.15	0.73±0.9	0.43
Mean gradient (mm Hg)	40.8±10.7	41.3±10.2	0.35
Femoral access	101 (100)	103 (98.1)	0.16
Subclavian access	-	2 (1.9)	0.16
Pre-dilation	58 (57.4)	92 (87.6)	<0.001
Post-dilation	25 (24.5)	36 (34.3)	0.92
Pop-Up	-	-	
Percutaneous closure	100 (99)	103 (98.1)	0.58

AV: atrioventricular. AVA: aortic valve area. CABG: coronary artery bypass grafting. CON: conventional COPD: chronic obstructive pulmonary disease. COVL: Cusp overlap. eGFR: estimated glomerular filtration rate LBBB: left bundle branch block. LVEF: left ventricular ejection fraction. MI: myocardial infarction. p.: patients. PCI: percutaneous coronary intervention. RBBB: right bundle branch block. SD: standard deviation. STS: Society of Thoracic Surgeons. TAVI: transcatheter aortic valve implantation. Categorical variables are presented as n(%) and continuous variables as mean ± SD.

but there was less need for PPM and lower incidence of LBBB, with no differences in mortality, acute MI, stroke, coronary obstruction, major vascular complications and major bleeding, cardiac surgery or reintervention.

Of the 7 p. in our series requiring PPM, 6 were ≥ 80 years and 5 presented a significant conduction disorder.

The presence of PVR has been related to valvular calcification with a generally asymmetrical pattern with dominating non-coronary leaflet and sinus calcification in most p. (15) Different studies have analyzed the presence of calcium and its quantity in the implant site (16,17) and demonstrated that asymmetry in calcification is related to PVR. (18) Some authors analyzed the presence of calcium in the left ventricular outflow tract which could be a risk factor for PVR. However, we must also consider that calcification of the annulus may contribute to annular rupture, especially in balloon-expandable valves in case of aggressive pre-dilation or post-dilation and need for a second valve. (19-21)

Total device landing zone calcium volume could predict the degree of PVR: none with 389 mm3, mild with 371 mm3, moderate with 690 mm3 and severe PVR with 777 mm3. We should also analyze asymmetry in the CT scan as it is a predictor of PVR. (22)

The risk of moderate or severe PVR is lower in women; this seems to be related to a smaller diameter annulus that facilitates perivalvular sealing. (23)

Table 2. Prosthetic valves implanted

	CON n (%)	COVL n (%)
Evolut-Evolut R®/PRO®	101 (100%)	79 (74.5)
Accurate Neo®	-	15 (14.3)
PORTICO®	-	11 (11.2)

The presence of moderate to severe regurgitation was more common at the beginning of the experience and with the first-generation devices. The learning curve of the operators, which has improved the implants, and the new devices with a perivalvular "skirt" at the base to improve sealing, have led to a significant reduction of this phenomenon.

Although the use of the COVL technique seems to help in the same sense (in fact, in our series PVR decreased by 50%), a greater number of patients would be needed to obtain considerable higher differences than those of our experience.

The presence of moderate or severe PVR is often associated with low functional class dyspnea or even hemolysis. One of the treatments proposed to avoid surgery is closure of PVR with plugs under transesophageal Doppler echocardiography. Although this strategy is not easy to perform and is not frequently used, it has demonstrated favorable outcome in some publications with a low rate of complications. (25)

An important meta-analysis evaluated the outcome of patients with PVR at 4 years. Those with moderate to severe PVR had higher mortality than those with mild or minimal PVR. But when first-generation valves were compared with second-generation valves, the incidence of PVR was significantly lower with second-generation valves. Mild PVR had higher 4-year mortality rate than minimal PVR. For this reason, it is currently necessary to be extremely accurate at the time of implantation, choosing the most suitable device and performing post-dilations if necessary to leave the minimal regurgitation possible; ideally, absolutely no regurgitation.

Our group started several years ago with the implantation of self-expandable valves with the COVL strategy. In our publications, we demonstrated a significant decrease in the need for PPM after implantation and a trend towards lower LBBB without increasing the incidence of complications or valve

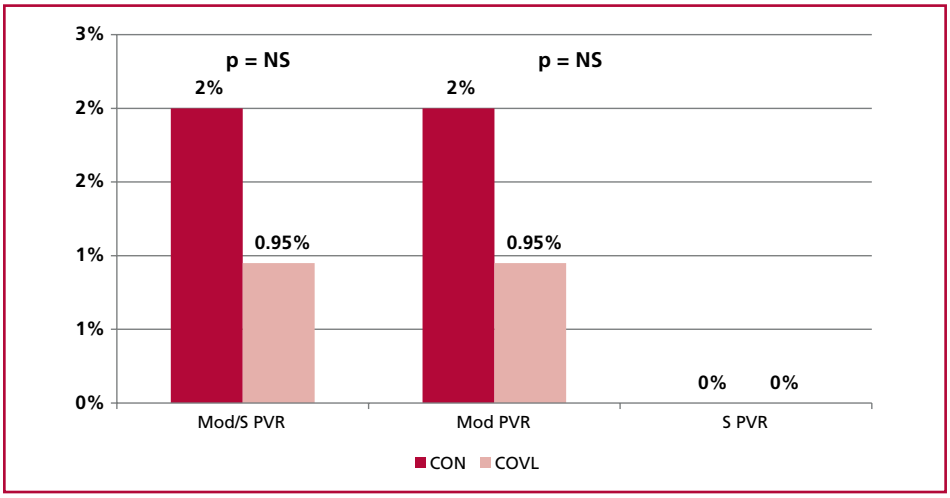


Fig. 1. Primary end point

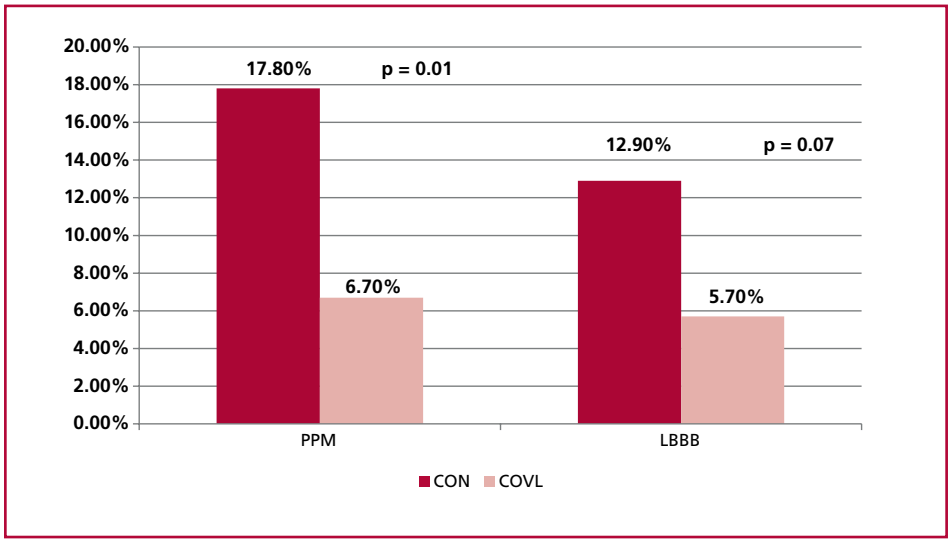
CON: conventional. COVL: Cusp overlap. Mod: moderate. PVR: paravalvular regurgitation. S: severe

Table 3. Outcomes at 30 days

	CON (101 p.) n (%)	COVL (105 p.) n (%)	*p*
Implant success	101 (100)	105 (100)	-
Clinical success	5 (4.9)	5 (4.8)	0.94
Moderate PVR	2 (2)	1 (0.95)	0.53
Severe PVR	-	-	-
Death	5 (4.9)	3 (2.8)	0.43
Infarction	-	1 (0.95)	1
Coronary obstruction	-	1 (0.95)	1
Stroke	-	1 (0.95)	1
Major bleeding	2 (2)	1 (0.95)	0.53
Vascular complication	2 (2)	4 (3.8)	0.43
PPM	18 (17.8)	7 (6.7%)	0.01
New-onset LBBB	13 (12.9)	6 (5.7)	0.07
Cardiac surgery	-	-	-
Reintervention	-	-	-

CON: conventional. COVL: Cusp overlap. LBBB: left bundle branch block. p.: patients. PPM: permanent pacemaker. PVR: paravalvular regurgitation

Fig. 2. Permanent pacemaker and new onset left bundle branch block.



CON: conventional. COVL: Cusp overlap. LBBB: left bundle branch block. PPM: permanent pacemaker.

embolization. In our publications, implants were performed with different self-expanding valves in the COVL group. (11,12)

We believe that this strategy offers benefits, and although we did not observe a significant difference in the incidence and severity of PVR that would have an impact on survival, the reduction in conduction disorders after implantation justifies its implementation, since conduction disorders also have an impact on survival and on hospital and long-term costs. (26,27)

Study limitations

The lack of randomization and the fact that this analysis was performed in a single center are the limitations of this study. In order to try to avoid the influence of the learning curve, a historical series of the last 101 patients treated with the CON strategy was compared with the first 105 patients treated with the higher transcatheter aortic valve implantation strategy.

CONCLUSIONS

In this single-center series, the strategy of high transcatheter aortic valve implantation showed no difference in the presence of moderate or severe PVR compared with the conventional strategy with no differences in complications and was associated with a lower need for definitive pacemaker and a trend towards lower incidence of LBBB at 30 days.

Conflicts of interest

Oscar A. Mendiz is proctor in Latin America for Evolut, Accurate and Edwards Valves.

(See authors conflicts of interest forms in the website/ Supplementary material)

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ORIGINAL ARTICLE

Prognostic Value of NT-proBNP in Asymptomatic Patients with Severe Aortic Stenosis and Preserved Left Ventricular Ejection Fraction

Utilidad del NT-proBNP en la evaluación pronóstica de pacientes con estenosis aórtica grave asintomáticos, con fracción de eyección ventricular izquierda preservada

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ABSTRACT

Background: The aortic valve replacement (AVR) indication in asymptomatic patients with severe aortic stenosis (AS) and preserved function is being increasingly discussed.
Objective: The aim of this study was to evaluate whether the elevation of N-terminal fraction of the pro-B-type natriuretic peptide (NT-proBNP) predicts the occurrence of symptoms and the AVR indication in patients with severe AS and preserved left ventricular ejection fraction (LVEF), initially asymptomatic.
Methods: Asymptomatic patients with severe AS, preserved LVEF (≥55%) and no initial AVR indication were prospectively included. All patients underwent laboratory tests measuring NT-proBNP at baseline, and an echocardiogram with tissue Doppler recording the lateral wall S wave (lat. S) and the E/e´ ratio. The endpoint was the aortic valve replacement indication at follow-up.
Results: We included 133 patients aged 69 ± 8 years, 49% of which were women. After a follow-up of 570 (interquartile range 380-680) days, 23.3% (n=31) of them required aortic valve replacement. In the multivariate analysis, NT-proBNP value and the E/e' ratio were independent predictors of surgery (HR 1.02, 95% CI 1.001-1.03, p<0.001 and HR 1.42, 95% CI 1.21-2.45, p< 0.001, respectively). NT-proBNP presented an area under the curve (AUC) greater than the E/e' ratio (0.88 versus 0.64, p=0.02). The best NT-proBNP cut-off point was determined as >350 pg./mL (adjusted HR 1.55, 95% CI 1.38-2.01, p<0.001).
Conclusion: NT-proBNP value and the E/e' ratio were independent predictors of AVR requirement. NT-proBNP had a very good discrimination capacity, greater than the E/e´ ratio.

Keywords: Aortic Valve Stenosis- Biomarkers - Natriuretic Peptide, Brain

RESUMEN

Introducción: La indicación de reemplazo valvular aórtico (RVA) en pacientes con estenosis aórtica (EA) grave asintomáticos con función conservada es motivo de creciente debate.
Objetivo: Evaluar si la elevación del NT-proBNP predice la aparición de síntomas y la indicación de reemplazo valvular en pacientes inicialmente asintomáticos, con EA grave y fracción de eyección ventricular izquierda (FEVI) conservada.
Materiales y métodos: Se incluyeron en forma prospectiva pacientes con EA grave, FEVI conservada (≥55%) que fueron considerados asintomáticos, sin indicación inicial de RVA. A todos se les realizó laboratorio con medición de NT-proBNP en forma basal y ecocardiograma con Doppler tisular consignando la onda S de la pared lateral (S lat) y la relación E/e´. Se consideró como punto final el requerimiento de reemplazo valvular durante el seguimiento.
Resultados: Se incluyeron 133 pacientes con una edad de 69 ± 8 años, 49% mujeres. Luego de un seguimiento de 570 (rango intercuartilo 380-680) días, el 23,3 % (n=31) de los pacientes presentaron requerimiento de reemplazo valvular. En el análisis multivariado, el NT-proBNP y la relación E/e´ fueron predictores independientes de requerimiento de cirugía (HR 1,02, IC95% 1,001-1,03, p<0,001; y HR 1,42, IC95% 1,21-2,45, p<0,001, respectivamente). El NT-proBNP presentó un Área Bajo la Curva (ABC) mayor que la relación E/e´ (0,88 versus 0,64, p=0,02). Se estableció como mejor punto de corte de NT-proBNP un valor >350 pg/mL (HR ajustado 1,55, IC95% 1,38 – 2,01, p<0,001).
Conclusiones: El NT-proBNP y la relación E/e´ fueron predictores independientes de requerimiento de cirugía. El NT-proBNP presentó una muy buena capacidad de discriminación, mayor que la relación E/e´.

Palabras Clave: Estenosis de la válvula aórtica - Biomarcadores - Péptido Natriurético Encefálico

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INTRODUCTION

Aortic stenosis (AS) is the most common valvular disease in Western countries. Prevalence increases with age, reaching 4-7% in patients over 65. (1) The only effective treatment is aortic valve replacement (AVR), either via surgery or percutaneously. AVR indication is evident and recommended in symptomatic patients with severe AS, as well as in patients with impaired ventricular function despite absence of symptoms. (2-4)

While it is recognized that symptoms are one of the main prognostic markers of severe AS, (5,6) some series show that natural progress in asymptomatic patients is not exempt from complications. (7,8) In addition, surgical mortality has reduced over the years, (9) and percutaneous aortic replacement has advanced. (10) This makes the risk/benefit ratio of early intervention increasingly favorable. It is also important to note that symptoms, as defined, are subjective features which are highly variable according to the patient. This makes them difficult to identify, especially in elderly patients.

Therefore, using biomarkers for risk stratification of patients with severe AS has become more appealing. The N-terminal fraction of the pro-B-type natriuretic peptide (NT-proBNP) is one of the most common biomarkers resulting in an adverse and more fatal prognosis when increased. (11,12)

The objective of this study is to assess whether increased NT-proBNP can predict symptoms and AVR indication in patients with severe AS and preserved left ventricular ejection fraction (LVEF), initially asymptomatic.

METHODS

An observational, prospective, single-site study was conducted enrolling patients with severe AS and preserved LVEF under outpatient follow-up in the site's Valvular Heart Disease Department, who were considered asymptomatic and had no initial indication of aortic valve replacement. Patients were enrolled from July 2017 to July 2021.

All the patients had an echocardiogram performed with the Esaote MyLab Seven equipment (Florence, Italy) with a multi-frequency probe (1.5 MHz to 2.6 MHz), and the following parameters were evaluated: aortic valve peak velocity (V max), mean pressure gradient (MG), aortic valve area (AVA) by continuity equation, LV diastolic and systolic diameters (LVDD and LVSD, respectively), left ventricular mass index (LVMI), pulmonary artery systolic pressure (PASP), and LVEF using Simpson's biplane formula. Furthermore, the lateral wall tissue S wave (lat. S) and E/e' ratio were determined.

Severe AS was defined as a V max ≥4 m/s, MG ≥40 mmHg, and AVA ≤1 cm2. Ventricular function was considered preserved if LVEF was ≥55%.

Exclusion criteria: Patients who were symptomatic upon assessment, or for whom the physical examination showed clinical signs of heart failure. Patients with suspected symptoms had an exercise stress test according to the Naughton protocol. Patients with symptoms or a systolic pressure flat curve during exercise were considered symptomatic and therefore excluded. Patients with impaired ventricular function (LVEF ≤55%) and dilated left ventricle (diastolic diameter >60 mm) were also excluded.

An NT-proBNP assessment was required for all patients in the site's laboratory using Vitros 5600 equipment after the first visit.

Follow-up was performed by means of clinic visits. The primary endpoint was the AVR requirement.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, or median and interquartile range (IQR) based on a normal or abnormal distribution, and categories are expressed as percentages. For continuous variables, group comparisons between AVR and non-AVR patients were performed using Student's t test for normal distributions and Mann-Whitney test for abnormal distributions. Categorical variables were compared using the chi-square test or the Fisher exact test when a variable showed an absolute <5 frequency.

The univariate analysis was performed using Cox regression, considering AVR as the dependent variable, and both NT-proBNP and several echocardiographic parameters as predictive variables. Those variables that were significant for the univariate analysis (considering $p<0.05$) were analyzed using a multivariate model through the proportional hazards regression method to assess variables that are independently associated with the AVR requirement.

Then, receiver operating characteristic (ROC) curves were developed, with the corresponding area under the curve (AUC), and the best cutoff point was established for significant variables in the multivariate analysis.

Finally, an event-free survival test was performed using the Kaplan-Meier method.

Statistix 7 and Epidat 3.1 softwares were used for the analysis.

Ethical considerations

This observational study was approved by the ethics committee of the institution and all the patients included, signed the informed consent.

RESULTS

One hundred seventy-five patients were evaluated, 27 of whom were excluded as they were considered symptomatic (19 upon the initial interview, and 8 after an exercise stress test); 13 patients had impaired ventricular function, and 2 could not have an NT-proBNP assessment. Therefore, 133 patients aged 69 ± 8 were enrolled, 49% were female (n=65). The most common cause of AS was sclerodegenerative aortic valve (70%, n=93), followed by bicuspid (25.5%, n=34) and rheumatic (4.5%, n=6) aortic valve. Table 1 shows the patients' clinical and echocardiographic characteristics.

The median follow-up was 570 days (IQR 380-680), and 23.3% (n=31) of patients required an AVR. As observed in Table 1, the group requiring AVR had a higher baseline NT-proBNP: 290 (IQR 75-450) vs. 85 (IQR 55-180) pg/mL , $p=0.01$, with a higher E/e' ratio (8.6 ± 2 vs. 7.1 ± 1.3, $p=0.04$), a tendency towards a lower tissue S wave (0.07 ± 0.01 m/s vs. 0.08 ± 0.01 m/s, $p=0.07$), and no difference for the remaining parameters.

Table 2 shows the univariate and multivariate

Table 1. Baseline demographics

	Total (n=133)	AVR requirement (n=31)	No AVR requirement (n=102)	P
Age	69 ± 8	69 ± 5	69 ± 8	0.45
Female	65 (49.1)	15 (48.3)	50 (49)	0.31
SBP (mmHg)	130 ± 28	128 ± 32	130 ± 27	0.32
Medical history				
Hypertension	95 (71.4)	22 (70.9)	73 (71.5)	0.72
Diabetes	29 (21.8)	7 (22.5)	22 (21.5)	0.89
Atrial fibrillation	13 (9.7)	3 (9.6)	10 (9.8)	0.77
Echocardiogram				
LVEF (%)	64 ± 4	65 ± 3	64 ± 3	0.23
LVDD (mm)	49 ± 5	49 ± 8	49 ± 7	0.83
IVS (mm)	12 ± 3	13 ± 3	12 ± 4	0.12
LVMI (g/m^2)	98 ± 38	99 ± 41	97 ± 39	0.42
LAA (cm^2)	26.9 ± 6.7	27.2 ± 6.9	26.5 ± 6.5	0.11
Doppler				
V max (m/sec)	4.2 ± 0.4	4.5 ± 0.8	4.2 ± 0.5	0.11
AVA index (cm^2/m^2)	0.58 ± 0.09	0.57 ± 0.1	0.58 ± 0.09	0.62
MG (mmHg)	45 ± 5	46 ± 4	45 ± 4	0.32
Tissue				
Lateral S wave (m/sec)	0.08 ± 0.01	0.07 ± 0.01	0.08 ± 0.01	0.07
E/e´ ratio	7.3 ± 1.5	8.6 ± 2	7.1 ± 1.3	0.04
NT-proBNP (pg./mL)	110 (62.3-310)	290 (75-450)	85 (55-180)	0.01

Categorical variables are presented as n (%). Continuous variables are presented as mean ± standard deviation or median (interquartile range) AVA index: aortic valvular area indexed according to body surface. IVS: intraventricular septum. LAA: left atrium area. LVDD: left ventricular diastolic diameter LVEF: left ventricular ejection fraction. LVMI: left ventricular mass index. MG: mean gradient. SBP: systolic blood pressure. V max : maximum aortic valve velocity.

analysis. In the univariate analysis, NT-proBNP, the E/e´ ratio and lat. S were predictors of the AVR requirement. In the multivariate analysis, NT-proBNP and E/e´ ratio were independent predictors of the surgery requirement: HR 1.02 (95% CI 1.001-1.03), p<0.001, and HR 1.42 (95% CI 1.21-2.45), p<0.001, respectively.

The AUC for NT-ProBNP was 0.88 (95% CI 0.81-0.91), and the best cut-off point was 350 pg./mL, while the AUC for the E/e´ ratio was 0.64 (95% CI 0.52-0.68), significantly lower than that of the NT-proBNP (p=0.02). See Figure 1.

The NT-proBNP >350 pg./mL showed an adjusted HR of 1.55 (95% CI 1.38-2.01), p<0.001. Figure 2 shows the corresponding Kaplan-Meier curve.

DISCUSSION

Our study found that an elevated NT-proBNP was associated with the AVR requirement in asymptomatic patients with severe AS and preserved ventricular function after a 1-year follow-up. The biomarker had a very good discrimination capacity (AUC 0.88), and a value higher than 350 pg./mL was associated with an increased AVR requirement higher than 50% (HR: 1.55). As acknowledged, NT-proBNP and the active BNP hormone are released in response to ventricular and/or atrial cardiomyocyte stretch, mainly as a result of increased filling pressures. (13) Several studies have previously evaluated the prognostic value of natriuretic peptides in AS. Recently, White et al. (12) published a meta-analysis to assess the prognostic role of several biomarkers in AS. They considered 33 studies evaluating the NT-proBNP in 8597 patients. In the combined analysis, an elevated NT-proBNP predicted mortality at follow-up (HR 1.73). All studies included both asymptomatic and symptomatic patients, as well as AVR and non-AVR patients.

In addition, several studies have shown that elevated BNP and NT-proBNP are associated with symptoms and a higher V max in patients with severe AS and preserved function. (14-16)

As regards AS without symptoms, in 2014 Clavel et al. (11) published an observational study of nearly 2000 patients with moderate or severe AS, 560 of whom were asymptomatic at baseline. In this subgroup, an increased BNP was an independent predictor of mortality at follow-up. BNP values ≥3 times the reference value represented an adjusted risk of event nearly 4

Table 2. Univariate and multivariate analysis

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
SBP	1.00 (0.96-1.04)	0.33	--	
LVEF	0.98 (0.97-1.12)	0.56	--	
LVMI	1.01 (0.93-1.05)	0.22	--	
V max	1.03 (0.99-1.12)	0.11	--	
MG	1.02 (0.89-1.23)	0.23	--	
LAA	1.32 (0.99-1.98)	0.09	--	
Lateral S wave	1.21 (1.115-1.88)	0.01	1.18 (0.97-1.72)	0.09
E/e´ ratio	1.52 (1.22-2.63)	<0.001	1.42 (1.21-2.45)	<0.001
NT-proBNP	1.04 (1.01-1.04)	<0.001	1.02 (1.001-1.03)	<0.001

LAA: left atrium area. LVEF: left ventricular ejection fraction. LVMI: left ventricular mass index. MG: mean gradient. SBP: systolic blood pressure. V max : maximum aortic valve velocity

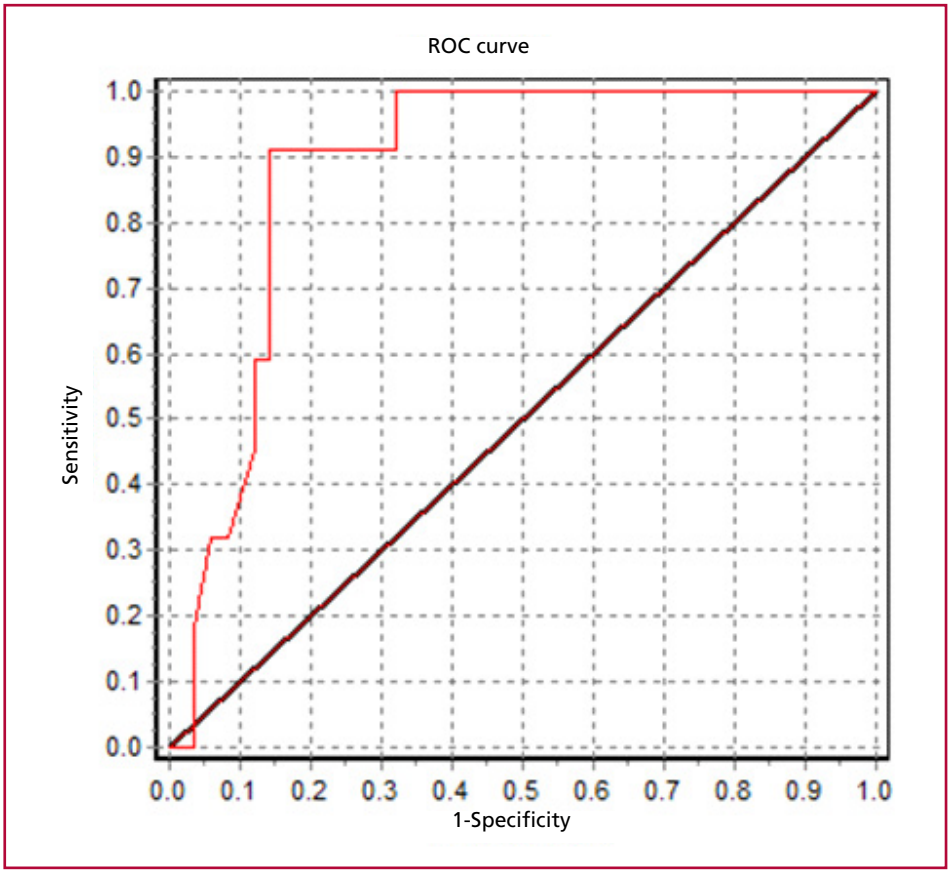

Fig. 1. ROC curve for the NT-proBNP.

times higher than normal BNP. In this sense, a Spanish study including 237 asymptomatic patients with moderate and severe AS evidenced that an increased NT-proBNP was an independent predictor of events (AVR requirement, mortality) at follow-up. (17) Unlike our study, they found a mild discrimination capacity (AUC 0.62). More recently, Henri et al. evaluated the purpose of a serial BNP measurement to predict events in asymptomatic patients with severe AS. (18) An annual 20 pg./mL increase in BNP was independently associated with a growing number of events at 3-year follow-up. A retrospective study of 74 patients found that NT-proBNP and the interventricular septum thickness were independent predictors of events (mortality and AVR requirement) at 4-year follow-up. (19) Previously, Monin et al. (20) found that BNP was associated with increased events and mortality in asymptomatic patients with severe AS and an AUC 0.74. They proposed

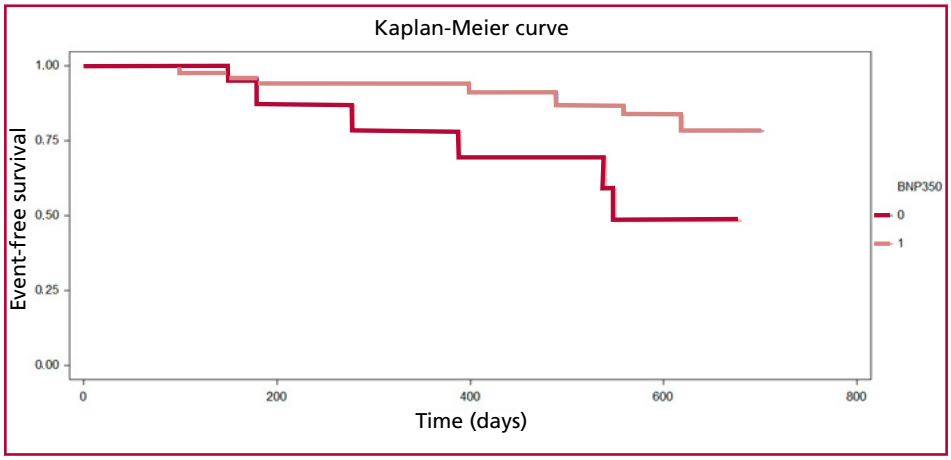

Fig. 2. AVR prediction based on the NT-proBNP value.

AVR: aortic valve replacement. BNP350: 0: ≤350 pg/mL. 1: >350 pg/mL

a risk score considering the BNP value, the V max, and the female sex, leading to better event prediction. This score was later validated by Farre et al., (17) using NT-proBNP instead of BNP. Based on these observations, the latest guidelines propose AVR as a Class IIA indication in patients with elevated natriuretic peptides. (3)

In our population, 23% of patients developed symptoms and required AVR during follow-up. This rate of events is lower than the rate reported in previous studies, where about half of the patients required AVR. The Spanish group (17) reported that 110 out of 237 patients required AVR in a follow-up similar to ours. In addition, they recorded a 12% mortality. This is remarkable, since they included a group with moderate AS. Our population was a little younger (69 versus 74 years old) and had a lower baseline NT-proBNP level (110 versus 490 pg./mL). This may partly explain the difference in events. Our patients were probably in an earlier stage of AS.

We also found that the E/e´ ratio was an independent predictor of AVR, with a mild predictive capacity (AUC 0.64). This is consistent with previous studies evaluating diastolic dysfunction parameters in AS. Especially the left atrium area (LAA) and the E/e´ ratio have been found to be independent markers of events in severe asymptomatic AS. (21,22) In our study, patients requiring AVR had a higher LAA than those who didn't; however, in the multivariate analysis, LAA lost independent predictive value, due to the E/e´ ratio and NT-proBNP. Something similar happened with the tissue S wave, which was significant in the univariate but not in the multivariate analysis. The V max is another parameter associated with worse AS progress. V max >5 m/sec indicates a very severe AS, and AVR is recommended in the absence of symptoms. (2,3) We have not found an association with the primary endpoint, probably because the average V max was 4.2 m/sec, and very few patients had a V max >5 m/sec.

The natural progress of severe AS and the time when AVR should be indicated while the disease is asymptomatic, is being increasingly discussed. The recommendation in the absence of adverse prognosis features is careful surveillance and immediate intervention as soon as symptoms occur. (2-4) The basis for this consensus is that the benefit of avoiding sudden death (1% per year in asymptomatic AS) may not be higher than AVR mortality. However, a recent retrospective study compared progress in patients with asymptomatic AS under a conservative treatment against a group of patients who had received AVR. Asymptomatic patients with no AVR at the beginning had higher mortality at 5-year follow-up than AVR patients. (23) Recently, the results of the RECOVERY study were published; (24) this study randomly assigned 145 asymptomatic patients with severe AS to early AVR versus a conservative treatment. The early AVR group had reduced events (death at surgery or within 30 days after surgery, or cardiovascular death during follow-up) versus the conservative treatment (1% vs. 15%, HR 0.09 and a large 95% CI, 0.01-0.67). However, this population was carefully picked, relatively young (aged 64), predominantly had a bicuspid etiology, and an average V max of 5.1 m/sec. Several randomized studies are currently being conducted to evaluate the early AVR strategy for asymptomatic AS: EARLY TAVR (NCT03042104), EASY-AS (NCT04204915), EVOLVED (NCT03094143) (clinicalstrials.gob).

As we have said, the value of natriuretic peptides increases with higher filling pressures. The increase in these and other biomarkers may serve to identify a subgroup of patients who, even if they are asymptomatic, are not so well adjusted to a higher afterload caused by AS, and therefore, have worse progress. This subgroup could benefit from early intervention. (25,26) In this sense, the study by Nakatsuma et al. (27) included 380 asymptomatic patients with severe AS and ventricular function that were divided based on their baseline BNP levels. The rate of events in the group with BNP <100 pg/mL was low both after a year and after 3 years (2.1% and 6.2 %, respectively), while in the group with BNP >300 pg./mL, the rate

of events was considerably higher (22% and 42% after 1 and 3 years, respectively). The results of our study contribute to the hypothesis that natriuretic peptides may be a major factor when making decisions about asymptomatic patients with severe AS and preserved function.

Limitations

Our study has several limitations. It is a single-site study, so it is difficult to extrapolate results to other populations. Follow-up was relatively short; therefore, the impact of baseline NT-proBNP cannot be assessed in the long term, and the discrimination capacity of events might be overestimated. Nevertheless, one of the objectives was to evaluate factors helping to identify patients with a higher risk that might benefit from early intervention. As a result, we believe that a 36-month follow-up is sufficient for the study objectives. Lastly, as this is an observational prospective study, the NT-proBNP value may have affected the medical decision to perform an AVR, which may also help to overestimate the event discrimination capacity of the biomarker.

Conclusions

At follow-up, more than 20% of patients developed symptoms and required valvular replacement. The NT-proBNP and E/e´ ratio were independent predictors of the AVR requirement. The NT-proBNP had a very good discrimination capacity, higher than the E/e' ratio.

Conflicts of interest

None declared.

(See authors conflicts of interest forms in the website/ Supplementary material)

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ORIGINAL ARTICLE

Implications of the COVID-19 Pandemic and Social Isolation on the Cardiometabolic Profile of a Cohort of Individuals from the City of Buenos Aires

Implicancias de la pandemia por covid-19 y el aislamiento social sobre el perfil cardiometabólico de una cohorte de individuos en la Ciudad de Buenos Aires

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ABSTRACT

Background: The COVID-19 pandemic has shocked humanity. During the pandemic, the need for social isolation has encouraged low adherence to a healthy lifestyle in many individuals. However, evidence of the metabolic impact of COVID-19 pandemic on our field is scarce.
Objective: To evaluate the impact of social isolation produced by the COVID-19 pandemic on the body weight and the cardiometabolic parameters of an adult population in the Autonomous City of Buenos Aires.
Methods: Based on an observational design, we analyzed the data from patients who attended a prevention and health promotion program in the City of Buenos Aires. Data from participants who attended for testing in 2019 and repeated testing in 2021 were individualized. Medical records were used as source for collecting general data, anthropometric measurements, and laboratory values. The National Cholesterol Education Program (NCEP) criteria were used to define the presence of metabolic syndrome (MS).
Results: A total of 558 patients with available evaluations in 2019 and 2021 were identified. The average age of the population was 52.2 ± 12.8 years, and 41% was female. An increase in body weight (82.1 ± 17.7 kg vs. 83.1 ± 18.5 kg; p<0.0001) and body mass index (29.4 ± 5.4 vs. 29.8 ± 5.7, p<0.0001) was observed. Increases in systolic (123.1 ± 15.1 mmHg vs. 126.6 ± 16.3 mmHg; p<0.0001) and diastolic (77.7 ± 9.3 mmHg vs. 79.6 mmHg± 9.4 mmHg, p<0.0001) blood pressure values were also observed. As regards the laboratory parameters, we noted an increase in plasma glucose levels with a median and an interquartile range (IQR) of 95 (89-103 mg/dL) vs. 99 (92-107 mg/dL), p<0.0001, and a decrease in HDL cholesterol (51, 8 ± 12.7 mg/dL vs. 49.3 ± 12.8 mg/dL, p<0.0001). No changes were observed in LDL cholesterol (116.4 ± 32.6 mg/dL vs. 116.1 ± 34 mg/dL; p=NS), total cholesterol (194.9 ± 37.4 vs. 193 ± 39.6 mg/dL; p=NS) or triglyceride levels, with a median (IQR) of 114.5 (83.2-162.7 mg/dL) vs. 118 (88-169 mg/dL; p=NS). This was accompanied by an increased prevalence of MS (21.5% vs. 34%; p<0.0001). The proportion of patients with carotid plaques also increased, without reaching statistical significance (36.4% vs. 40.7%; p=NS). Besides, it was observed that 18.8% of the patients increased their body weight by more than 5%. This population was represented by younger patients (47.6 ± 14 years vs. 53.3 ± 12 years; p< 0.0001) showing a reverse correlation between age and scope of weight increase (r=-0.1; p<0.02).
Conclusion: Social isolation during the COVID-19 pandemic was shown to have important consequences on the risk factors of the population studied. The prospective implications of these findings might become apparent in the next few years if these metabolic alterations are not reversed.

Keywords: Heart Risk Factors - Obesity - Hypertension - Treatment Adherence and Compliance -COVID-19

RESUMEN

Introducción: La pandemia por COVID-19 ha conmocionado a la humanidad. Durante la misma, la necesidad de aislamiento social ha fomentado la baja adherencia a un estilo de vida saludable en muchos individuos. Sin embargo, existe poca evidencia del impacto metabólico que ha tenido la pandemia por COVID-19 en nuestro medio.
Objetivos: Evaluar el impacto del aislamiento social producido por la pandemia COVID-19 sobre el peso corporal y los parámetros cardiometabólicos de una población de adultos en la Ciudad Autónoma de Buenos Aires.
Materiales y métodos: En un diseño observacional, se analizaron los datos de pacientes que asistieron a un programa de prevención y promoción de salud en la Ciudad de Buenos Aires. Se individualizaron datos de participantes que concurrieron a realizarse estudios en el año 2019 y repitieron los mismos en el año 2021. Los registros médicos se utilizaron como fuente para la recopilación de datos

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generales, medidas antropométricas y valores de laboratorios. Se utilizaron los criterios NCEP para definir la presencia de Síndrome Metabólico (SM).
Resultados: Se identificaron un total de 558 pacientes. con evaluaciones disponibles en 2019 y 2021. La edad promedio de la población fue 52,2 ± 12,8 años, con 41% de mujeres. Se observó un incremento en el peso corporal (82,1 ± 17,7kg vs. 83,1 ± 18,5kg; p<0,0001) y del índice de masa corporal (29,4 ± 5,4 vs. 29,8 ± 5,7, p<0,0001). También se observaron incrementos en la presión arterial sistólica (123,1 ± 15,1 mmHg vs. 126,6 ± 16,3 mmHg; p<0,0001) y diastólica (77,7 ± 9,3 mmHg vs. 79,6 ± 9,4 mmHg; p<0,0001). Dentro de los parámetros de laboratorio, se evidenció un incremento en los valores de glucemia plasmática, con mediana y rango intercuartílico (RIC) de 95 (89-103 mg/dL) vs. 99 (92-107 mg/dL), p<0,0001; y descenso del colesterol HDL (51,8 ± 12,7 mg/dL vs. 49,3 ± 12,8 mg/dL; p<0,0001). No se observaron cambios en el colesterol LDL (116,4 ± 32,6 mg/dL vs. 116,1 ± 34 mg/dL; p=NS), colesterol total (194,9 ± 37,4 vs. 193 ± 39,6 mg/dL; p=NS) o la concentración de triglicéridos, con mediana (RIC) de 114,5 (83,2-162,7 mg/dL) vs. 118 (88-169 mg/dL), p=NS. Esto se acompañó de un aumento de la prevalencia de SM (21,5% vs 34%; p<0,0001). También se incrementó la proporción de pacientes. con placas a nivel carotídeo, sin llegar a significancia estadística (36,4% vs. 40,7%; p=NS). El 18,8% de los pacientes. incrementaron su peso corporal más del 5%. Esta población estuvo representada por pacientes. más jóvenes (47,6 ± 14 años vs. 53,3 ± 12 años; p< 0,0001), y se observó correlación inversa entre edad y magnitud del incremento del peso (r=-0,1; p<0,02).
Conclusiones: El aislamiento social, durante la pandemia COVID-19, mostró tener importantes consecuencias en los factores de riesgo de la población estudiada. Las implicancias prospectivas de estos hallazgos podrían verse en los próximos años, si estas alteraciones metabólicas no se revierten.

Palabras clave: Factores de Riesgos Cardíacos - Obesidad - Hipertensión - Cumplimiento y Adherencia al tratamiento - COVID-19

INTRODUCTION

In December 2019, 27 index cases of a pneumonia of unknown etiology in Wuhan (Hubei, China) led to a pandemic caused by SARS-CoV-2 that shocked humanity. (1) COVID-19 infection, at first of a respiratory nature, progresses to a severe multisystem condition with an etiology consisting of strong inflammatory and immunological activation caused by the virus. (2) Epidemiological studies have early shown that patients with a higher risk of serious complications are elderly patients with underlying cardiovascular or pulmonary disease, or those with a higher cardiovascular risk as a result of blood hypertension (HTN), diabetes mellitus (DM), dyslipidemia, or obesity. (3) To reduce the impact of the pandemic, global social distancing and quarantine actions were taken with both direct and indirect consequences on people's health. (4, 5)

Permanent isolation evidenced increased morbidity and mortality as a result of non- COVID-19 conditions. (6) Factors such as decreased physical activity, stress, and diet changes were typical during this period. (7-9) The pandemic and social isolation, in particular, increased the already high prevalence of obesity, an aspect that seems to be exacerbated in our region. (10, 11) In addition, it is known that even mild increases in body mass index (BMI) may have a strong long-term impact on cardiovascular health. (12, 13) All these aspects promote emergence or impair management of cardiovascular risk factors (CVRF), such as hypertension, dyslipidemia, and diabetes.

Measuring the impact of this period of time on the cardiometabolic profile will provide relevant information helpful to establish management strategies avoiding any long-term consequences. Therefore, the aim of this study was to assess the cardiometabolic profile of a population before and after COVID-19 lockdown. It was also to analyze the prevalence and characteristics of the population with increased weight and obesity in this period.

METHODS

An observational retrospective cohort design was used to compare the times before and after lockdown as a result of the COVID-19 pandemic. This study was conducted at Hospital Universitario René G. Favaloro, in the Autonomous City of Buenos Aires, Argentina. Fundación Favaloro has a Cardiovascular Health Prevention Program (Programa de Prevención de Salud Cardiovascular, PPS) aimed at monitoring general health, giving advice, educating on healthy lifestyle habits, and identifying patients with a high cardiovascular risk. In Argentina, the national government ordered the start of preventive and mandatory social isolation on March 19, 2020. Thereafter, medical services were restricted, and healthcare was readjusted to the requirements of the pandemic. The program began to become flexible and reopened after December 2020. All male and female individuals aged over 18 taking part in the program during 2019 (the time immediately preceding the pandemic) were included and took part again in 2021 (the time following the strict lockdown). The aim was to have individual information on each participant before and after lockdown. Patients with untreated hypothyroidism, a history of acute or chronic hepatic and/or renal disease, pregnant or breastfeeding women, and patients with malignancies or diseases with less than one year life expectancy were excluded. For HTN and type 2 DM, the incidence of new cases was compared to a similar period of time in patients attending the program between 2017 and 2019.

Data were collected from medical records, including anthropometric parameters, medical history, and laboratory results. Only data derived from clinic visits on the days scheduled for the program were considered.

Night fasting venous blood samples were collected from each subject. Fasting glycemia (GLY), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and glycosylated hemoglobin (HbA1c) were measured using colorimetric methods with a semi-automatic biochemistry analyzer (Architect 8000/4000, Abbott Diagnostics, USA). Low-density lipoprotein cholesterol (LDL-C) was

estimated using the Friedewald's formula.

The waist circumference (WC) was measured using a non-expanding metric tape on a midpoint between the lower edge of ribs and the iliac crests with the patient standing in normal exhalation. The BMI, weight/height2, was estimated, and obesity was diagnosed with an BMI of ≥30 kg/m2. The characteristics of the group of patients with a higher than 5% increase in their body weight (W+5%) were explored and compared to the rest of the population (W-5%). DM was diagnosed when the patient had a history of fasting glycemia ≥126 mg/dL in at least 2 measurements, or was administered insulin or oral hypoglycemic drugs. (14) HTN was considered with a repeated systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg, or use of antihypertensive drugs. (15) Smoking (SMK) was considered with a history of >100 cigarettes in a lifetime and ex-smoker (ex-SMK) with no cigarette use in the last six months. (16) Metabolic syndrome (MS) was diagnosed based on National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) criteria. (17)

Subclinical carotid atheromatosis, as a dichotomic variant, was evaluated through an ultrasound using an Affinity 50 ultrasound system (Philips HealthCare, USA) and a vascular 9-12 Mhz probe. Images were defined as a focal protrusion towards arterial lumen with a thickness over 0.5 mm, or an increase over 50% in the adjacent intima-media thickness (IMT), or a diffuse >1.5-mm increase in the IMT measured between the media-adventitia and intima-lumen. (18.19)
This study was approved by the institutional ethics committee.

Statistical analysis

Quantitative variables are described as the mean ± standard deviation, or median and interquartile range, based on distribution. Comparisons before and after the pandemic were made using the Student's t-test for paired data, or Wilcoxon test for paired data, as appropriate. Categorical variables were described as the total number and percentage and compared with the Chi-square test or the Fisher's exact test, or McNemar test in case of paired proportions. The odds ratio was estimated with its corresponding 95% confidence interval when comparing the incidence of DM and HTN between 2017-2019 and 2019-2021. To evaluate the correlation between increased weight and age, the Pearson correlation test, expressed with the correlation coefficient r and its statistical significance, was used. All tests were 2-tailed, and a <0.05 p-value was considered to be statistically significant.

RESULTS

There were 5423 patients in the PPS in 2019, and 3423 patients in 2021. Patients who were part of the program both in 2019 and 2021 were 558. In 2019, the average age was 52.2 ± 12.8 years, and 41.2% were women. An average of 1.8 ± 0.5 years elapsed between both evaluations. Table 1 shows baseline demographics and compares data in 2019 to data in 2021. A mild but significant 1.2% increase was observed in body weight (p<0.0001), similar for the BMI (1.4% increase; p<0.0001). No changes were observed in the percentage of patients with obesity. There was an absolute 3% increase in HTN diagnosis during the pandemic, together with increased mean SBP and DBP levels. As for glycemia, 3% new cases of DM were diagnosed. The median glycemia increased 4 mg/dL in the 2-year follow-up (p<0.0001). In the overall population, the frequency of SMK and ex-SMK was similar between visits, with 4.5% (n=25) new smokers in 2021, and 3% (n=17) patients who had quitted smoking upon the evaluation that year. The lipid profile was affected, with an HDL-C decrease (51.8 ± 12.7 vs. 49.3 ± 12.8 mg/dL; p<0.0001), and no changes in other aspects under analysis. MS diagnosis significantly increased in the population (21.5% vs. 34.1%; p<0.0001) (Figure 1). The average criteria in the MS increased from 1.5 ± 1.2 to 2 ± 1.3 (p<0.0001).

New HTN and DM diagnoses in 2017-2019 and in 2019-2021 were evaluated. There were 7884 participants in the PPS in 2017, of whom 2111 repeated the test in 2019. Of these, 165 had DM and 629 were hypertensive patients at the beginning of the period. In 2017-2019, 23 new cases of DM and 26 new cases of HTN were identified. The incidence of new cases was higher in 2019-2021, with 17 newly diagnosed cases of DM (OR 3.5, 95% CI 1.8-6.7; p<0.001) and 16 of HTN (OR 2.4, 95% CI 1.3-4.6; p<0.005).

In the W+5% group (n=105), no differences were observed in the baseline weight in 2019 (W+5% 81.8 ± 20.3 kg vs. W-5% 82.1 ± 17.1 kg; p=NS) or the BMI (W+5% 29.3 ± 5.2 vs. W-5% 29.6 ± 6.3 kg/m2; p=NS). However, this population was represented by younger patients (W+5% 47.6 ± 14 years vs W-5% 53.3 ± 12 years; p<0.0001), and a significant reverse correlation was observed between age and scope of weight increase (r=-0.1; p<0.02). In addition, it was observed that W+5% patients were less likely to have HTN (22.8% vs 33.6%; p<0.05). No differences were observed in this group as for DM (W+5% 7.6% vs W-5% 9%; p=NS), SMK (W+5% 20.9% vs W-5% 15.9%; p=NS), ex-SMK (W+5% 27.6% vs W-5% 29.6%; p=NS), frequency for females (W+5% 48.6% vs W-5% 39.5%; p=NS), or a history of cardiovascular disease (W+5% 1.9% vs W-5% 4.2%; p=NS).

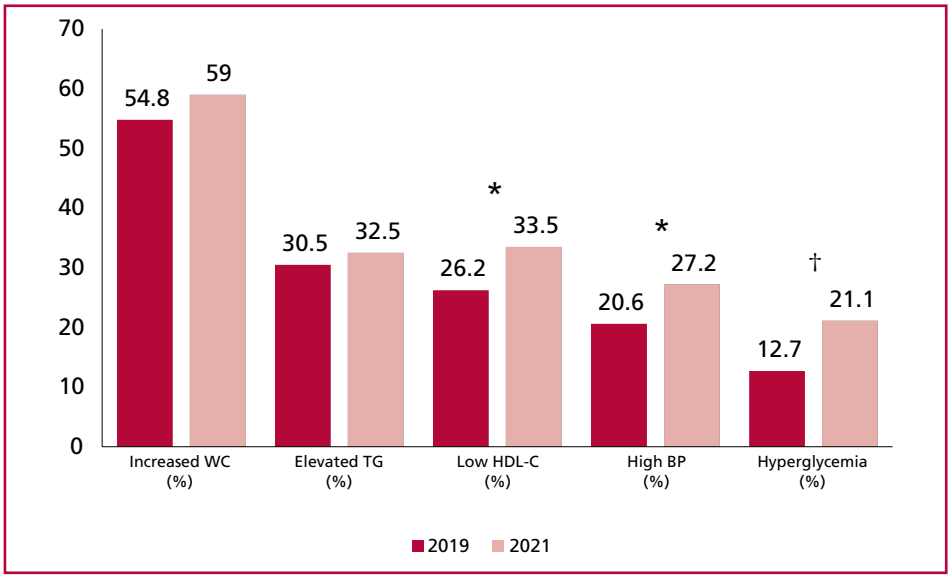
The analysis of adherence to treatment showed that, out of 39 patients using metformin in 2019, 3 (7.7%) discontinued this drug. However, out of 13 patients using another antidiabetic treatment, 23.1% (3 patients) discontinued their medication. Of the total number of patients with HTN in 2019, 96% (169 patients) received drug therapy. In 2021, 19.9% of patients with HTN had discontinued their medication, 12.5% (22 patients) reduced the number of drugs, and 11.4% (20 patients) increased the number of drugs used. The most common hypolipidemic agent in 2019 were statins (116 patients, 20.8%), followed by ezetimibe (9 patients, 1.6%) and fibrates (8 patients, 1.4%). By 2021, the use of statins among participants was 24.7% (138 patients), fibrates 2.3% (13 patients), and ezetimibe 2% (11 patients), with no significant differences as compared to 2019. Of the total number of patients receiving statins in 2019, 14.6% (17 patients) discontinued treatment. During the study period, 7% of the population (39 patients) began to use statins.

The evaluation of carotid atheromatosis showed

	Before the pandemic (n = 558)	After the pandemic (n = 558)	p-value
Weight (kg)	82.1 ± 17.7	83.1 ± 18.5	<0.0001
BMI (kg/m2)	29.4 ± 5.4	29.8 ± 5.7	<0.0001
Obesity (%)	227 (40.7)	236 (42.3)	NS
Hypertension, n (%)	176 (31.5)	192 (34.4)	<0.01
Type 2 diabetes, n (%)	49 (8.8)	66 (11.8)	<0.001
Glycemia (mg/dL)			
Median	95	99	<0.0001
Interquartile range	89-103	92-107	
Smoking, n (%)	94 (16.8)	86 (15.4)	NS
Ex-smoker, n (%)	163 (29.2)	177 (31.7)	NS
SBP (mmHg)	123.1 ± 15.1	126.6 ± 16.3	<0.0001
DBP (mmHg)	77.7 ± 9.3	79 ± 9.4	<0.001
Total cholesterol (mg/dL)	194.9 ± 37.4	193 ± 39.6	NS
HDL cholesterol (mg/dL)	51.8 ± 12.7	49.3 ± 12.8	<0.0001
Triglycerides (mg/dL)			
Median	114.5	118	NS
Interquartile range	83.2-162.7	88-169	
LDL cholesterol (mg/dL)	116.4 ± 32.6	116.1 ± 34	NS

BMI: Body Mass Index. DBP: Diastolic Blood Pressure. HDL: High-Density Lipoproteins
LDL: Low-Density Lipoproteins. SBP: Systolic Blood Pressure
Quantitative variables are expressed as the mean ± standard deviation, or the median and interquartile range

Table 1. Demographics



BP: Blood Pressure; HDL-C: High-Density Lipoprotein Cholesterol; TG: Triglycerides; WC: Waist Circumference.
* p<0.01, † p<0.0005

Fig. 1. Prevalence of metabolic syndrome diagnostic criteria in 2019 vs. 2021

a non-significant increase between 2019 and 2021 (36.4% vs 40.7%; p=NS). In the period under analysis, patients had 3 acute myocardial infarctions, 2 coronary angioplasties, and 1 coronary artery bypass grafting.

DISCUSSION

The COVID-19 pandemic has shocked the world. The World Health Organization (WHO) defines a disaster as a series of events that disrupt daily life in a community or society causing material, economic or environmental damage. (20) The COVID-19 pandemic is a biological disaster which is still unsolved and with consequences for many years to come. (21) This paper could identify an increased prevalence of risk factors in the period before and after the pandemic, reflected by a higher prevalence of hypertension, dyslipidemia (characterized by lower HDL-C), high BMI, hyperglycemia, and type 2 DM. This was associated to an increased prevalence of MS, particularly as a

result of more frequent hyperglycemia, low HDL-C, and elevated blood pressure. Various studies have assessed the incidence of new cases of DM, HTN, and dyslipidemia, with inconsistent results. Particularly glycemia worsened in patients with DM, with no changes in glycosylated hemoglobin according to a recent meta-analysis. (22) Burekovic et al. have shown more new cases of DM in a period similar to the one under analysis. (23) These authors also suggest that acute COVID-19 infection might favor hyperglycemia and a subsequent DM diagnosis. During the pandemic and lockdown, increased HTN has also been observed; the direct impact of the infection and interaction with the renin-angiotensin-aldosterone system as the root cause cannot be ruled out. (24) The incidence observed in new cases of DM and HTN was significantly higher in 2019-2021, as compared to 2017-2019; this result suggests an increase due to the pandemic and lockdown. Further studies should elucidate whether the impaired cardiometabolic profile results from adverse lifestyle changes or the direct influence of COVID-19 infection.

Observations regarding the BMI and obesity should be considered separately. Several reports have shown increased obesity and overweight relative to lockdown. (10, 11) This may be because physical and social isolation are well-known risk factors for obesity. (25) A lower-quality diet has also contributed. The combination of lack of physical activity, staying at home, increased intake of snacks and high-calorie meals lead to rapid weight gain. (26) Overeating is particularly increased when there are emergency food stocks available. (27) It is important to note that about 1 in 5 patients increased weight by more than 5%. In this respect, Mozaffarian et al. showed that moderate weight gain has an adverse effect on metabolism, increases the risk of diabetes and the incidence of cardiovascular events. (12) Therefore, preventing the weight gain frequently observed in the pandemic may be one major way to avoid long-term consequences. In our study, weight gain was associated to a younger age. Simone et al. showed that 70% of individuals from a young population admitted that the events related to the COVID-19 pandemic affected their eating habits. (28) This group mentioned lack of concern about food, higher food intake, or eating "to bear the situation," among other characteristics of their eating habits during the pandemic. Variables relative to these findings were anxiety/depression, stress management, financial difficulties, and sudden changes of schedule. These factors, associated with a lower concern for the future consequences of weight changes, might partly explain this.

Adherence to treatment was one major health problem during the pandemic, mainly due to impaired access to drugs. (29) In a study evaluating difficulties in access to drugs for 1103 patients with chronic diseases, 51% of patients found it hard to find their medication during the pandemic and lockdown, and the most reported cause was doctor's unavailability. (30) Many of these conditions were likely to be temporary in the first stage of the period. In our population, the patients most prone to discontinue medication were those who received antihypertensive agents and those with diabetes under treatment with a combination of drugs. There was no lack of adherence to hypolipidemic agents.

Note that our study had some limitations. The population consists in PPS participants, rather than the general population. Even so, the frequency of CVRF is similar to the one reported in the 4th National Survey on Risk Factors. (31) The retrospective design makes it impossible for us to know what happened between both periods of time under analysis. This is important, as many of the variables being assessed may have been temporarily altered (e.g., changes in bodyweight or medication availability) throughout the pandemic.

In conclusion, our study shows increased exposure to CVRF during the pandemic and social isolation because of COVID-19. This aggravates the adverse landscape of exposure to such factors, already present before the pandemic. We need to identify the changes above, particularly those relative to an increased BMI in young individuals, to seek a healthy lifestyle for our patients. The prospective implications of these findings might become apparent in the next few years if these metabolic changes are not reversed. Future studies need to prospectively monitor the progress of these findings.

Conflicts of interest

No conflicts of Interest or financing concerning the study have been declared.

(See authors' conflict of interests forms on the web/Additional material.)

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ORIGINAL ARTICLE

Reverse Electrical Remodeling in Patients Under Cardiac Resynchronization Therapy

Remodelado eléctrico reverso en pacientes tratados con terapia de resincronización cardíaca

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is indicated in patients who often present cardiac remodeling due to dilatation and contractile dyssynchrony. CRT contributes to reverse remodeling which is associated with reduced mortality and heart failure (HF) hospitalizations. Improvements in intraventricular conduction with decreased ventricular activation time have also been observed. The quantification of reverse electrical remodeling has been underused as a parameter of response, and there are few reports on its association with the clinical-structural response.
Objective: To analyze intraventricular reverse electrical remodeling as a parameter of response to CRT in living individuals.
Methods: We included patients implanted at least 6 months ago. A deactivated stimulation ECG (post-CRT intrinsic QRS, iQRS) was obtained, and by means of transthoracic echocardiography (TTE), the left ventricular ejection fraction (LVEF), the left ventricular end-diastolic diameter (LVEDD) and the presence of mitral regurgitation were defined. Patients were classified according to their clinical-structural response. Electrical remodeling was characterized by comparing pre- and post-CRT QRS duration and assessing QRS changes (ΔiQRS) between groups.
Results: A total of 23 patients were included, 39% of which showed a >10 msec decrease in iQRS. We observed a ΔiQRS of -9.3±20.7 msec in responders, and 11.25±18.9 msec in non-responders (p=0.027), more marked in hyper-responders (ΔiQRS: -14.44±17.40 msec, p=0.026). Women with pre-CRT QRS ≥150 msec showed a significant decrease in iQRS (p=0.0195).
Conclusion: Reverse electrical remodeling was found in 39% of the patients under CRT. We noted a significant relationship between ΔiQRS and clinical-structural response, higher in hyper-responders. Women with wider pre-CRT QRS showed more marked reverse electrical remodeling. This parameter is accessible and easy to read in outpatient visits.

Keywords: Cardiac resynchronization therapy, response, reverse electrical remodeling.

RESUMEN

Introducción: La terapia de resincronización cardíaca (TRC) se indica en pacientes que habitualmente presentan remodelado cardíaco generado por dilatación y disincronía contráctil. La TRC contribuye al remodelado reverso, relacionado con menor mortalidad y hospitalizaciones por insuficiencia cardíaca (IC). Se han observado además mejoras en la conducción intraventricular, con reducción del tiempo de activación. La cuantificación del remodelado eléctrico reverso se ha subutilizado como parámetro de respuesta, con escasos reportes sobre su asociación con la respuesta clínica-estructural.
Objetivo: Analizar el remodelado eléctrico reverso intraventricular como parámetro de respuesta a la TRC.
Material y Métodos: Se incluyeron pacientes con más de 6 meses de implante. Se obtuvo un ECG con estimulación desactivada (QRS intrínseco, QRSi, post-TRC), y por ecocardiograma transtorácico se definió la fracción de eyección ventricular izquierda (FEVI), el diámetro de fin de diástole del ventrículo izquierdo (DFDVI) y la presencia de insuficiencia mitral. Se clasificó a los pacientes según la respuesta clínica-estructural. El remodelado eléctrico se caracterizó con la comparación de la duración del QRS pre-y post-TRC y la valoración de los cambios del QRS (ΔQRSi) entre grupos.
Resultados: Se incluyeron 23 pacientes. Un 39% presentó disminución >10 mseg del QRSi. Observamos un ΔQRSi de -9,3±20,7 mseg en respondedores, y 11,25±18,9 mseg en no respondedores (p=0,027), más acentuada en los hiper respondedores (ΔQRSi: -14,44±17,40 mseg, p=0,026). Las mujeres con QRS ≥150 mseg pre TRC exhibieron disminución significativa del QRSi (p=0,0195).
Conclusiones: El remodelado eléctrico reverso se comprobó en 39% de los pacientes que recibieron TRC. Observamos una relación significativa del ΔQRSi con la respuesta clínica-estructural, mayor en hiper respondedores. Mujeres con QRS ancho pre-TRC exhiben remodelado eléctrico reverso más acentuado. Este es un parámetro de fácil acceso e interpretación durante los controles ambulatorios.

Palabras claves: Terapia de resincronización cardíaca, Respuesta, Remodelado eléctrico reverso.

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INTRODUCTION

Heart failure (HF) affects 1-2% of the adult population. It has been typically divided into two phenotypes based on the left ventricular ejection fraction (LVEF): HF with slightly reduced or preserved LVEF, and HF with reduced LVEF (HFREF). Cardiac resynchronization therapy (CRT) is mostly indicated for patients with HFREF and major cardiac remodeling, dilated chambers, and impaired ventricular conduction, both closely related to poor prognosis. (1–5)

CRT intends to correct cardiac dyssynchrony by stimulating both ventricles and achieve a more physiological activation and contraction. (6,7) From 25% to 50% individuals with a >120-msec QRS complex have HFREF, and 15-27% experience complete left bundle-branch block (LBBB). (8–10) Maximum benefit has been observed in addition to medical treatment in symptomatic patients with New York Heart Association (NYHA) functional class (FC) II-III, with sinus rhythm and LVEF ≤35%, a QRS longer than 150 msec, and LBBB morphology. (1,2)

This technique has shown the ability to optimize cardiac function and reduce chamber dimensions (reverse remodeling), improve symptoms, anticipate a better condition, and reduce HF hospitalizations and deaths when the patient has been properly screened. (11–15) The degree of reverse remodeling has been directly associated with reduced mortality and hospitalizations. (16–18) To evaluate response (even with heterogeneous definitions), different clinical parameters are used, such as an improved NYHA FC, HF hospitalization rate, and deaths. The most common technique to measure the structural and functional impact is the echocardiography, which is used to estimate the presence and extent of reverse modeling in LV dimensions, generally through end-systolic volume and LVEF improvement. A 15% or higher reduction in ventricular volumes or diameters and at least a 10% increase in LVEF is considered a "positive" response (despite variable cutoff values, according to the registry). The term "hyper-responders" refers to patients with a ≥30% reduction in ventricular volume, or a better systolic function with LVEF >50%. These patients are less likely to be hospitalized because of HF and have a longer survival. (19)

Despite these considerations and multiple technical improvements relative to imaging tests, implantation technique, and availability of more modern and reliable devices, 20% to 40% of patients do not show a favorable response to CRT (non-responders).

This leads to a concern for new and more accurate markers of response, which are easy to access and read. (16,20) The so-called reverse electrical remodeling has been described as another potential tool to measure response to CRT; it leads to reduced QRS, and decreased native (intrinsic) ventricular activation time. (21-23) However, very few reports evaluate its practicality, and there are controversial data on their association with clinical and structural response, though it has been mostly associated with structural remodeling and has even been suggested as a rapid, easy, and low-cost parameter to predict a positive response to CRT. (24-27) Our experience intends to evaluate electrical remodeling as a potential parameter of response in patients under CRT.

OBJECTIVE

To analyze intraventricular reverse electrical remodeling as a parameter of response to CRT in individuals implanted at least 6 months ago.

METHODS

Design

This is an analytical, observational, longitudinal, retrospective, and single-center study.

Population

The study enrolled living patients with chronic HF treated at the Centro Cardiovascular Universitario del Hospital de Clínicas de Montevideo from 2015 to 2021 by implanting a cardiac resynchronizer, with or without an associated defibrillator (CRT-D and CRT-P respectively), within at least 6 months. All patients had permanent complete LBBB at the time of CRT. Complete LBBB was defined according to AHA/ACCF/HRS recommendations. (28) All patients were in NYHA FC II or III at the time of implantation, and a CRT indication based on the guidelines of the European Society of Cardiology. (1,2)

Patients with a pacemaker or with no sinus rhythm at the time of implantation or follow-up, or patients with a resynchronizer implanted as an upgrade to a pacemaker with previous right ventricular stimulation were excluded. Patients with a non-complete LBBB QRS morphology, such as complete right bundle-branch block (RBBB), were also excluded. (1,2) After meeting inclusion and no exclusion criteria, 23 patients were enrolled. Figure 1 shows the study design.

Clinical variables

Clinical data, structural and functional ECGs were collected at the time of implantation based on each patient's medical history and procedure report. In addition, data from outpatient follow-up (Figure 1) were collected, including a brief case history on subjective clinical improvement after CRT, current NYHA FC, and details on the pharmacological treatment.

Device control, records, and surface ECG measures

Based on each patient's medical history, the most recent ECG before the date of CRT implantation was obtained ("pre-CRT" QRS complex, Figure 1). The day when the patient returned for follow-up, the device was followed with programmers. The biventricular stimulation percentage (%BiV) was obtained at the time. There were two new standard 12-lead ECGs per patient, using a FUKUDA DENSHI CARDIMAX FX-2111 electrocardiograph gauged at a 25 mm/s paper speed and with a 0.1 mV/mm voltage. The first ECG was performed with the CRT device stimulated according to usual patient programming (stimulated QRS). To assess intrinsic ventricular activation ("post-CRT" iQRS), a second ECG was performed 5 minutes after temporary implantation discontinuation, programming the device as an off (ODO) or on-demand (VVI) CRT with a HR of 40 bpm.

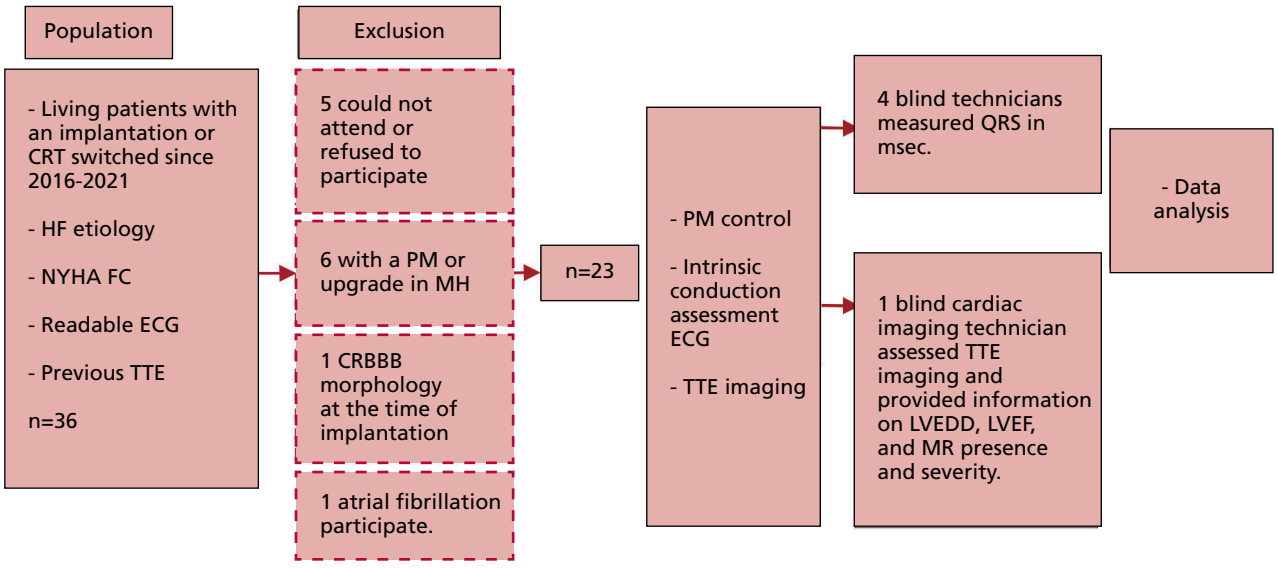

Fig. 1. Study design. CRBB: complete right bundle block. CRT: cardiac resynchronization therapy. ECG: electrocardiogram HF: heart failure. LVEDD: left ventricular end-diastolic diameter. LVEF: left ventricular ejection fraction. MH: medical history. MR: mitral regurgitation. NYHA: New York Heart Association. PM: pacemaker. TTE: transthoracic echocardiography

After recording, the device was reprogrammed with the patient's previous setup.

These ECG showed presence or absence of sinus rhythm. Three electrophysiologists and one electrophysiology-trained cardiologist were asked to measure the duration of QRS complexes (msec) with the most representative leads, concealing any data that might identify the patients and ensuring that those measuring QRS complexes ignored CRT response.

Structural variables (TTE)

The transthoracic echocardiography (TTE) report closest to, and before the date of CRT implantation was obtained from the patient's previous medical history. These reports showed pre-CRT LVEF data, the left ventricular end-diastolic diameter (pre-CRT LVEDD), and the presence and extent of mitral valve regurgitation (pre-CRT MR).

On the day of the new ECG, and after checking the device, each patient had a new TTE performed using ultrasound General Electric Vivid iQ equipment with a 3.5 Mhz transducer, as recommended by the American Society of Echocardiography. Images of two and four chambers apical and left parasternal areas were captured using color Doppler. An echocardiography technician, also blind to clinical data, read the images, estimated the LVEF using the biplane Simpson method (post-CRT LVEF), measured the LVEDD, and defined the presence and severity of mitral regurgitation (post-CRT MR).

CRT response definition

The patient was categorized as a "clinical responder" and/or "structural responder" based on the most common criteria to evaluate response to CRT (13,16,29–31):

- A "clinical responder" is someone with subjective improvement and at least one level improvement (reduction) in the NYHA functional class as compared to the value before the implantation.
- A "structural responder" is someone with reduced LV diameters by at least 15% and/or increased LVEF by at least 10%.
- A "hyper-responder" is someone with reduced LV diameters by 30% and/or normal LVEF.

Statistical analysis

Normal data distribution was checked using the Anderson-Darling normality test. Continuous variables are presented as mean ± standard deviation (SD), or median and interquartile range (IQR) of 25-75%, as appropriate. Categorical variables are presented with absolute and relative frequencies. To evaluate changes in the continuous variable of interest, iQRS, in response to CRT (pre/post CRT analysis), the t test or Wilcoxon test for paired data was used, as appropriate. Also, behavior of ΔiQRS as a continuous variable (post-CRT QRS – pre-CRT QRS in msec) was compared in responders vs. non-responders (paired t test or Mann-Whitney test, as appropriate). These analyses were performed for the clinical-structural (CS) response and hyper-response across the sample and certain subgroups of patients (female vs. male, baseline QRS >150 msec vs. <150 msec, females with a baseline QRS >150 msec vs QRS <150 msec, patients with vs without improved MR). A p-value <0.05 was considered statistically significant. All graphical analyses used software Graph Pad Prism, version 9.0.

Ethical considerations

The ethical principles set forth in the Declaration of Helsinki and latest amendments for research in humans were followed. All patients were called to be informed about the study prior to enrollment. At the time of evaluation in the clinic, each patient gave their written informed consent. The study and informed consent provided to the patients had been previously approved by the Hospital de Clínicas Ethics Committee.

Table 1. Baseline study population characteristics (pre-CRT)

Clinical variables	
Female, n (%)	12 (52)
Age at the time of implantation (years), mean+SD	60±12
Time since implantation (months), mean+SD	43±20
Non-ischemic etiology (n, %)	19 (82)
Medications, n (%)	
o ACEi/ARB	20 (86)
o BB	23 (100)
o MRA	18 (78)
o OMT	17 (73)
Pre-CRT NYHA FC, n (%)	
o II	9 (39)
o III	14 (61)
Echocardiographic variables	
LVEF (%) mean+SD	26.3±5.7
LVEDD (mm), mean+SD	66.6±12.7
At least moderate MR, n (%)	10 (43)
ECG variables	
Duration of intrinsic QRS (msec), median (IQR 25-75)	160 (150-170)
Duration of stimulated QRS (msec), mean+SD	119±19
BiV implantation (%), median (IQR 25-75)	99 (95-100)

ACEi: angiotensin-converting enzyme inhibitors. ARB: angiotensin II receptor blockers. BB: beta-blockers. BiV: bi ventricular. CRT: cardiac resynchronization therapy. IQR: interquartile range. LVEDD: left ventricular end-diastolic diameter. LVEF: left ventricular ejection fraction. MR: mitral regurgitation. MRA: mineralocorticoid receptor antagonists. NYHA FC: New York Heart Association functional class. OMT: optimal medical therapy. SD: standard deviation.

RESULTS

Study population characteristics

A total number of 23 patients were enrolled. Clinical, echocardiographic, implant-related, and electrocardiographic variables are displayed in Table 1.

The patients across the sample showed a similar per-sex distribution; 12 were female (52%). Four (18%) patients had ischemic heart disease, and 19 (82%) patients had non-ischemic heart disease. The average age at the time of implantation was 60±12 years, while the age at the time of follow-up was 64±12 years. The mean follow-up from implantation to control was 43±20 months, ranging from 7 to 96 months.

A high rate of treatment adherence was observed among patients; 73% were under simultaneous therapy with beta-blocker (BB), angiotensin converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARB)/sacubitril-valsartan, and mineralocorticoid receptor antagonists (MRA). All patients were receiving BB at the time of follow-up.

The duration of the intrinsic QRS complex prior to CRT was 160 (150-170) msec, and after the CRT, it was 160 (140-160) msec. Nine (39%) patients showed at least a 10 msec reduction in the iQRS duration. Maximum reduction was 40 msec and occurred in three patients. The iQRS increased in eight patients and remained stable in six.

Analysis of response to CRT

Table 2 shows the characteristics of CRT responders. Twenty-one (91%) patients in our study were "clinical responders". The ΔiQRS in this group was -4.7±20.4 msec. Structurally and functionally, both LVEDD and increased LVEF showed enhanced response to CRT during follow-up. LVEDD decreased from 66.6±12.7

Table 2. ECG and clinical response to CRT (pre- and post-CRT analysis)

Response parameters	Pre-CRT	Post-CRT	p-value
Structural variables			
LVEF (%) mean+SD	26.3±5.7	41.6±13.4	<0.0001
LVEDD (mm), mean+SD	66.6±12.7	61.7±12.9	<0.0001
ECG variables			
QRS (msec), median (IQR 25-75)	160 (150-170)	160 (140-160)	0.63

CRT: cardiac resynchronization therapy. LVEDD: left ventricular end-diastolic diameter. LVEF: left ventricular ejection fraction;

mm pre-CRT to 61.7±12.9 mm post-CRT, with a higher than 15% reduction in 7 patients (30.4%). LVEF increased from 26.3±5.7% to 41.6±13.4%, with a higher than 10% increase in 16 patients (70%).

Fifteen (65%) patients were considered "responders" based on both structural and clinical criteria. The LVEDD was significantly reduced from 64.6±8.7 mm to 59.8±7.5 mm, and the LVEF increased from a baseline value of 25.5±6.8% to 40.6±9.5% (Table 2). Nine (39%) patients were "hyper-responders". All of them had clinical response.

As shown in Table 2, the pre- and post-CRT analysis of the total number of patients found that the duration of QRS did not vary significantly following the CRT.

Figure 2 shows a sample case, with iQRS measurements before and after the CRT in a "responder".

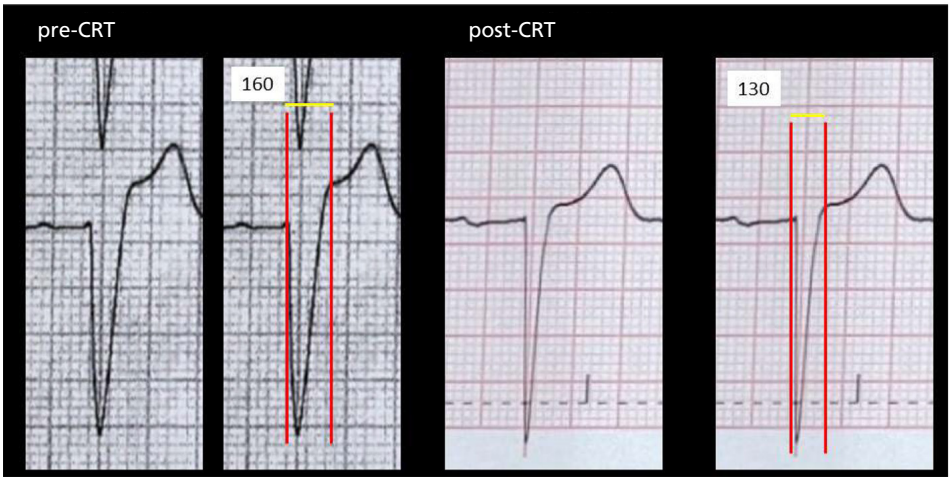

Fig. 2. Reverse electrical remodeling of the left ventricle before and after CRT. (Images are repeated using calipers and measures.) This patient showed increased LVEF from 28% to 52%, and decreased LVEDD from 77 to 58 mm.
CRT: cardiac resynchronization therapy

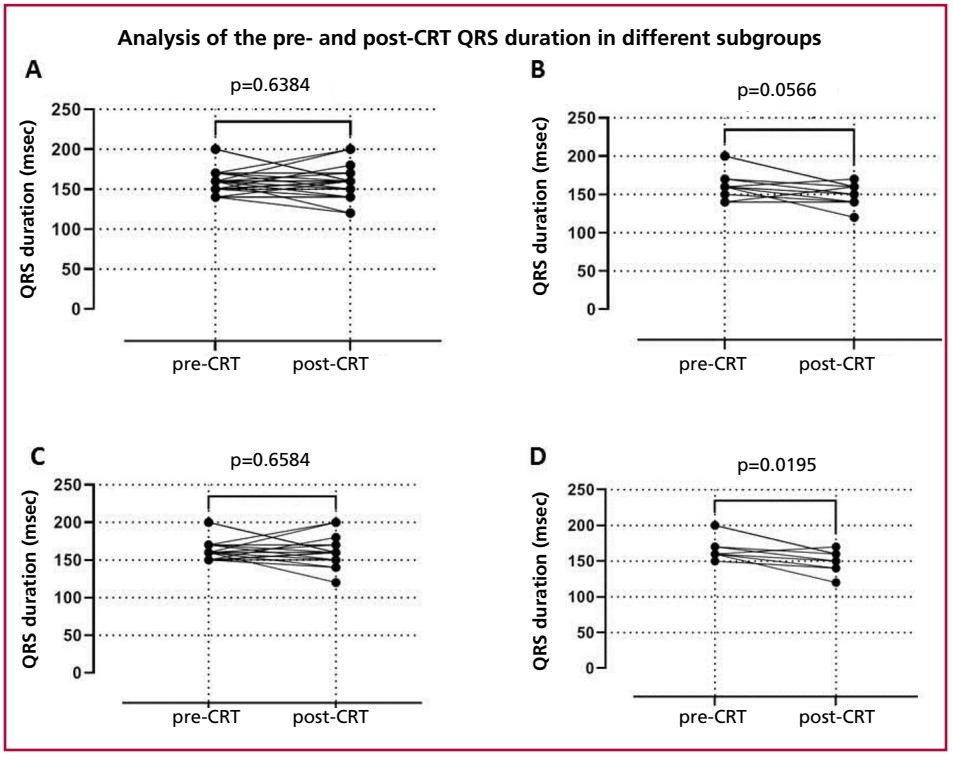

Fig. 3. Differences in iQRS before and after the CRT in the entire population (A), the female subgroup (B), individuals with an initial QRS ≥150 msec (C), and women with an initial QRS ≥150 msec (D).
CRT: cardiac resynchronization therapy.

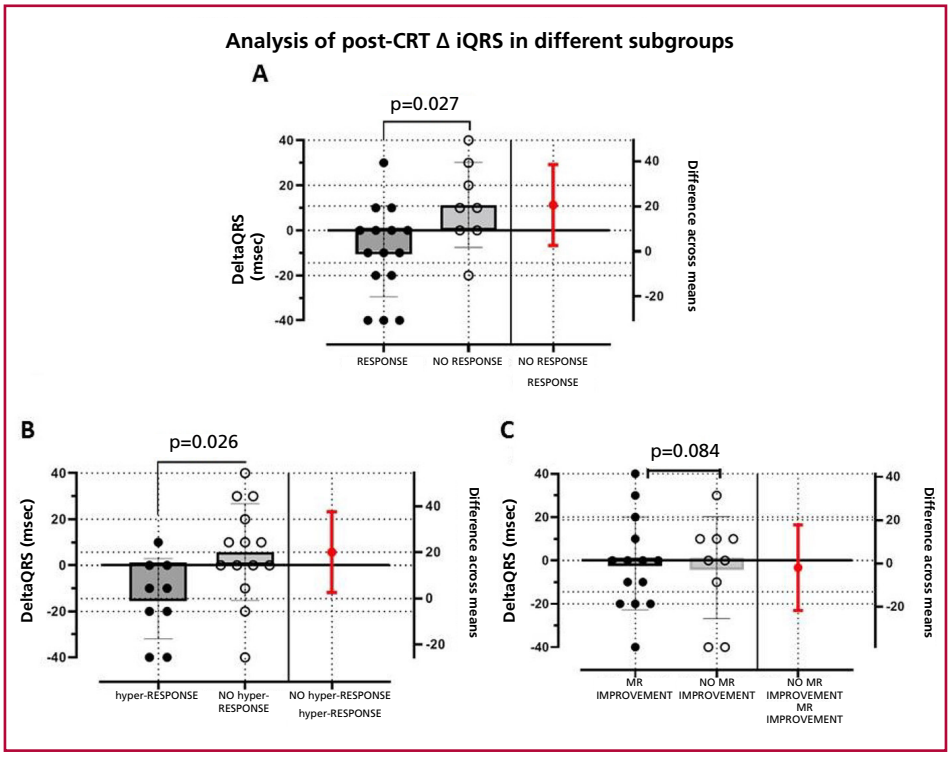

Fig. 4. ΔiQRS charts are shown by subgroups. A: Clinical-structural response to CRT (p=0.027); B: Hyper-responders; C: Mitral regurgitation improvement.
CRT: cardiac resynchronization therapy

Subgroup analysis

There was a trend in iQRS duration variation after the CRT in the female subgroup, though it lacked statistical significance (p=0.056, Figure 3B). Changes in the duration of iQRS were not higher in those with a baseline QRS of ≥150 msec (p=0.65, Figure 3C). Upon analysis of the subgroup of women with an initial QRS ≥150 msec prior to CRT, significant reduction of the iQRS was observed (p=0.0195, Figure 3D).

The change in pre- and post-CRT iQRS duration was unrelated to the non-ischemic etiology (p=0.72) or to age (p=0.78).

The ΔiQRS was -9.3±20.7 msec among clinical-structural "responders," and 11.25±18.9 msec among non-responders (p=0.027). This difference was slightly larger among "hyper-responders," with a ΔiQRS of -14.44±17.40 msec (p=0.026). There was no significant association of ΔiQRS with MR improvement (p=0.84). (Figure 4)

DISCUSSION

To the best of our knowledge, this is the first study to describe reverse electrical remodeling in patients under local and regional CRT.

After CRT, the duration of iQRS was reduced at least 10 msec in nine of the patients, though this lacked statistical significance. In observational studies like ours, QRS reduction was significant and generally associated with increased LVEF. (21) Subgroup analysis shows that ΔiQRS is related to clinical-structural response, more markedly in patients having a "hyper-response" to CRT. Despite sample size limitations, our findings contribute to the hypothesis that a shorter QRS leads to an improved intraventricular conduction system, and therefore, reverse LV remodeling. Further investigation is required to assess this hypothesis.

We showed a tendency towards stronger electrical remodeling in women with a wider baseline QRS. This is consistent with traditional response definitions. (1, 31-33)

Mechanisms resulting in reverse electrical remodeling are not fully known. It might be said that improvements in the size of chambers favor faster conduction upon myocardium contraction. It has also been suggested that this may happen as a result of full or partial recovery of the specialized conduction system itself. (22, 33,34) Another possible CRT-related effect is reduced cardiac fibrosis. (35) The underlying question also involves pathophysiological complete LBBB mechanisms and their multiple physiological and anatomical variants, an electrocardiographic pattern that may lead to completely interrupted or delayed conduction across the left bundle branch, which might result in right bundle branch overexpression. (36)

The cutoff point used to define electrical remodeling is even less consistent. Sebag et al. prospectively enrolled 85 patients with CRT indication, and evaluated clinical, echocardiographic, and electrocardiographic variables before and 12 months after the CRT. They found 19 and 18 msec cutoff points, with a sensitivity and specificity of 86/60% and 84/60%, respectively, to associate ΔiQRS with the clinical and echocardiographic response, respectively. Following a multivariate analysis, ΔiQRS ≥20 msec was an independent predictor of the echocardiographic response. (26)

We showed a tendency towards a reduced native QRS relative to improved MR, reaching no significance. The study by Karaca et al. found that reverse electrical remodeling is associated with improved MR and geometry of the mitral valve anatomy. (34) According to them, in addition to secondary improvement thanks to the cited ventricular remodeling, reversed papillary muscles dyssynchrony may lead to a

major CRT-related benefit, and both clinical and functional enhancement.

Future prospective investigations are required to assess the clinical, structural and electrical response in several specific subpopulations of patients undergoing CRT, in an attempt to better understand the pathophysiology of its effects. We consider this becomes more relevant and that it will merit new studies to know if the reverse electric remodeling is similar or more accentuated in the era of stimulationof the specific conduction system. (37, 38)

Conflicts of interest

None declared.

(See authors conflicts of interest forms in the website/ Supplementary material)

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ORIGINAL ARTICLE

Multisystem Inflammatory Syndrome in Children: The Importance of Early Evaluation of Laboratory Parameters

Síndrome inflamatorio multisistémico en pediatría: importancia de la evaluación inicial de los parámetros de laboratorio

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ABSTRACT

Background: Multisystem inflammatory syndrome in children (MIS-C) is an uncommon condition associated with COVID-19 with a wide spectrum of presentations, ranging from Kawasaki-like disease to multisystem involvement with shock. The association between the laboratory characteristics and unfavorable outcome has been described, but the cut-off points associated with higher risk have not yet been defined.
Objective: The aim of this study was to describe and analyze the characteristics of patients with MIS-C and their associations with the laboratory findings.
Methods: We conducted an analytical and retrospective study of pediatric patients hospitalized between May 2020 and June 2021 with diagnosis of MIS-C in Hospital General de Niños Dr. Ricardo Gutiérrez (HNRG). The cohort was made up of 23 patients, 17 female (53.13%) and 15 male (46.87%); mean age was 7.67 years (range 0.5-14.91). Ten patients (31.25%) presented shock.
Clinical and echocardiographic data and values of high-sensitive troponin I, N-terminal pro–B-type natriuretic peptide (NT-proBNP), platelets and lymphocytes at the time of diagnosis were obtained and compared between those with shock during evolution (group 1) and those without shock (group 2).
Results: There was a significant difference in baseline elevated NT-proBNP values between both groups (p = 0.008), but not in troponin levels and lymphocyte and platelet counts. Of the 13 patients who required inotropic agents, 58% had baseline lymphopenia (p = 0.006 vs those who did not require inotropic drugs).
Conclusions: Although mortality due to MIS-C is low, cardiac involvement and hemodynamic impairment may be common. The availability of a commonly used laboratory tool for patient categorization could help to mitigate risks and obtain early referral to specialized centers.

Key words: Systemic Inflammatory Response Syndrome - COVID-19/Complications - Natriuretic Peptide, Brain - Lymphopenia - Thrombocytopenia - Child- Child, Preschool

RESUMEN

Introducción: El síndrome inflamatorio multisistémico en pediatría (SIM-C) es una infrecuente entidad asociada a COVID-19 con un amplio espectro de presentación: desde un cuadro similar a la enfermedad de Kawasaki a una afectación multisistémica con shock. Se han descripto asociaciones entre valores de laboratorio y mala evolución, pero no existen puntos de corte que predigan la misma.
Objetivo: El objetivo de este estudio fue describir y analizar las características de los pacientes con SIM-C y las relaciones de estas con los hallazgos de laboratorio.
Material y métodos: Se realizó un estudio analítico y retrospectivo de niños internados con diagnóstico de SIM-C entre mayo 2020 y junio 2021 en el HNRG. Se estudiaron 32 pacientes, 17 femeninas (53,13%) y 15 masculinos (46,87%), edad promedio de 7,67 años (rango 0,5-14,91). Diez de los pacientes (31,25%) presentaron shock. Se obtuvieron datos clínicos, ecocardiográficos y valores de troponina I ultrasensible, NT-proBNP, plaquetas y linfocitos al momento del diagnóstico; y se analizaron comparativamente entre quienes presentaron shock durante la evolución (Grupo 1) y quienes no (Grupo 2).
Resultados: La diferencia en un valor inicial de NT-proBNP elevado fue estadísticamente significativa entre ambos grupos (p=0,008), en tanto que la troponina y el recuento de linfocitos y plaquetas, no. De los 13 pacientes que requirieron inotrópicos, el 58% presentó linfopenia inicialmente (p=0,006 vs aquellos que no los necesitaron)
Conclusiones: Si bien la mortalidad debido al SIM-C es baja, la afectación cardiovascular y el compromiso hemodinámico en los pacientes que presentaron este síndrome puede ser frecuente. Poder contar con una herramienta de laboratorio amplia¬mente difundida para la categorización de pacientes podría ayudar a mitigar riesgos y obtener una derivación temprana a centros especializados.

Palabras claves: Síndrome de Respuesta Inflamatoria Sistémica - COVID-19/Complicaciones - Péptido Natriurético Encefálico - Linfopenia - Trombocitopenia - Niño - Preescolar

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INTRODUCTION

Since the SARS-CoV-2 infection emerged in December 2019, multiple presentations and associated syndromes have been described. Multisystem inflammatory syndrome in children (MIS-C or PIMS) is one of the most aggressive presentations. This rare complication usually occurs between 2 to 6 weeks after the onset of SARS-CoV-2 infection.

Initially, severe pediatric cases were rare, and SARS-CoV-2 did not severely affect the pediatric population. Then, isolated cases of incomplete or atypical Kawasaki-like disease and toxic shock syndrome temporally associated with SARS-CoV-2 infection began to be reported. (1,2)

Nowadays, MIS-C has a wide spectrum of presentations, ranging from a Kawasaki-like syndrome to multisystem involvement with shock. The incidence of Kawasaki-like disease is 3.7 to 30 times higher than the usual incidence of typical cases. (2,3) Cardiac involvement in MIS-C is greater than that of typical Kawasaki's disease, (4) ranging from 30% to 80%, (2,5-7) and accounts for the highest morbidity and mortality rates.

The association between the laboratory characteristics and unfavorable outcome (8,9) has been described, but the cut-off points associated with higher risk have not yet been defined.

The primary objective of the study was to describe the clinical presentation and compare baseline laboratory parameters between patients with diagnosis of MIS-C with shock and without shock in a pediatric referral center in the Autonomous City of Buenos Aires. The secondary objective was to analyze the difference in positive troponin and N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels, and to establish cut-off points for these parameters.

METHODS

We conducted an analytical and retrospective study of patients hospitalized between May 2020 and June 2021 with diagnosis of MIS-C in Hospital General de Niños Dr. Ricardo Gutiérrez (HNRG). A total of 32 patients were admitted during that period.

Multisystem inflammatory syndrome in children was considered following the definition of the National Ministry of Health (https://www.argentina.gob.ar/salud/coronavirus-COVID-19/casos-pediatria):

- Patients between 0–19 years of age with fever ≥ 3 days and documented SARS-CoV-2 infection; with ≥2 of the following:

1. Cutaneous rash or non-purulent conjunctivitis or signs of mucocutaneous involvement (mouth, hands or feet).
2. Hypotension or shock.
3. Signs of myocardial dysfunction, pericarditis, valvulitis or coronary artery anomalies (including echocardiographic findings or elevated troponins and NT-proBNP).
4. Evidence of coagulopathy: elevated prothrombin time (PT), elevated partial thromboplastin time (PTT), elevated d-dimer.
5. Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)

- AND elevated markers of inflammation: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or procalcitonin and no other obvious cause of inflammation.

The clinical, cardiological and laboratory data of each patient were retrieved from the medical records (MR). The patients were classified in two groups: group 1 (with shock) and group 2 (without shock). Shock was defined as hypotension (blood pressure < 2 SD below the 50th percentile for sex, height and age, Argentine Society of Pediatrics) refractory to fluid resuscitation, and requirement of pressor drugs documented in the MR.

The laboratory parameters analyzed were high-sensitive troponin I (VIDAS® High-sensitive troponin I assay- BioMerieux), NT-proBNP (VIDAS® NT-proBNP2- BioMerieux), platelets and lymphocytes at the time of diagnosis. The cut-off points reported by the reference laboratory were used to determine whether these values were abnormal: troponin I >19 ng/L; lymphopenia: < 1000 lymphocytes/mm3; thrombocytopenia: platelet count < 150 000/mm3 and NT proBNP > 300 pg/mL.

These parameters were considered because, according to the literature, troponin is a marker of cardiac injury, thrombocytopenia has a high positive predictive value for cardiac involvement, NT proBNP showed correlation with cardiac dysfunction and severe lymphopenia has a high association with shock. (8-10)

At the same time, complementary cardiological tests, as electrocardiogram (ECG) and echocardiography, were performed to evaluate parameters of cardiac involvement during the disease. To define cardiac involvement, we used a synthesis of the definitions provided by Pignatelli (5) and Valverde (7): *presence of any arrhythmia, premature atrial or ventricular contractions, sustained or nonsustained atrial or ventricular tachycardias, atrioventricular (AV) block of any degree, ventricular repolarization changes; reduced left ventricular systolic function (measured by any method); left ventricular (LV) dilation > +2 z score values; valvular regurgitation; any type of pericardial effusion; dilation of coronary arteries; or elevated cardiac enzymes (CK-MB, troponin)*. Sinus tachycardia was not included as sign of organ injury because this symptom is nonspecific in patients with fever.

Fractional shortening (FS) was used to determine left ventricular systolic function and measured in M-mode echocardiography in a circumferential section of the left ventricle at the level of the papillary muscles using left ventricular diastolic dimension (LVDD) and left ventricular systolic dimension (LVSD) as reference: (LVDD-LVSD)/LVDD x 100. A reduction in FS below 30% was considered systolic dysfunction.

Statistical analysis

Firstly, we made a descriptive analysis of the population included and studied the differences between group 1 and group 2. Qualitative variables are presented as absolute value and percentage and were compared with the chi-square test or Fisher's exact test. Quantitative variables are presented as mean and standard deviation and are compared with the t-test. Then, we compared the clinical and mean laboratory parameters between both groups and reported the differences. Finally, ROC curves were constructed to analyze the discrimination ability of troponin and NT-proBNP between both groups, and cut-off values were established. All the statistical calculations were performed using SPSS Statistic 25.0 software package (IBM, Chicago, IL).

Ethical considerations

As this was an observational and retrospective study, we did not perform any intervention on the patients that did not comply with clinical practice standards and consensus statements corresponding to the disease. The study was conducted following the Law 3301 of the city of Buenos Aires, the recommendations of the Declaration of Helsinki and the Guidelines for Good Clinical Practice. The data are encrypted to protect patients' confidentiality (Law 25 326).

RESULTS

A total of 32 patients with diagnosis of MIS-C were analyzed; 15 were male (46.9%) and 17 were female (53.1%). Mean age on presentation was 7.67 years (range 0.5-14.91 years). Cardiac diseases and anomalies of the kidney and urinary tract were the most common comorbidities (Table 1). Most patients had positive serological test for SARS-CoV-2 (28 patients of 32); of the remaining 4, 2 had a previously documented infection and the other 2 had positive epidemiological linkage for COVID-19.

Group 1 was made up of 10 patients (31.2%) and group 2 of 22 (68.8%) Baseline NT proBNP value was not obtained in 3 patients (all in group 2) and baseline lymphocyte and platelet counts were not recorded in 1 patient in group 1. Mean age in group 1 was 6.2 years, ranging from 2.41 to 10.16 years, and 8.33 years in group 2, with a wider range of 0.5 to 14.91 years. Almost 70% of patients in both groups came from the Province of Buenos Aires. There were no significant differences in the baseline characteristics of each group in terms of age, sex, place of residence and comorbidities. (Table 1)

Congenital heart defects were the most common comorbidities (levo transposition of the great arteries, atrial septal defect, repaired ventricular septal defect without residual shunt, and mitral valve dysplasia without dysfunction), and history of anomalies of the kidney and urinary tract (rapidly progressive glomerulonephritis, grade 3 vesicoureteral reflux, chronic kidney disease and a patient with one kidney and myelomeningocele).

After obtaining the clinical, echocardiographic and laboratory data, the mean results in each group were compared (Table 2, Figure 1). Mean length of hospital stay was 11.6 days, significantly longer in patients with shock requiring admission to the pediatric intensive care unit (PICU): 17 days vs. 9.2 days ($p < 0.001$). Twp patients in group 2 had prolonged hospitalization due to social issues. A total of 13 children required inotropic agents (due to shock or myocardial dysfunction without shock).

The incidence of cardiac involvement was 84.4% (27 patients), all with at least one abnormal parameter. The most common abnormalities were elevation of high-sensitive troponin I above the laboratory reference values (21 patients, 77%), mitral or aortic valvular regurgitation of any kind in 19 patients (70%), repolarization abnormalities in the electrocardiogram (13 patients, 48%) and systolic dysfunction (8 patients, 29.6%). Coronary artery dilations occurred in 4 patients (12.5%), 3 in group 1 and 1 in group 2 ($p=0.009$). Other disorders included first- or second-degree AV block and incomplete right bundle branch block; all these findings recovered after appropriate treatment was initiated. Ventricular function measured by FS was reduced in group 1: 31.7 ± 1.97 vs. 39.2 ± 2.15% ($p = 0.027$). Pericardial effusion documented by echocardiography was significantly more common in patients with shock (80% vs. 22.7%; $p = 0.001$)

Thrombocytopenia (platelet count < 150 000/mm3) on admission was present in 30% (3/10) of patients with shock, while in group 2 the incidence was 13% (3/22), $p = 0.138$. Lymphopenia (lymphocyte count < 1000/mm3) was present in 4 patients in group 1 (40%) and in 4 in the control group (18%), with no statistically significant differences ($p = 0.14$). Among those requiring any inotropic agent, lymphopenia was present in 7 (58.3%) of the 12 patients with baseline lymphocyte count available, while among the 19 patients who did not require inotropic drugs, only 1 (5.2%) had lymphopenia upon diagnosis (p =

Table 1. Demographic characteristics and comorbidities

Baseline characteristics	Group 1 (patients with shock)	Group 2 (patients without shock)	p value
Age	6.2 ± 0.77 years	8.33 ± 0.99 years	0.20
Female sex	50%	54%	0.80
Place of residence (PBA)	70%	68%	0.92
Comorbidities	2/10 patients: 1 with one kidney. myelomeningocele with ventriculoperitoneal shunt and 1 levo transposition of great arteries	6/22 patients: 1 VSD repaired; 1 malnourished with ASD; 1 chronic kidney disease; 1 rapidly progressive glomerulonephritis; 1 mitral valve dysplasia; 1 grade 4 vesicoureteral reflux.	0.66

ASD: atrial septal defect. PBA: Province of Buenos Aires. VSD: ventricular septal defect.

Table 2. Clinical, echocardiographic, and laboratory data in patients with and without shock

	Group 1 (patients with shock)	Group 2 (patients without shock)	p value
Number of patients	10	22	–
Length of hospital stay	17 ± 2.2 days	9.2 ± 1.5 days	< 0.001
Cardiac involvement	9 (90%)	18 (81%)	0.551
Left-sided valve regurgitation	8 (80%)	11 (50%)	0.108
2.<t0/>First or second-degree AV block.	1 (10%)	3 (13.6%)	0.772
Repolarization abnormalities †.	4 (40%)	9 (40%)	0.964
Pericardial effusion	8 (80%)	5 (22.7%)	0.001
Coronary artery dilation	3 (30%)	1 (4.5%)	0.009
FS (%)	31.7 ± 1.97	39.2 ± 2.15	0.027
Troponin I (ng/L)	643.7 ± 478.7	171.3 ± 70.8	0.188
NT-proBNP (pg/mL)	19 770 ± 9024	7332. ± 5109.3	0.008
Platelets (n/mm^3)	166 333 ± 27 079	219 590 ± 19 129	0.154
Lymphocytes (n/mm^3)	2853 ± 1220	1893 ± 259	0.766

† repolarization abnormalities: T wave flattening, T wave inversion, ST-segment elevation. FS: fractional shortening.

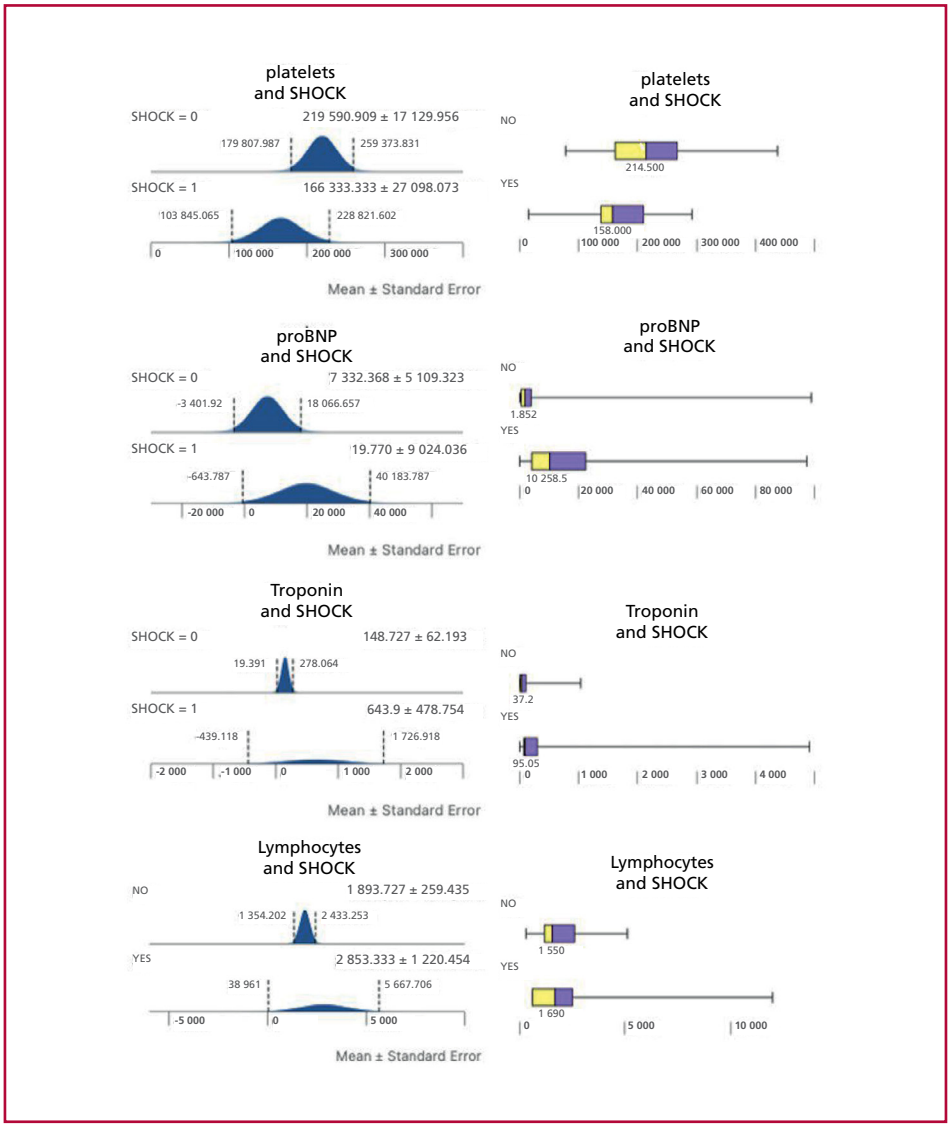

Fig. 1. The left of each row shows the distribution of a determined value (platelets, proBNP, high-sensitive troponin I and lymphocytes) expressed as mean and standard error according to the presence (1 or YES) or absence (0 or NO) of shock. The right side shows the distribution chart for each value expressed as median and the dispersion of values also according to the presence (1 or YES) or absence (0 or NO) of shock.

0.006). The specificity of lymphopenia for the use of inotropic drugs was 95%, with a positive predictive value of 88%. There were no differences in the absolute value of platelets and lymphocytes between both groups.

High-sensitive troponin I was elevated (> 19 ng/L) in 21/32 patients (65.6%), 80% (8/10) in group 1 and 59% (13/22) in group 2. Mean troponin value was higher in group 1, but this difference was not statistically significant (p = 0.188). The best cut-off value of troponin I defined by the ROC curve was 50 ng/L, and when we used this value as a dichotomous variable (positive-negative), the positivity rate was 80% in group 1 vs. 31.8% in group 2 (p = 0.01).

With the cut-off point of NT-proBNP established by the reference laboratory (high if > 300 pg/mL), a baseline positivity rate of 90% (9/10) was observed in patients with shock, and of 89% (17/19 tested) in the control group. Mean NT-proBNP levels were significantly higher in patients with shock (19 770 vs. 7332 pg/mL, p = 0.008).

The analysis of the ROC curve demonstrated that the best cut-off value of NT-proBNP to predict shock was 3900 pg./mL. This cut-off value and the adjusted cut-off value of high-sensitive troponin I (50 ng/L) were used in combination. These variables were dichotomized (both values positive vs. any other combination) and analyzed. The combination had a negative predictive value (NPV) of 86% for shock.

DISCUSSION

We described 32 patients meeting criteria for MIS-C. The characteristics of the population in terms of age on presentation and distribution by sex are similar to those described in other series, (6-8,11-13) with a slight predominance of female patients. Patients in group 1 were younger. While 31% presented shock during disease progression, 40% required use of any inotropic agent.

Cardiac involvement did not differ from other publications and was about 84%. While the incidence of coronary artery dilation reported by international publications was 8-24%, the incidence in our series was 12.5%. (4,5,8,11,14,15) Pericardial effusion was present in 40% of patients, with significant differences between group 1 and group 2.

The main difference between the studies by Valverde and Pignatelli in the definition of cardiac involvement lies in the classification of valvular regurgitation; Pignatelli's criteria are more restrictive, as they only include moderate or severe regurgitation. We believe that trivial, mild or moderate left-sided valve regurgitations should be considered as markers of organ injury despite having healed after treatment, even though this criterion increases the total number of patients with cardiac involvement.

Although mortality associated with this disease has been reported, there were no deaths in our series. (5)

Pignatelli found that elevated troponin values and thrombocytopenia had high sensitivity and negative predictive value for requirement of PICU stay. In our series, patients with the highest mean troponin and NT-proBNP values and the lowest platelet count had an unfavorable course with shock, although the only statistically significant value was that of NT-proBNP. After adjusting for ROC curves, elevated troponin levels were also associated with shock.

When analyzing laboratory data in relation with the use of inotropic agents, the results are similar to those of the international literature (described in patients requiring PICU): high-sensitive troponin I (p = 0.029), NT-proBNP (p = 0.002), and lymphopenia (p < 0.001), showed a statistically significant difference between patients who required inotropic agents and those who did not.

According to our experience, we consider that the role of pediatric cardiologists is still essential when considering the best therapy for each patient. The possible cardiac involvement implies routine collection of samples for laboratory tests and performing an ECG and echocardiogram on hospital admission.

The strength of this study lies in the collection of most of the data searched, since there were few missing values in the context of the health emergency due to the pandemic. The general characteristics of the population were not significantly different from those of the populations reported in other studies. The statistically significant data obtained can be associated with an adverse clinical course in patients with MIS-C.

The number of patients and the retrospective design constitute the main weakness of this study. While not all centers have availability of measuring troponin or NT-proBNP, blood differential and platelet count are widely available.

CONCLUSION

Multisystem inflammatory syndrome in children may affect any organ. In our study we observed a high incidence of cardiac involvement and significant differences in coronary artery dilation and pericardial effusion between those with and without shock; therefore, we consider that the initial evaluation by pediatric cardiologists is essential for the management of patients. The presence of lymphopenia or elevated NT-proBNP and troponin values should be considered for the initial therapeutic approach in both peripheral centers and referral hospitals.

Conflict of Interests

No conflicts of Interest or financing concerning the study have been declared.

(See authors' conflict of interests forms on the web/Additional material.)

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None

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ORIGINAL ARTICLE

A Preliminary Study of the Phenotype-Genotype Correlation in Cardiomyopathies in Patients Referred to a Tertiary Healthcare Center in the Suburbs of Buenos Aires

Estudio preliminar de correlación fenotipo-genotipo en miocardiopatías de pacientes derivados a un centro de alta complejidad del conurbano bonaerense

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ABSTRACT

Background: Cardiomyopathies are defined as a disorder of the myocardium in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension (HT), valvular heart disease and congenital heart disease. These diseases are relatively common and a major cause of morbidity and mortality worldwide.
Although genetic testing is recommended for family screening, lack of solid data on specific genotype-phenotype associations has reduced its impact on clinical management.
Objectives: This study aims to analyze the frequency of mutations in a population of patients with cardiomyopathy referred to a tertiary healthcare center and to analyze the genotype-phenotype correlation of the identified mutations.
Methods: We prospectively included 102 patients with suspected familial hypertrophic cardiomyopathy (HCM), 70 of which were index cases, from an ambispective cohort of patients with cardiomyopathies treated in a tertiary healthcare public hospital in the province of Buenos Aires, from January 2012 to August 30, 2022.
Results: Of 102 patients, 83 were considered affected. Of these, 31 were HCM and 52 were phenocopies, with no difference in prognosis. A genetic study was carried out in 77 patients, of whom 57 presented recognizable mutations, in 80% of the cases coinciding with a Mayo Score ≥3. Twenty-eight variants of uncertain significance were detected.
Conclusions: It was confirmed that molecular testing guided by the Mayo Score provided high probability of detecting mutations. Molecular testing proved to be important due to the phenotypic and genotypic overlap in cardiomyopathies. Understanding the causative genetic variant, nowadays, does not affect the clinical management of most HCM patients, but is helpful in a small group of genes with treatment options.

Key words: Cardiomyopathies - Cardiomyopathy Hypertrophic/genetics - Sarcomeres - Genetic Association Studies - Genetic Testing

RESUMEN

Introducción: Las miocardiopatías se definen como un trastorno del miocardio en el que el músculo cardíaco es estructural y funcionalmente anormal, en ausencia de enfermedad arterial coronaria, hipertensión arterial (HTA), enfermedad valvular y enfermedad cardíaca congénita. Estas enfermedades son relativamente frecuentes, y suponen una importante causa de morbimortalidad a nivel global.
Aunque el estudio genético se recomienda para el cribado familiar, la falta de datos robustos sobre asociaciones genotipo-fenotipo específicas ha reducido su impacto en el manejo clínico.
Objetivos: El objetivo de este estudio es analizar la frecuencia de mutaciones en una población de pacientes con miocardiopatía derivados a un centro de alta complejidad y el análisis de la correlación genotipo-fenotipo en las mutaciones identificadas.
Material y métodos: Se estudiaron en forma prospectiva 102 pacientes con sospecha de miocardiopatía hipertrófica (MCH) familiar, de los cuales 70 constituían casos índices, de una cohorte ambispectiva de pacientes con miocardiopatías controladas en un hospital público de alta Complejidad de tercer nivel de atención de la provincia de Buenos Aires, desde enero 2012 al 30 agosto 2022.
Resultados: De 102 pacientes 83 fueron considerados afectados. De eelos, 31 eran MCH y 52 fenocopias, sin diferencia en el pronóstico. Se realizó estudio genético en 77 pacientes, de los cuales 57 presentaron mutaciones reconocibles, en el 80% de los casos coincidentes con un Score de Mayo ≥3. Se detectaron 28 variantes de significado incierto.
Conclusiones: Se comprobó que realizar estudio molecular guiado por el Score de Mayo permitió obtener un alto grado de probabilidad de detectar mutaciones. Se evidenció la importancia del estudio molecular debido a la existencia de solapamiento fenotípico y genotípico de las miocardiopatías. El conocimiento de la variante genética causal actualmente no afecta el manejo clínico de la mayoría de los pacientes con MCH, pero es de ayuda ante un pequeño grupo de genes que tienen opciones de tratamiento.

Palabras clave: Cardiomiopatías - Cardiomiopatía Hipertrófica - Sarcómeros - Estudio de Asociación Genética - Pruebas Genética

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INTRODUCTION

Cardiomyopathies are defined as a disorder of the myocardium in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension (HT), valvular heart disease and congenital heart disease. These diseases are relatively common and a major cause of morbidity and mortality worldwide. (1)

There are several classifications which are intended to differentiate some cardiomyopathies from others, although in many cases they are more confusing than helpful. (2,3)

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease affecting both sexes, caused by mutations of genes encoding sarcomere proteins, with an estimated prevalence of up to 1/200-500 people, often inherited, with a complex genetic and phenotypic expression and a natural history. (4-7)

Thousands of mutations in more than 50 genes have been described to be associated with HCM; however, the frequency of the mutations identified may vary in different studies, and data available are scarce. (4-7)

The mechanisms by which sarcomere variants result in the clinical phenotype have not yet been elucidated. Sarcomere genes trigger changes in the myocardium which lead to hypertrophy and fibrosis, a small and stiff ventricle with impaired systolic and diastolic function despite the preserved left ventricular ejection fraction (LVEF). Several features, such as abnormal intramural coronary arteries responsible for ischemia and mitral valve abnormalities, appear to have no direct association with the sarcomere variants. (4-7)

Patients lacking a pathogenic variant are believed to have non-Mendelian HCM and probably better prognosis than patients with sarcomere pathogenic mutations. Identifying the genetic basis of HCM creates opportunities to understand how the disease develops and how to disrupt its progression. (5)

Although genetic testing is recommended for family screening, lack of solid data on specific genotype-phenotype associations has reduced its impact on clinical management. (5)

This study aims to analyze the frequency of mutations in a population of patients with cardiomyopathy referred to a tertiary healthcare center and the genotype-phenotype correlation of the identified mutations.

METHODS

Study population

We prospectively included 102 patients with suspected familial HCM, 70 of which were index cases, from an ambispective cohort of patients with cardiomyopathies treated in a tertiary healthcare public hospital in the province of Buenos Aires from January 2012 to August 30, 2022.

The diagnosis of HCM was obtained according to the criteria of the WHO and the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases. (1)

The patients diagnosed with HCM were those presenting 1 major electrocardiographic (ECG) or transthoracic echocardiographic (TTE) criterion or 2 minor TTE criteria plus 1 minor ECG criterion, or 2 minor ECG criteria plus 1 minor TTE criterion. (7)

Patients diagnosed with cardiomyopathy were asked about relevant medical and family history considering three generations, underwent a physical examination, a genogram, an ECG, a TTE, a Holter ECG (in affected patients), an exercise stress test or a cardiopulmonary exercise test (in affected patients), a complete blood count with NT-proBNP and troponin counts (in affected patients).

Echocardiographic parameters

The studies were performed with an Epiq 7 CVx 3D echocardiograph (Philips Medical Systems) using an S5-1 transducer. Measurements of LVEF and diastolic function were obtained according to the recommendations of the American Society of Echocardiography. (8,9)

Values of LVEF <52% in men and <54% in women were considered depressed.

The Speckle-tracking analysis was performed according to current EACI/ASE consensus recommendations. (10) Cine loops from three standard LV apical views (four, two and three chambers) were recorded using grey-scale harmonic imaging at the highest possible frame rate (55-90 frames/s). The analysis of the recorded files was performed off-line by an experienced echocardiographer unblinded to the patient's diagnosis.

The 2D global longitudinal strain (GLS) was evaluated in 16 LV segments on average (Strain post-processing software: TOMTEC. Dynamic Heart Model). The operator manually adjusted the region of interest in segments that could not be correctly traced. Normal value of global GLS Philips: -21±2%.

Cardiac magnetic resonance (CMR)

A Philips Medical Systems Achieva X Series 3T machine was used. Anatomical images of the heart were obtained with dark-blood and bright-blood sequences. A functional study with triggered cine imaging was performed. Images were acquired by enhaced T1- and T2-weighted sequences, fat suppression, sequences with variable TE and tagging. First-pass (0.1 mmol/kg) and late images (late enhancement) sequences were obtained with gadolinium injection (total dose: 0.2 mmol/kg), which were then post-processed and assessed with Extended MR Space 2.6.3.3 software.

Mutational analysis

The Mayo HCM genotype predictor score (Mayo Score) was used to predict the diagnostic yield of genetic testing and guide the use of next generation sequencing (NGS) method. (11,12)

Molecular testing was performed on those with Mayo Score ≥3 (range -1 to 5) or relatives of patients with positive mutations. First-degree relatives underwent a physical examination, an ECG and a TTE to identify those who were affected. They were offered to undergo genetic testing.

The technical component of the confirmatory sequencing was performed by Invitae Corporation from saliva samples collected by oral swabbing. The classification of identified variants was carried out pursuant to the guidelines of the American College of Medical Genetics and Genomics. (13)

All patients signed an informed consent form, and the study was approved by the institution's ethics committee.

Study of the genotype-phenotype correlation

For the description of the phenotypic characteristics, the classical four phenotypes of Maron´s classification based on the location and degree of hypertrophy was used. (14)

To correlate phenotype (F) with genotype (G), the Lever's classification was used to evaluate the pretest probability based on the anatomical subtype. (15)

HCM was defined as obstructive when it had a significant intraventricular pressure gradient (≥30 mmHg) at rest, as latent obstructive when the gradient was evident following provocation maneuvers (Valsalva/standing/exercise) and as non-obstructive when the gradient was <30 mmHg.

The definitions are shown in the Appendix.

Cardiovascular events

Cardiovascular (CV) events were defined as the presence or absence of the following:

- Need for implantable cardioverter defibrillator (ICD) or pacemaker implantation.
- Sudden death
- Cardiovascular hospitalization
- Septal myectomy or alcohol septal ablation

The follow-up lasted 3 years following the diagnosis by means of outpatient clinic visits or telephone calls.

Statistical analysis

The statistical softwares Epi Info for PC version 7.2.4.0 and Statistix 7 were used.

Qualitative variables were described using numbers and percentages. Quantitative variables were described using mean and standard deviation or median and interquartile range (IQR), depending on normal or non-normal distribution, respectively.

For comparisons between groups, Student's t test was used for continuous variables with normal distribution, and non-parametric tests, such as Mann-Whitney U test for continuous variables with non-normal distribution and Chi-square test (χ^2) or Fisher's exact test for categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 102 patients were evaluated. The diagnostic flow diagram is shown in Figure 1.

The presence of a phenotype compatible with HCM was determined based on electrocardiographic and echocardiographic criteria. Patients were classified into two groups: "affected" (n= 83, 81.4%, 95% CI 72.4-88.4%) and "non-affected" (n=19, 18.6%, 95% CI 11.6-27.5%) (Table 1).

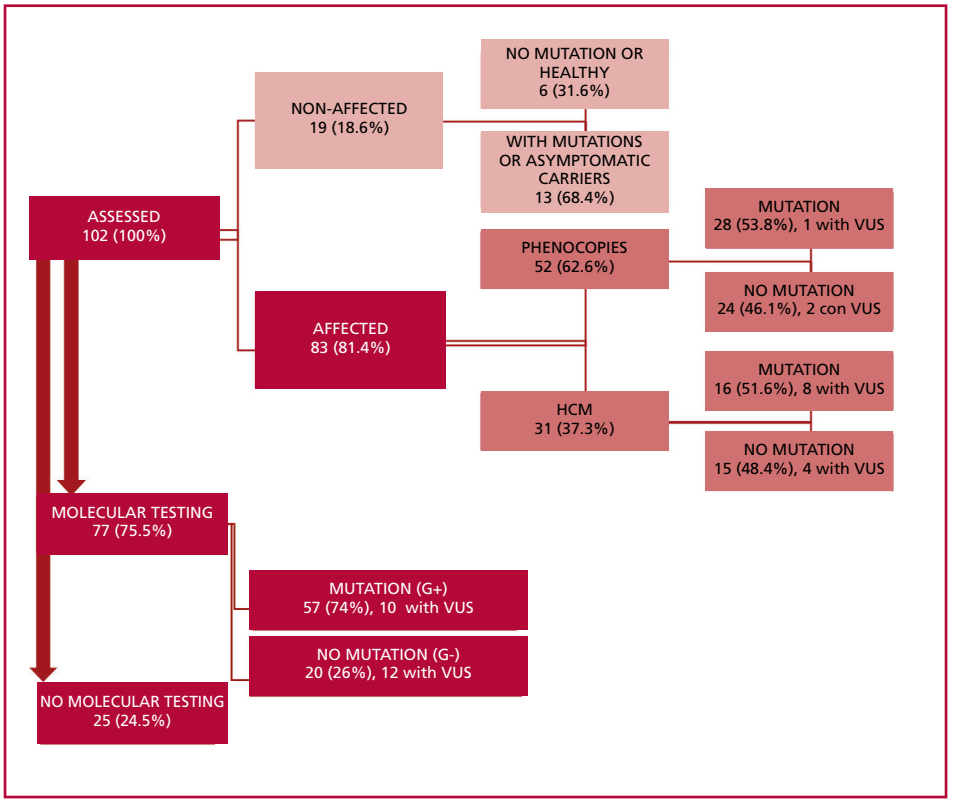
The mean age of symptom diagnosis was 39±16.7 years, with earlier onset in women (34.7±15 years; p<0.001), those with family history (36.7±16 years; p<0.001) and pathogenic TNNT2 variants.

Among those affected, the presence of symptoms was more frequent in men (n=43) than women (n=40), and dyspnea was the most frequent symptom.

ECG and TTE were performed in 100% of patients and CMR in 64 (62.7%). CMR was not performed in some patients due to claustrophobia, denial, or cardiac devices.

Table 1B shows the characteristics of the 83 "affected" patients. A total of 71% (n=59) had preserved

Fig. 1. Diagnostic flowchart



HCM: hypertrophic cardiomyopathy; VUS: variant of uncertain significance

Table 1. Studied population characteristics

A. Clinical and electrocardiographic parameters

Clinical parameters	Patients (N=102)	Affected (N=83)	Non-affected (n=19	p
Current age (years)	45 ± 16	47.6 ± 16	33.7 ± 10	<0.001
Age at diagnosis (years)	39 ± 16.7	41.9 ± 16	28.8 ± 14	0.001
Symptomatic	83 (97.6%)	81 (97.6%)	2 (10.5%)	<0.001
Female	56 (54.9%)	40 (48.2%)	16 (84.2%)	0.003
Family history	71 (69.6%)	52 (62.6%)	19 (100%)	<0.001
Weight (kg)	70 ± 18	70 ± 18	69 ± 18	0.9
Hypertension	24 (23.5%)	23 (27.7%)	1 (5.3%)	0.02
Systolic blood pressure (mmHg)	107 ± 16.8	105 ± 16	117 ± 14	0.005
Obesity	22 (21.5%)	18 (21.7%)	4 (21%)	0.6
Heart rate (beats/minute)	71.6 ± 15	71.3 ± 16	73.2 ± 8.3	0.62
Diabetes	8 (7.8%)	7 (8.4%)	1 (5.2%)	0.53
Dyslipidemia	10 (9.8%)	10 (12%)	0	0.11
Dyspnea NYHA Functional Classification ≥II	80 (78.4%)	80 (96.4%)	0	<0.001
Angina	38 (37.2%)	37 (44.5%)	1 (5.3%)	<0.001
Syncope	50 (49%)	48 (57.8%)	2 (10.5%)	< 0.001
Coronary artery disease	4 (3.9%)	4 (4.8%)	0	0.43
BNP value (pg./mL)		986 (122-3237)		
Troponin I		12.5 (4-59.5)		
Electrocardiogram				
Abnormal	88 (86.3%)	82 (98.8%)	6 (31.6%)	<0.001
Negative T waves	34 (33.3%)	33 (39.7%)	1 (5.3%)	< 0.001
LVH signs	54 (52.9%)	51 (61.4%)	3 (15.8%)	< 0.001
CLBBB	12 (11.7%)	12 (14.4%)	0	0.07
CRBBB	4 (3.9%)	4 (4.8%)	0	0.43
LAHB	23(22.5%)	23 (27.7%)	0	<0.001
QS pattern	52 (50.9%)	51 (61.4%)	1 (5.3%)	<0.001
Microvoltage	25 (24.5%)	25 (30.1%)	0	0.01
Sinus rhythm	92 (90.2%)	73 (87.9%)	19 (100%)	0.24
Paroxysmal or permanent AF	18 (17.6%)	18 (21.7%)	0	0.01
Ventricular tachycardia	12 (11.7%)	12 (14.4%)	0	0.07
Echocardiography				
Normal LVEF	78 (76.5%)	59 (71%)	19 (100%)	<0.001
LVEF (%)	62 (55-66)	60 (52-67)	66 (61-70)	0.03
LV hypertrophy	61 (59.8%)	61 (73.5%)	0	<0.001
LA dilatation	79 (77.4%)	76 (91.5%)	3 (15.8%)	<0.001
Diastolic dysfunction	82 (80.4%)	80 (96.4%)	2 (10.5%)	<0.001
E/e´ ratio	11.6 ± 4.6	12.7 ± 4.2	6.6 ± 1.7	<0.001
Average GLS (%)	17 (12-20)	16 (10-19)	22 (20-22)	<0.001

AF: atrial fibrillation; CLBBB: complete left bundle branch block; CRBBB: complete right bundle branch block; GLS: global longitudinal strain; LA: left atrium ; LAHB: left anterior hemiblock; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; LVSF: left ventricular systolic function; SBP: systolic blood pressure.

Qualitative variables are expressed as n (%) and quantitative variables as mean ± standard deviation or median and interquartile range.

LVEF compared to 100% in those non-affected; p<0.001. A total of 37.4% (n=31) had HCM and 62.6% (n=52) were phenocopies. In approximately half of the patients, the HCM was classified as obstructive (51.6%), and most of them (25) had preserved LVEF (80%). The mean GLS of patients with amyloidosis was 14% (9-17) and statistically different (p=0.01) from that of patients with HCM, and the LVEF/GLS index with a cut-off value ≥4.3±1.6 allowed to differentiate amyloidosis from HCM (p<0.001), as in previous studies. (16)

Identified mutations

A molecular testing was performed in 77 patients (75.5%), 57 of which (74%) had mutations (G+) and 20 (26%) did not have (G-). Forty-six (80.7%) out of the 57 G+ patients had a Mayo Score ≥3 , p<0.001 vs. G- patients. Twenty-two (28.5%) variants of uncertain significance (VUS) were detected (Figures 2 and 3). Two patients had double heterozygosity pathogenic variants and 10 had VUS in addition to the pathogenic mutation.

Among the 19 non-affected patients, disease could be ruled out in 6 (31.6%), while 13 (68.4%) were asymptomatic carriers. Disease penetrance ("affected patients with mutations") was 77.2% (44 out of the 57 G+ patients); 16 (36.4%) out of the 44 had HCM.

Genotype-phenotype correlation

According to Maron's classification, the most frequent forms of presentation were type 1 and type 3 (septal and anterolateral involvement, respectively), with

Table 1. Studied population characteristics

B. Echocardiographic and cardiac magnetic resonance characteristics of "affected" population

Echocardiographic parameters	Affected n=83	HCM n=31	Phenocopy n=52	p
Normal LVEF	59 (71%)	25 (80.6%)	34 (65.4%)	0.10
LVEF (%)	60 (52-67)	64 (55-69)	58 (44-66)	0.09
IVS thickness (mm)	13 (9-17)	18 (15-28)	12 (9.5-15)	<0.001
LVMI (g/m²)	109 (78-141)	138 (119-185)	109 (86-133)	0.001
LVOTO	16 (19.3%)	16 (51.6%)	0	<0.001
LA dilatation	76 (91.9%)	30 (96.7%)	46 (88.4%)	0.18
LAVI (ml/m²)	41 (32-56)	51.5 (43-82.5)	40 (36-55)	0.003
Diastolic dysfunction	80 (96.4%)	31 (100%)	49 (94.2%)	0.24
1- Prolonged relaxation	8 (9.6%)	0	8 (15.4%)	0.1
2- Pseudonormal	57 (67.5%)	24 (77.4%)	32 (61.5%)	0.1
3- Restrictive	11 (13.2%)	3 (9.7%)	8 (15.4%)	0.1
4- Monophasic	8 (9.6%)	4 (12.9%)	3 (5.7%)	0.1
E/e´ ratio	12.7 ± 4.2	13.4 ± 3.9	12.3 ± 4.4	0.27
Subaortic membrane	2 (2.4%)	2(6.4%)	0	0.13
Bicuspid AV	2 (2.4%)	2(6.4%)	0	0.13
Aortic regurgitation	16 (19.3%)	10 (32.2%)	6 (11.5%)	0.02
Mitral regurgitation	63 (76%)	26 (83.8%)	37 (71.1%)	0.19
Tricuspid regurgitation	68 (82%)	28 (90.3%)	40 (77%)	0.10
sPAP	27 (0-39)	33 (25-43)	30 (0-40)	0.15
Average GLS (%)	16 (10-19)	17 (13-19)	15 (9-17)	<0.001
LVEF/GLS	3.7 (3.3-4.7)	3.6 (3.2-4.2)	3.9 (3.4-5.3)	0.27
CARDIAC MAGNETIC RESONANCE	63 (75.9%)	25 (80.6%)	38 (73%)	0.43
	80 (62-96)	85 (62-122)	73 (62-90)	0.24
LVEF (%)	61 (44-71)	70 (59-73)	60 (40-67)	<0.001
RVEF (%)	72 (61-78)	71 (64-81)	72 (60-77)	0.34
LGE	44 (72.1%)	18 (85.7%)	26 (65%)	0.07

GLS: global longitudinal strain; HCM: hypertrophic cardiomyopathy; IVS: interventricular septum; LA: left atrium; LAVI: left atrial volume index; LGE: late gadolinium enhancement; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; LVOTO: left ventricular outflow tract obstruction; RVEF: right ventricular ejection fraction;;; sPAP: systolic pulmonary artery pressure

Qualitative variables are expressed as n (%) and quantitative variables as mean ± standard deviation or median and interquartile range.

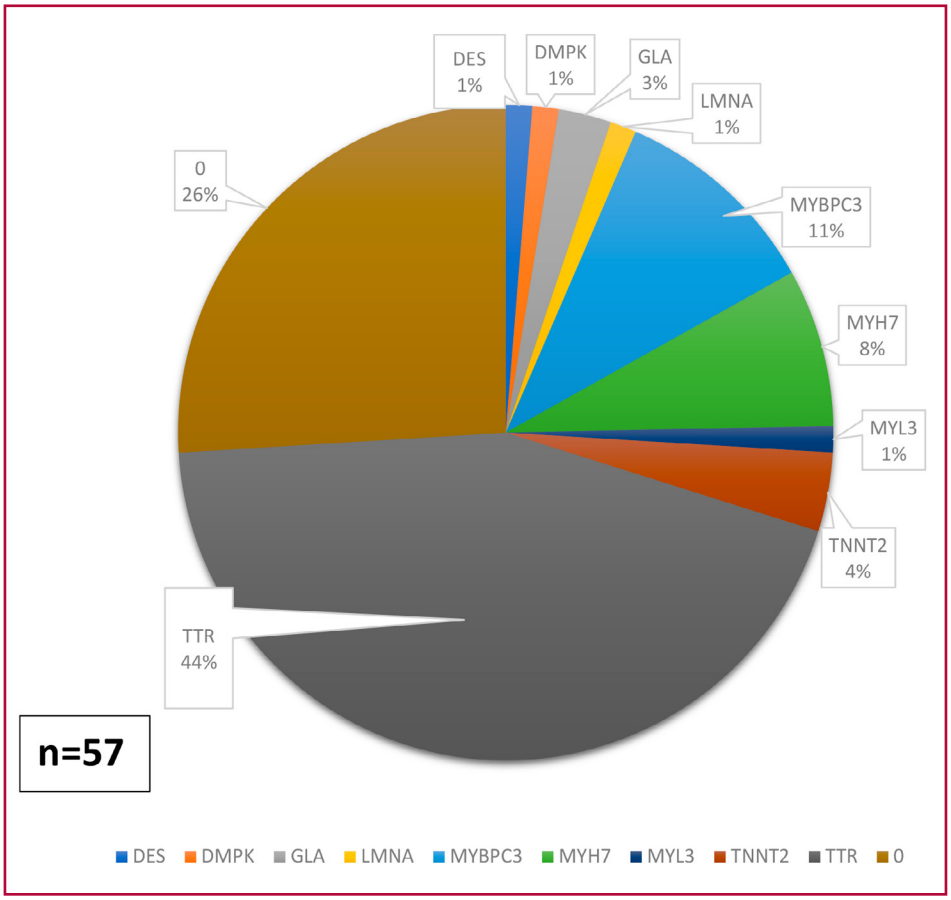


Fig. 2. Identified genetic variants

Gene	Variant	n
DES	c.1360C>T - p.(Arg454Trp)	1
DMPK	605377: 19q13.32	1
GLA	c.1244T>C p.(Leu415Pro)	1
LMNA	c.205del (p.Val69Trpfs*27)	1
MYBPC3	c.1808_1821del (p.Ile603Thrfs*6)	4
	c.3192dup (p.Lys1065Glnfs*12)	1
	c.1624G>C (p.Glu542Gln)	1
	c.1877 C>G (p.Ser626)	1
MYH7	c.485A>G (p.Tyr162Cys)	1
	c.788T>C (p.Ile263Thr)	1
	c.2770G>A (p.Glu924Lys)	2
	c.1208G>A (p.Arg403Gln)	3
MYL3	c.454G>A - p.(Glu152Lys)	1
TNNT2	c.812A>T (p.Asn271Ile)	2
	c.487_489del (p.Glu163del)	1
TTR	Thr60Ala	1
	Val50Met	27
	Val122Ile	6
N	TOTAL	57

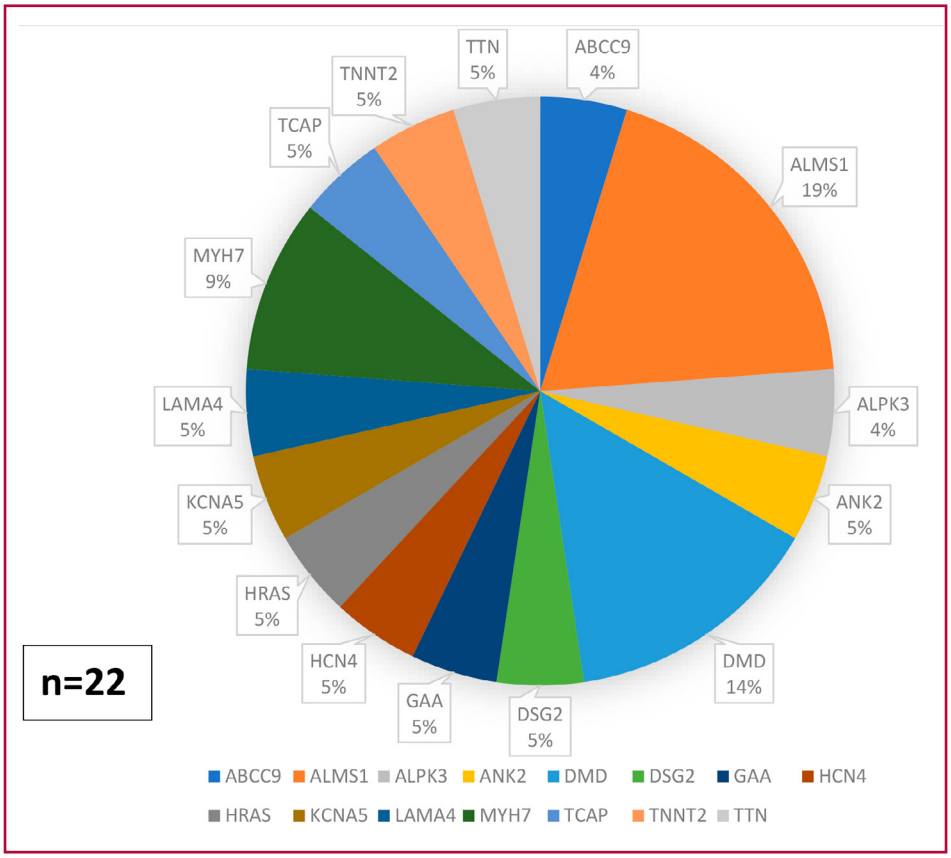


Fig. 3. Variants of uncertain significance (VUS)

more G+ detected in type 1 in HCM (9, 75%) and in type 3 in phenocopies (13, 68.4%), p<0.001.

Lever´s classification into 2 and 4 (reverse curvature septum and neutral septum, respectively) was useful when assessing the likelihood of having G+ based on the anatomical phenotype expressed by the patient (Table 2 and Figure 4).

There were no significant differences in CV events, medical treatments or procedures performed between G+ and G- patients (Figure 5).

The median time from the cardiomyopathy onset to the CV event was 2.4 years. Patients with phenocopies (29, 55.7%) experienced the same number of CV events as those with HCM (17, 54.8%), p=0.93. More cardiovascular deaths occurred in men (10, 21.7%) than women (3, 5.3%); p=0.01.

DISCUSSION

Cardiomyopathies are a heterogeneous group of myocardial diseases associated with mechanical and/or electrical dysfunction that usually present with inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes, frequently genetic. (1)

For genetics to become useful in clinical decision-making, it is necessary to get detailed information about the clinical and morphological characteristics of the carriers of different mutations, such as that provided by this study.

The Mayo Score enabled a better selection of probands and a cost-effective molecular testing, with a clear financial limitation.

Hypertrophic remodeling also occurs in disorders that clinically mimic HCM, including Fabry's disease (mutations in GLA) and transthyretin (TTR) amyloidosis, among others. More than 1500 mutations in at least 8 sarcomere protein genes have been reported in HCM, although most (80%) mutations alter the -myosin heavy chain (MYH7) or the myosin-binding protein C gene (MYBPC3). The diverse molecular origin combined with the background genomic variability and lifestyle differences between patients have made it difficult to definitively understand the genotypic and phenotypic relationships. (4)

Previous studies suggest that mutations in MYH7 cause about 15-30% of HCM cases. (17,18) In our patients, mutations in this gene are less frequent and appear in 7.5% of the studied families. This difference may be related to the degree of selection of the studied population.

Although we found no significant differences in age at diagnosis, the mean age in patients with G+ was 37.4±15 years compared to 42.4±18 years in patients with G-, similar to other series. (19,20)

An interesting finding in our study was the higher frequency of mutations identified in women (36, 63%; p=0.06), without statistical significance; but as HCM is usually inherited in an autosomal dominant manner, it would be expected that 50% of patients were female. However, in nearly all series described, the proportion of women is about 30-40%, and they are usually older at the time of diagnosis. In our study, it was the opposite (age at diagnosis in women: 37±15 years compared to 46.5±15 years in men; p<0.01). (17-20)

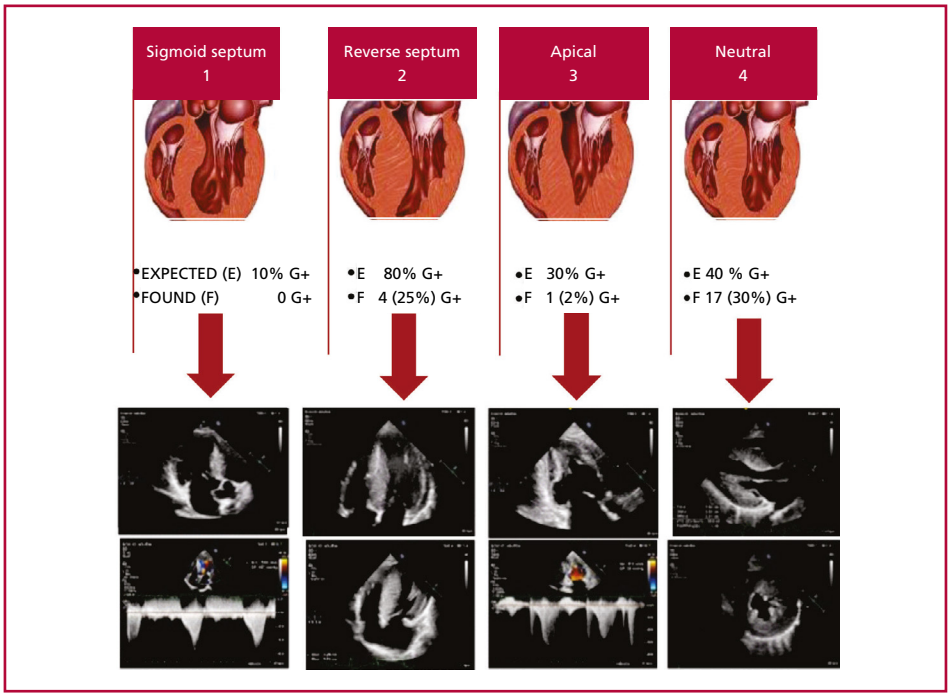
Women had a higher prevalence of the obstructive phe-

Table 1. Studied population characteristics

B. Echocardiographic and cardiac magnetic resonance characteristics of "affected" population

Phenotypes	Patients n=77	With mutations (G+) n=57	Without mutations (G-) n=20	p
Phenocopies	42 (54.5%)	33 (57.8%)	9 (45%)	0.46
HCM	21 (27.3%)	16 (28%)	5 (25%)	0.52
MARON Maron 1	17 (22%)	13 (23%)	4 (20%)	0.53
MARON Maron 2	6 (7.8%)	5 (8.7%)	1 (5%)	0.88
MARON Maron 3	21 (27.3%)	14 (24.6%)	7 (35%)	0.26
MARON Maron 4	6 (7.8%)	5 (8.7%)	1 (5%)	0.88
LEVER Lever 1	1 (1.3%)	0	1 (5%)	0.39
Lever 2	18 (23.4%)	14 (24.5%)	4 (20%)	0.46
Lever 3	1 (1.3%)	1 (1.75%)	0	0.39
Lever 4	25 (32.4%)	17 (29.8%)	8 (40%)	0.39
Age at diagnosis	38 (29-48)	36 (28-44)	45.5 (37.5-51.5)	0.05
Female	46 (59.7%)	36 (63.1%)	10 (50%)	0.44
HT	15 (19.5%)	8 (14%)	7 (35%)	0.04
CV events	33 (42.8%)	22 (38.6%)	11 (55%)	0.31
Heart transplant	1 (4%)	1 (2.2%)	0	0.44
Ventricular tachycardia	14 (13.8%)	5 (8.7%)	3 (15%)	0.34
ICD	16 (20.8%)	11 (19.3%)	5 (25%)	0.40
Pacemaker	12 (15.6%)	8 (14%)	4 (20%)	0.37
Myectomy	6 (7.8%)	4 (7%)	2 (10%)	0.49
CV hospitalization	26 (33.7%)	16 (28%)	10 (50%)	0.06
CV death	11 (14.3%)	8 (14%)	3 (15%)	0.58

CV: cardiovascular; HT: hypertension; ICD: implantable cardioverter defibrillator;



Color Doppler echocardiography image from own source. Figure modified from Lever HM, Karam RF, Currie PJ, Healy BP. Hypertrophic cardiomyopathy in the elderly. Distinctions from the Young based on cardiac shape. Circulation 1989; 79(3):580-9.

Fig. 4. Hypertrophy patterns according to the classification of Lever et al. Pretest probability for a positive genetic testing result according to the anatomical subtype.

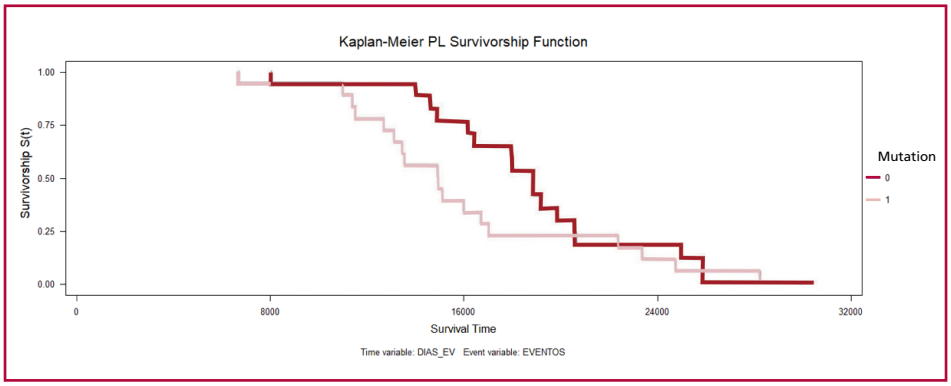


Fig. 5. Kaplan-Meier event-free survival curve. Patients with G+ have a mortality hazard ratio (HR) of 1.67 compared to those with G-, p=0.14.

notype, more severe symptoms requiring septal reduction therapy and one patient even underwent a transplant. However, there was higher mortality in men than women.

The identification of mutations in different families allows a more accurate assessment of the genotype-phenotype correlation and the proper interpretation of the pathogenic role of each mutation. Several findings from our study emphasize the importance of a complete family study. While in some mutations, such as TNNT2 c.812A>T (p.Asn271Ile), the phenotype is reproduced similarly in most carriers, in others, such as MYBPC3 c.1808_1821del (p.Ile603Thrfs*6), there is a remarkable difference between the phenotype of index cases (severe hypertrophy in young patients) and family carriers with mild hypertrophy, in spite of having similar or older ages. In these cases, it should be considered that additional genetic or environmental factors may account for the large difference in expression. Several studies have shown that HCM patients may have more than one mutation and that the presence of double mutations is associated with a more severe expression of the disease, as was the case in two patients in our study. (6, 17-20)

In clinical practice, HCM frequently coexists with hypertension (8 patients with HCM in our study, 25.8%) due to the high prevalence of both diseases. This hemodynamic situation inevitably modifies the HCM phenotype as well as exercise (athlete's heart) and other comorbidities (diabetes mellitus, obesity, and chronic renal failure). It is clear that it is often impossible to recognize the real cause or the main modifier of LV hypertrophy.

Nowadays, it is believed that wild-type (wt) TTR amyloidosis (wtTTR), which has been intensively studied and underdiagnosed, has relatively high prevalence. In our study we detected 46 patients with cardiac amyloidosis (45%), 60.7% of which were TTR amyloidosis variant (TTRv), 26% wtTTR, and the rest other types of amyloidosis. We believe that amyloidosis was a contributor to higher mortality in the "phenocopies" group in comparison with the HCM group.

Limitations

It was a single-center study conducted at a tertiary healthcare center in individuals who were likely to be more severely ill and symptomatic.

There may be some additional mutations that have not been identified because of the use of predetermined gene panels.

Samples are impossible to be collected in deceased subjects or in those who declined to participate in the study or were not notified to be an index case.

Conclusions

It was confirmed that molecular testing guided by the Mayo Score provided high probability of detecting mutations. Molecular testing proved to be important due to the phenotypic and genotypic overlap in cardiomyopathies.

Understanding the causative genetic variant does not currently affect the clinical management of most HCM patients, but it is helpful in a small group of genes, such as GAA, GLA, LAMP2, PRKAG2 and TTR, which are undoubtedly associated with diseases that mimic HCM and have different clinical profiles, inheritance patterns and treatment options; therefore, in those cases, molecular testing represents a significant step towards customized approaches.

Conflicts of interest

None declared.

(See authors conflicts of interest forms in the website/ Supplementary material)

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ANNEX 1

Diagnostic criteria for HCM. World Health Organization/International Society and Federation of Cardiology 1997

Major Criteria	Minor Criteria
Echocardiographic (TTE)	- Anterior septum or posterior wall ≥12 mm
- Anterior septum or posterior wall ≥13 mm	- Posterior septum or free wall ≥ 14 mm
- Posterior septum or free wall ≥ 15 mm	- Moderate SAM
- Severe SAM	- Redundant mitral valve leaflets
Electrocardiographic (ECG)	
- LVH + repolarization changes	- CLBBB or intraventricular conduction defect in left ventricular leads
- T wave inversion in leads I and aVL, V3-V6 (≥3 mm), or II, III, aVF (≥5 mm)	- Minor repolarization changes in left ventricular leads
- Abnormal Q waves (>40 ms or >25% R wave) in at least 2 leads from II, III, aVF, V1-4 or I aVL or V5-6	- Deep S waves in V2 (>25 mm)
Clinical	Unexplained syncope, dyspnea, or precordial pain
Diagnosis of hypertrophic cardiomyopathy	
1 major criterion, or	2 minor TTE criteria + 1 minor ECG criterion

SAM: systolic anterior motion; LVH: left ventricular hypertrophy; CLBBB: complete left bundle branch block.
Table modified from McKenna WJ, Spirito P, Desnos M, Dubourg O, Komajda M. Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families. Heart 1997;77(2):130-132Heart 1997;77(2):130-132

ESC Diagnostic Criteria for HCM 2008

Adults

Wall thickness ≥15 mm in one or more LV segments – determined by any imaging technique: echocardiography, cardiac magnetic resonance (CMR) or computed tomography (CT)– that may not be explained by loading conditions only.

Children

LV wall thickening with a Z score >2 standard deviations from the expected mean.

Family members

Unexplained presence of an increase in LV thickness ≥13 mm in one or more LV segments, determined by any imaging technique (echocardiography, CMR or CT).

From Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008;29(2):270-6

- **HCM phenocopies (imitations)**": Cardiac or systemic diseases capable of producing LVH that should not be labelled as HCM. The use of HCM to describe increased LV wall thickness associated with systemic disorders or secondary causes of LV hypertrophy (LVH) may be confusing. Systemic disorders include metabolic and multi-organ syndromes, such as the RASopathies (variants in several genes involved in RAS-MAPK signaling pathway), mitochondrial myopathies, glycogen/lysosomal storage diseases in children, and Fabry's cardiomyopathy, amyloidosis, sarcoidosis, hemochromatosis and Danon's cardiomyopathy in adults. In these diseases, although the magnitude and distribution of LV wall thickening may be similar to those of the isolated HCM caused by variants in sarcomere genes, the pathophysiological mechanisms responsible for the hypertrophy, the natural history and the treatment strategies are different.
- Echocardiographic criteria for amyloidosis were defined by the presence of LVH with a cut-off point ≥12 mm at the septal level or posterior wall according to the 10th International Symposium on Amyloidosis, 2004.

Clinical variable	Points
Age <45 years	1
Left ventricular wall thickness >20 mm	1
Family history of HCM	1
Family history of sudden cardiac death	1
Reverse septal curvature	1
Hypertension (HT)	-1

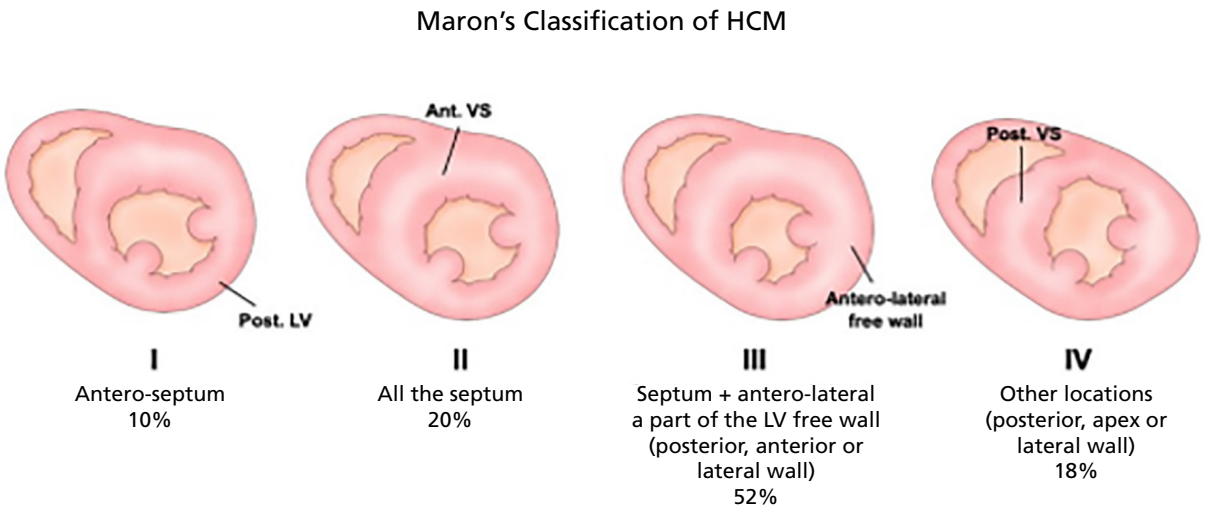
Mayo HCM Genotype Predictor Score

NGS results were compared to the Mayo Score (range -1 to 5) according to clinical and echocardiographic variables. One patient with a Mayo Score of 5 had a pathogenic mutation (100% yield). Patients with a Mayo Score of 4 had a pathogenic mutation in 71% of the cases. Patients with a Mayo score of 3 or 2 had a pathogenic mutation in 50% and 35% of the cases, respectively. The yield of genetic testing with a score of -1 to 1 was low (6-21%).

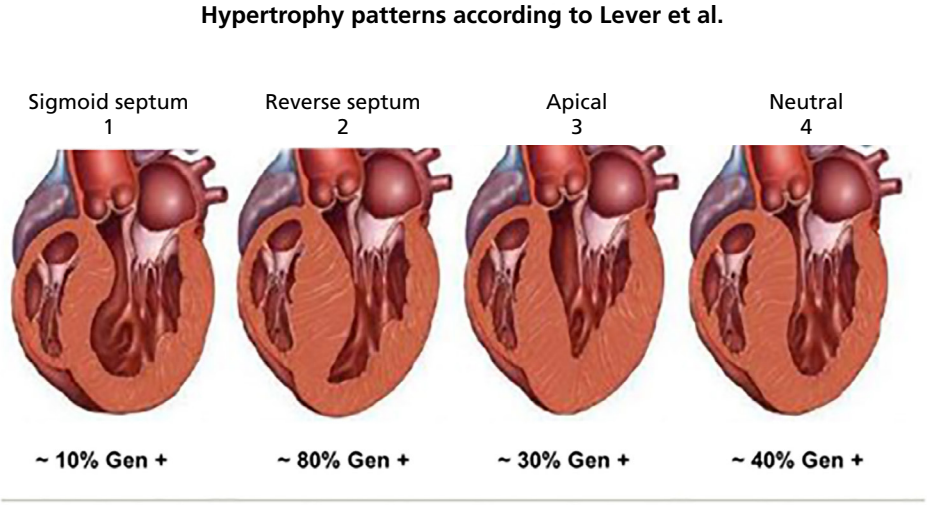
Bonaventura J, Norambuena P, Tomašov P, Jindrová D, Šedivá H, Macek M Jr, Veselka J. The utility of the Mayo Score for predicting the yield of genetic testing in patients with hypertrophic cardiomyopathy. Arch Med Sci. 2019 May;15(3):641-649. doi: 10.5114/aoms.2018.78767 Epub 2018 Oct 8. PMID: 31110529; PMCID: PMC6524174.

ANNEX 2

Maron et al.9 have established a morphological classification into four types: type I, septal-anterior hypertrophy; type II, septal-anterior and septal-posterior hypertrophy; type III, septal and anterolateral hypertrophy;



and type IV, septal-posterior and/or anterolateral hypertrophy.
Modified from Maron BJ. Hypertrophic cardiomyopathy. Curr Probl Cardiol. 1993 Nov;18(11):639-704. doi: 10.1016/0146-2806(93)90025-w. PMID: 7903919.

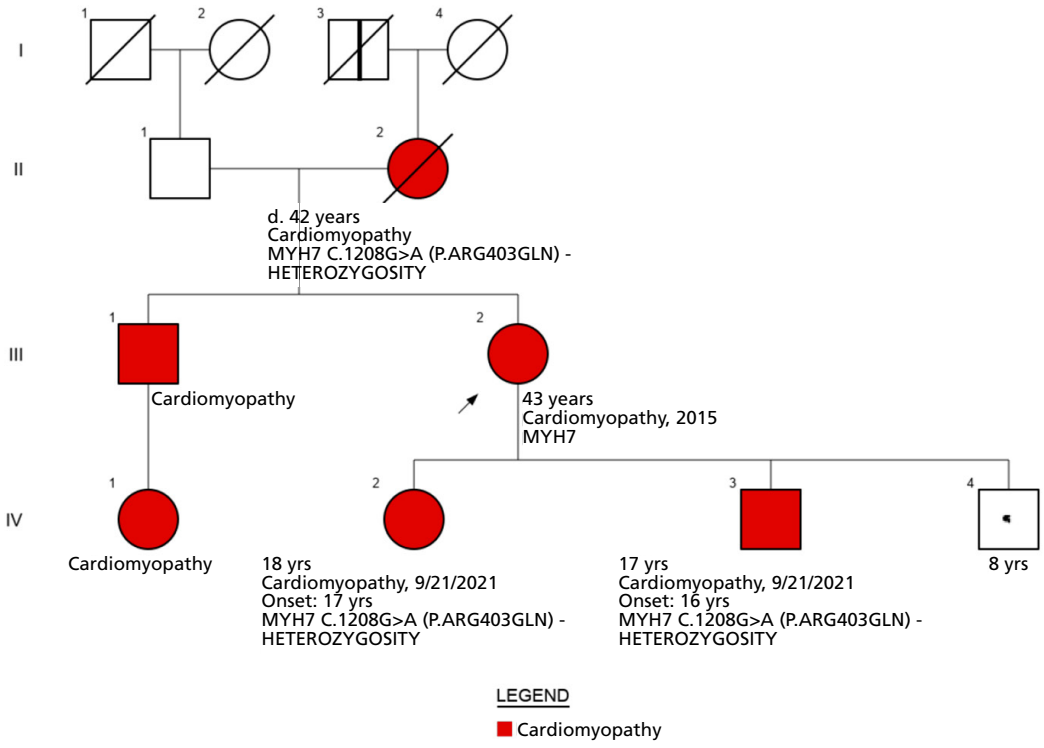


Pretest probability for a positive genetic testing result according to the anatomical subtype

This classification has proved to be very useful when considering the probability of presenting a positive genetic testing based on the anatomical phenotype expressed by the patient, the so-called echocardiography-guided genetic testing.
Modified from Lever HM, Karam RF, Currie PJ, Healy BP. Hypertrophic cardiomyopathy in the elderly. Distinctions from the young based on cardiac shape. Circulation 1989 Mar; 79(3):580-9.

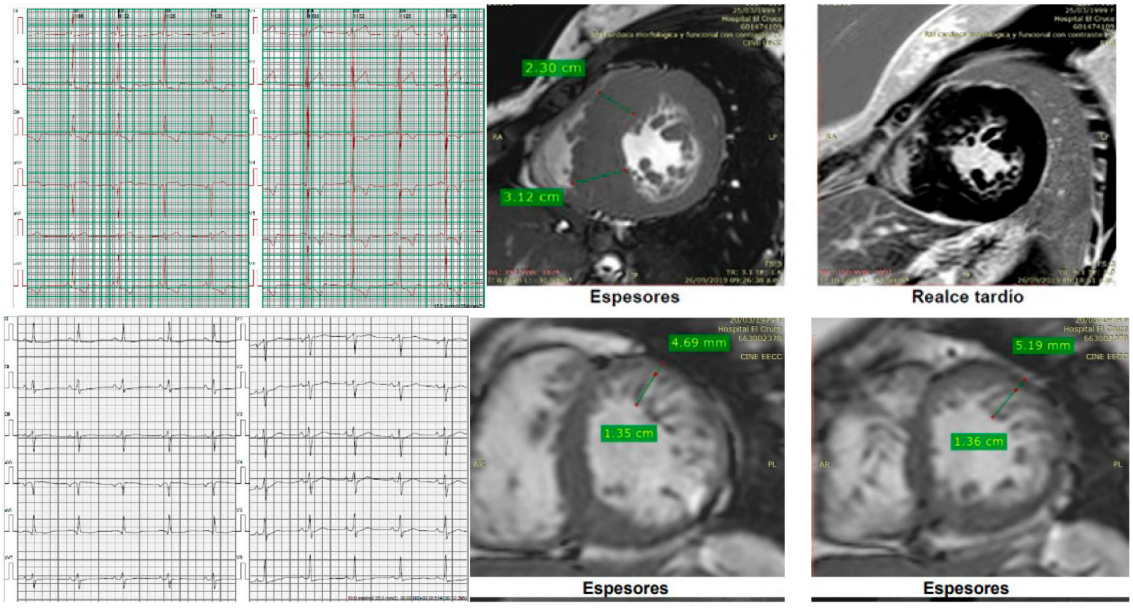
ANNEX 3

Examples of clinical cases:

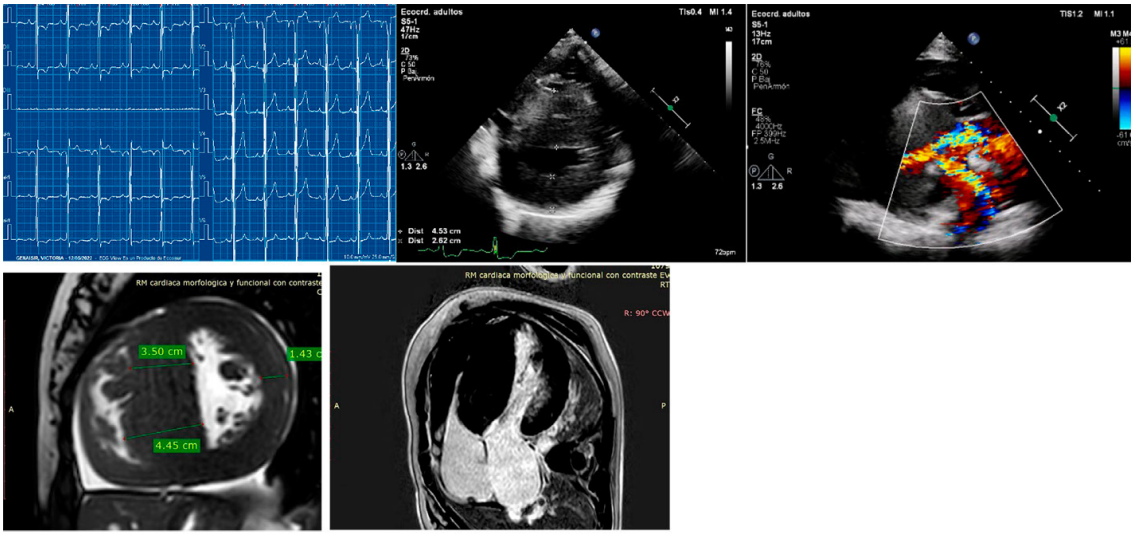


Example of a studied family's genogram. References: squares: men, circles: women, red: patients with clinical diagnosis of HCM, white: patients without HCM or mutation or not assessed, symbols with central black dot:

mutation carriers without HCM phenotype, symbols with vertical black bar: subjects with possible HCM by medical history (not proven). Diagonal line: deceased patients, arrow: index case.
The index case is a woman with severe hypertrophy diagnosed at the age of 37, with ICD implantation for syncopal sustained monomorphic ventricular tachycardia (VT) at the age of 47. The CMR showed non-compacted myocardium (NCM) and G+ (MYH7: c.1208G>A (p. Arg403Gln). Her 3 sons have G+, two of them with F+, pathological ECG (left ventricular hypertrophy and negative T waves on the anterolateral side). Above: ECG and CMR of one of her sons. Below: patient's ECG and CMR.



Case 2. A 17-year-old adolescent with effort angina (F+ and G-) and VUS+.



ANNEX 4

Mutational analysis

On the basis of the saliva samples collected by oral swabbing, the targeted regions of genomic DNA obtained from the sample are enriched by hybridization-based protocol and sequenced by Illumina technology. All targeted regions are sequenced with a depth ≥50x or supplemented with additional analyses.

Reads are aligned to a reference sequence (GRCh37) and sequence changes are identified and interpreted in the context of a single clinically relevant transcript, as listed below.

Enrichment and analysis focus on the coding sequence of the indicated transcripts, 20 bp of flanking intronic sequence and other specific genomic regions shown to be responsible for the disease at the time of assay design. Promoters, untranslated regions, and other non-coding regions are not otherwise interrogated. For some genes, only targeted loci (as indicated in the table above) are analyzed. Exonic deletions and duplications are called by an internal algorithm that determines the number of copies at each target by comparing the read depth for each target in the proband sequence with the mean read depth and the read depth distribution, obtained from a clinical dataset. Markers in the X and Y chromosomes are analyzed for quality control purposes and may detect deviations from the expected sex chromosome complement. Such deviations may be included in the report in accordance with internal guidelines. Confirmation of the presence and location of reportable variants is performed according to strict criteria established by Invitae (1400 16th Street, San Francisco, CA 94103, # 05D2040778), as necessary, using one of several validated orthogonal approaches (PubMed ID 30610921). The following analyses are performed if relevant to the request. For PMS2 exons 12-15, the reference genome was modified to force all sequence reads derived from PMS2 and the PMS2CL pseudogene to align to PMS2, and variant calling algorithms were modified to admit an expectation of 4 alleles. If a rare SNP or indel variant is identified by this method, both PMS2 and the PMS2CL pseudogene are amplified by long-range PCR and the location of the variant is determined by Pacific Biosciences (PacBio) SMRT sequencing of the relevant exon in both long-range amplicons. If a CNV is identified, MLPA or MLPA-seq is run to confirm the variant. If confirmed, both PMS2 and PMS2CL are amplified by long-range PCR, and PacBio sequences the identity of the fixed differences between PMS2 and PMS2CL from the long-range amplicon to disambiguate the location of the CNV.

The technical component of the confirmatory sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). For the C9orf72 repeat expansion testing, hexanucleotide repeat units are detected by repeat primed PCR (RP-PCR) with fluorescently labelled primers, followed by capillary electrophoresis. Interpretation reference ranges: benign (normal range): <25 repeat units, uncertain: 25-30 repeated units, pathogenic (full mutation): ≥31 repeated units. A second round of RP-PCR using a non-overlapping primer set is used to confirm the initial call in the case of suspected allele sizes of 22 or more repeats. For RNA analysis of the genes listed in the Genes Analyzed table, complementary DNA is synthesized by reverse transcription from RNA derived from a blood sample and enriched with specific gene sequences using capture hybridization. After high-throughput sequencing with Illumina technology, the output reads are aligned to a reference sequence (genome build GRCh37; custom derivative of the RefSeq transcriptome) to identify the locations of exon junctions through the detection of split reads. The relative usage of exon junctions in a test sample is quantitatively assessed and compared to the usage observed in control samples. Abnormal exonic junction usage is evaluated as evidence in the Sherloc variant interpretation framework. If an abnormal splicing pattern is predicted based on a DNA variant outside the typical reportable range, as described above, the presence of the variant is confirmed by targeted DNA sequencing. RNA sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2094793). Invitae Corporation (5 Technology Drive, Irvine CA 92618, #05D1052995) performs the technical component of fibroblast cell culture and gDNA extraction from a skin punch biopsy.

A PMID is a unique identifier that refers to a published scientific article. Search by PMID at http://www.ncbi.nlm.nih.gov/pubmed.

An rsID is a unique identifier that refers to a single genomic position and is used to associate population frequency information with sequence changes at that position. The reported population frequencies are derived from several public sites that aggregate data from large-scale population sequencing projects, including ExAC (http://exac.broadinstitute.org), gnomAD (http://gnomad.broadinstitute.org) and dbSNP (http://ncbi.nlm.nih.gov/SNP).

A MedGen ID is a unique identifier that refers to an article in MedGen, NCBI's centralized database of information on genetic disorders and phenotypes.

Search by MedGen ID at http://www.ncbi.nlm.nih.gov/medgen. An OMIM number is a unique identifier that refers to a complete entry in the Online Mendelian Inheritance of Man (OMIM). Search by OMIM number at http://omim.org/. Invitae uses information from individuals undergoing testing to inform variant interpretation. If "Invitae" is cited as a reference in the variant details, this may refer to the individual in this request and/or to historical internal observations.

REVIEW ARTICLE

Alcohol Impact on the Heart and Cardiovascular System - Hypertrophy, Remodeling and Strain Impairment - Contemporary State-of-the-Art

Efecto del alcohol sobre el corazón y el sistema cardiovascular: hipertrofia, remodelamiento y disminución del strain. Información actual

PIOTR HAMALA[1], KARINA WIERZBOWSKA-DRABIK[2]

ABSTRACT

The recent data show that chronic overuse of alcohol may lead to cardiovascular dysfunction, starting from traditionally judged as low ethanol doses, since the burden of arrhythmias, including atrial fibrillation, increases even in moderate alcohol consumers.
The other common mechanisms of the disadvantageous impact of ethanol are related to the development of hypertension and its direct aftermath, hypertrophy, fibrosis, and diastolic dysfunction.
Since the chance of the reversibility of cardiac remodeling depends on the early diagnosis of cardiac dysfunction, the wider application of novel and sensitive methods of myocardial function assessment, including longitudinal strain of the left and right ventricles, as well as the adapted protocols for stress echocardiography, should be recommended.

Keywords: Ethanol - Alcohol Cardiomyopathy - Toxic Cardiomyopathy

RESUMEN

Datos recientes muestran que el abuso crónico de alcohol puede conducir a disfunción cardiovascular, a partir de dosis de etanol tradicionalmente consideradas bajas, ya que la aparición de arritmias, incluyendo la fibrilación auricular, aumenta aún en consumidores de alcohol moderados.
Los otros mecanismos comunes del impacto negativo del etanol están relacionados con el desarrollo de hipertensión y su consecuencia directa, la hipertrofia, fibrosis y disfunción diastólica.
Debido a que la probabilidad de reversibilidad del remodelamiento cardíaco depende de un diagnóstico temprano de disfunción cardíaca, se debería recomendar la aplicación más amplia de métodos nuevos y más sensibles de evaluación de la función miocárdica, incluyendo el strain longitudinal ventricular izquierdo y derecho, así como de los protocolos adaptados a la ecocardiografía de estrés.

Palabras clave: Etanol - Miocardiopatía Alcohólica - Miocardiopatía Tóxica

INTRODUCTION

According to recent WHO reports, 40% of the world's adult population consumes alcohol. In Europe this value is even higher and reaches 60%. To alcohol related diseases belong cardiac arrhythmias, especially atrial fibrillation, alcohol cardiomyopathy, hypertension, stroke, epilepsy, depression, hepatic steatosis, and cirrhosis, as well as pancreatitis and numerous cancers. Alcohol related myocardial damage in early stages is believed to be reversible after cessation of drinking, but the predictors of reversibility are not well-defined. Similarly, the exact alcohol amount that can be recommended, while still remaining safe for health, changes according to different subjects, their sex, age, and general as well as cardiovascular status. Nevertheless, the knowledge in this field has been recently intensively widened with studies providing associations between clinical and laboratory data, consumed amount of alcohol, and novel echocardiographic parameters describing heart morphology and function. The present review shortly recalls the epidemiology and pathophysiology of alcohol overuse, as well as summarizes the current data concerning the impact of alcohol consumption on the cardiovascular

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system and heart function.

Epidemiology of alcohol consumption

According to the World Health Organization (WHO) report from 2018, approximately 2.4 billion people in the world drink alcohol, 43% of the world's adult population over 15 years old. (1) The highest alcohol consumption burden is reported in Europe and reaches 60% of the population. The second region with highest alcohol consumption is South and North America, in which it achieves 54%. In comparison, tobacco use is estimated in 1.33 billion persons (22%) in a worldwide scale. (2)

The world's alcohol consumption, presented as liters of pure ethanol per capita per year (APC - alcohol per capita, including persons older then >15 years), has been increasing since 2000. According to the cited WHO report, in 2000 APC reached 5.7 liters and it rose to 6.4 liters in 2016. Interestingly, simultaneously with the increase of the APC index, the number of alcohol drinkers decreased by about 683 million. (1) As far as the sex-difference in consumption is concerned, in Europe 69% of men and 50% of women drink alcohol, whereas in South and North America alcohol is consumed by 67% of men and 42% of women. (1)

The alcohol impact on health

Genetic factors may have an influence on the level of alcohol consumption as well as on ethanol tolerance. Holmes et al. investigated a group of 260 000 subjects to evaluate the impact of the rs 1229984 mutation in the gene encoding 1B alcohol dehydrogenase (ADH1B) on drinking behavior. The rs 1229984 mutation seems to be related to specific drinking behavior characterized by the tendency to consume lower alcohol volumes (17% lower compared with the group without this mutation). Since the mutation carriers were exposed to more severe symptoms connected with alcohol metabolism, by limiting the amount of consumed ethanol, they showed thereafter lower risk of alcohol related complications. In this study, the lower risk of ischemic heart disease was observed in the group with the mentioned mutation (Odds Ratio [OR] 0.90 and 95% Confidence Interval [95%CI] 0.84-0.96). (3)

Nevertheless, the beneficial effect of low to moderate alcohol consumption on the human body was also postulated. The beneficial effect was jointed with documented reduction of the onset of ischemic heart disease, stroke, and diabetes. (1) In a meta-analysis performer by Di Castelnuovo and co-authors, based on 209 418 patients, cardiovascular risk reduction was observed (relative ratio [RR] 0.68, 95%CI 0.59 – 0.77) in the group consuming 150 mL wine per day, compared with teetotalers. (4) The beneficial effect of wine and beer was connected with the presence of specific ingredients belonging to the polyphenols, as resveratrol, whose molecular effect is based on triggering signal tracks like Nrf2 (nuclear factor erythroid 2-related factor 2), NF-κB (nuclear fac-

ETHANOL

Acute damage:	Chronic damage:
Heart and blood vessels (atrial fibrillation, ventricular fibrillation)	**Heart and blood vessels** (cardiomyopathy, arterial hypertension)
Central Nervous System (epilepsy, alcohol abstinence syndrome)	**Central Nervous System** (Wernicki encephalopathy, Korsakov encephalopathy)
Liver (liver encephalopathy)	**Peripheral Nervous System** (alcoholic atrophy of the cerebellum, central pontine myelinolysis, alcoholic myopathy, alcoholic polyneuropathy),
Pancreas (acute pancreatitis)	**Digestive system: esophagus, stomach, duodenum, liver, pancreas** (esophageal varices, chronic gastritis, pancreatitis, cirrhosis, hepatocellular carcinoma, planoepithelial cancer)
Respiratory track (pneumonia)	**Respiratory track** (laryngeal cancer)
Mental disease (delirium tremens)	**Mental disorders** (psychosis, depression)
	Musculo- skeletal system (osteoporosis)
	Reproductive system (infertility, fetal alcohol syndrome)

Fig. 1. Target organs of alcohol toxic impact.

tor kappa-light-chain-enhancer of activated B cells), Sirt1 (NAD-dependent deacetylase sirtuin-1), AMPK (5'AMP-activated protein kinase), as well as the reduction of oxidative stress and apoptosis, which was observed in experimental studies. (5,6) In a meta-analysis including 1 902 605 participants, low alcohol doses (10 - 14 grams per day) induced 18% reduction of diabetes onset in women. (7) The postulated mechanism of this effect was the higher insulin sensitivity related to alcohol consumption. The variety of harmful alcohol impacts on the human body is presented in Figure 1. (1,8,9)

Alcohol metabolism

In the main pathway of alcohol metabolism two enzymes are engaged: alcohol dehydrogenase (ADH) and P450 2E1 cytochrome (CYP450). The intermediate product of this reaction is acetaldehyde, responsible for the toxic influence on the human body. Further, acetaldehyde is metabolized by acetaldehyde dehydrogenase and acetaldehyde oxidase to acetic acid, which enters the Krebs cycle. A certain amount of the acetaldehyde leaves the liver and is directed to peripheral tissues where it is metabolized to acetyl coenzyme A (acetyl – CoA) as well as to cholesterol, steroids, fatty acids, ketones and CO_2 (Figure 2). Alcohol metabolism starts in the gastric mucosa whose cells contain ADH. After absorption in the gastrointestinal system through the portal vein, alcohol goes to the hepatocytes where the main part of the metabolism is performed, since the hepatocytes' cytoplasm, mitochondria and microsomes contain the highest amounts of ADH and CYP450. (10) A variety of factors can modify the rate of alcohol metabolism. The afternoon body temperature increase, connected with the daily cycle, accelerates alcohol metabolism. Physical exercise has insignificant influence on alcohol metabolism acceleration, which is connected rather with body temperature elevation. Young age is a factor reducing the pace of alcohol metabolism due to lower expression of ADH and CYP450. The ADH Beta3 isoform characterizes higher efficiency of alcohol metabolism compared with other isoforms. Cederbaum and co-authors observed the higher prevalence of ADH Beta3 isoform among Afro-Americans (15%), and less frequent among Japanese, South Americans (except indigenous peoples) and Europeans. The ADH Beta3 isoform prevalence in this groups determines the rate of alcohol metabolism and the risk of alcohol related complications. (10) According to lower content of body water compared with men, women are more sensitive to alcohol toxic effects. Other factors having impact on alcohol metabolism are nutrition level, and exposition on other drugs like nicotine, cannabinoids, and cocaine. (11,12)

Alcohol consumption influence on the cardiovascular system

First studies

In 1861 Friedrich L. Goltz documented the relationship between heart hypertrophy and persistent alcohol overuse. Further, in 1873 Walter H. Walshe as the author of the medical textbook entitled "The Physical Diagnosis of Diseases of the Lungs" implemented the term "cirrhosis of the heart" to describe phenomena

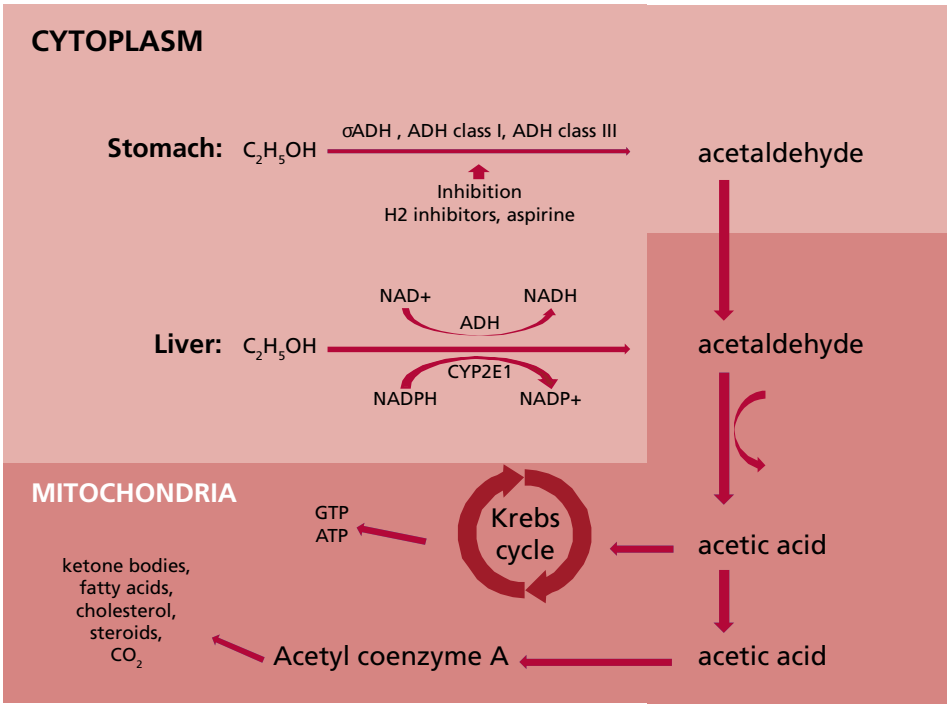

Fig. 2. Diagram illustrating alcohol metabolism in stomach and liver cells. σADH: alcohol dehydrogenase sigma isoform. ADH class I: alcohol dehydrogenase class one.ADH class III: alcohol dehydrogenase class three. ATP: adenosine triphosphate. CYP2E1: Cytochrome P450 2E1. ALDH2: mitochondrial aldehyde dehydrogenase 2/ acetaldehyde oxidase. C_2H_5OH: ethanol. CO2: carbon dioxide. GTP: Guanosine triphosphate. H2: histamine receptor type 2. NAD+: oxidized nicotinamide adenine dinucleotide. NADP+: oxidized nicotinamide adenine dinucleotide phosphate. NADH: reduced nicotinamide adenine dinucleotide. NADPH: reduced nicotinamide adenine dinucleotide phosphate

of fibrosis observed simultaneously in both the heart and the liver in patients with alcohol overuse history. (13,14) In 1884, in Munich, Otto von Bollinger described "beer heart" cases ("Bierherz") and linked this observation to a history of beer overuse, reaching up to 432 liters of beer per year. The "beer heart" in histopathology studies is characterized by hypotrophy, fibrosis, and steatosis. (15,16) At the end of the 19th century Graham Steell proved the relationship between heart failure and chronic high-dose alcohol consumption. (17) In 1969, in Quebec, a series of patients with cardiomyopathy related to beer drinking were observed. All mentioned cases were reported in a seven-month period. Interestingly, all patients consumed beer derived from the same origin, and ingredient analysis proved excess cobalt concentration (in this time, cobalt was applied as foam stabilizer in beer). (18) The authors postulated alcohol and cobalt as the etiology of cardiomyopathy in the above-mentioned cases.

Cardiotoxic alcohol dose

One of the first reports mentioning the relationship between alcohol dose and its cardiotoxic impact was published by Tadashi Koide and co-authors in 1974. The authors investigated the association between left ventricular enlargement in chest radiograms and the dose of consumed alcohol. The study showed that a pure ethanol dose ≥125 mL per day was related to the increase of the cardio-thoracic index (CTI) above 0.5. Higher CTI rates were observed in 33% of patients drinking ≥125 mL per day and in 4% of patients drinking from 75 to 125 mL, as well as in 2.9 % of patients drinking <75 mL. The authors did not mention time duration of consumption in this group of patients. (19) Other authors suggest that J or U – shaped curves can describe the relationship between the alcohol dose and the harmful cardiac effect. (20) For example, Ronksley et al., in a meta-analysis including 84 studies, revealed that drinking 15 - 30 grams of pure alcohol per day resulted in the decrease of cardiovascular mortality rate, with hazard ratio (HR) 0.66 (95%CI 0.59 – 0.75), and in the group drinking 2.5-14.9 grams per day, with HR 0.80 (95%CI 0.74 – 0.87). The decline in all-cause mortality was observed in the drinking group compared with teetotalers, with HR 0.87 (95%CI 0.83 - 0.92). In this study the negative alcohol impact (ascending J curve arm) was observed in groups drinking 30 - 60 grams per day (HR 1.15 [95% CI 0.98 – 1.35]). (21)

In the studies considering chronic alcohol consumption and its relationship with cardiac toxicity, the alcohol dose is usually expressed as the amount of alcohol and the time duration of alcoholism. In the literature, the authors postulate a dose of 80 grams of pure ethanol drank every day during 5 years as a toxic dose. (22-25) Other proposed cut-offs are 40 grams per day, or on average of 14 grams per day during a minimum of 10 years. (20,26)

Alcohol-induced hypertension

The relationship between alcohol consumption and blood pressure elevation can be temporary, and stop after alcohol drinking cessation. (27) The hypertensive alcohol effect seems to be independent of body mass index (BMI), tobacco use, physical activity and coexisting arterial hypertension history. (20) This effect is caused by a few mechanisms: the increased activity of the renin-angiotensin-aldosterone axis and sympathetic nervous system, increased cortisol secretion, changed insulin sensitivity, endothelial dysfunction and reduced nitric oxide production. (28) The modulation of the central nervous system activity after alcohol exposure is an important reason for blood pressure elevation. The alcohol vulnerable nervous tracks are the rostral ventrolateral medulla and intermediolateral nucleus, as well as the baroreceptor reflex, which passes through the nucleus solitarius, and causes a hypertensive reaction. (20) According to the European Cardiac Society guidelines for hypertension management, an alcohol dose above 14 alcohol units (AU) per week (one AU contains 10 grams of ethanol) for men and 8 AU per week for women is not recommended. (29) The rise of the consumed dose has a linear positive correlation with the risk of arterial hypertension development. (28) This relationship is sex independent, but in women can be observed from a dose of 2 AU per week. (30) In a meta-analysis performed by Roerecke and co-authors, mean reductions of 5 mmHg in systolic blood pressure and 4 mmHg in diastolic blood pressure were observed in patients who reduced the consumed dose from 6 AU per day to 0 AU. (31)

Dilated cardiomyopathy

The prevalence of dilated cardiomyopathy in the study performed by Fernández-Solá and co-authors was higher among patients consuming alcohol compared with the general population and reached 0.43% in males (mean pure alcohol amount consumed during lifetime 30 ± 7 kg/kg body mass during an average time of 29 ± 6 years), and 0.25% among women (mean pure alcohol amount consumed during lifetime 17 ± 7 kg/kg body mass during an average time of 23 ± 7 years), whereas in the general population dilated cardiomyopathy prevalence reaches 1:2500 individuals (0,4‰).. (32-34) In the western countries, alcohol overuse is the leading cause of non-ischemic cardiomyopathy. In the literature, the estimated rate of alcohol overuse among patients diagnosed with dilated cardiomyopathy ranges from 3.8% to 47%. (23,35) Factors as malnutrition, kwashiorkor, vitamins, electrolytes and microelement deficiencies (sodium, potassium, calcium, magnesium, phosphorus and selenium), as well as the exposition to other psychostimulants like cocaine, amphetamine and nicotine, increase the risk of alcoholic cardiomyopathy. (33,36)

There are no typical histopathological signs of alcoholic cardiomyopathy. Similar to other dilated

cardiomyopathy etiologies, myofibril atrophy, mitochondriopathy (the abnormal differentiation of the mitochondria in size and forms due to the chronic exposition to toxins including ethanol, and the presence of megamitochondria), cardiomyocyte necrosis and fibrosis are present. (11,14) Myocardial muscle exposition to alcohol in the extracellular matrix leads to the activation of fibroblasts and the excessive production of type I collagen. (37) Additionally, in fibroblasts exposed to alcohol, the pro-inflammatory signal tracks are activated (the MAPK protein kinase groups, the transcription factor STAT3 and the nuclear factor NF-B) causing the pro-inflammatory cytokine release from the fibroblast (IL-6, TNF-α, IL-1β, IL-33), and cardiomyocyte dysfunction. (37,38) This process leads also to lower expression of genes encoding contractile proteins, like Acta1, Actc1 (encoding actin) and Myh7 (encoding the myosin heavy chain alpha and myosin beta). Moreover, alcohol exerts also a direct influence on cardiomyocytes (mediated by TNF-α, without fibroblast as a mediator of the reaction), intensifying the processes leading to a decrease of muscle fiber contractility. (37)

Acetaldehyde is an alcohol metabolite. Like ethanol, acetaldehyde has a negative effect on the heart muscle, but the influence of its cardiotoxic properties is even stronger than that of alcohol. (33) Both molecules have direct impact on protein synthesis in the myocytes and lipid peroxidation, reduce the contractility of myofibrils, and increase oxidative stress. (33,39) In magnetic resonance imaging, Liu S et al. observed shorter native T1 values and greater extracellular volume in the myocardium (similarly to images observed in heart amyloidosis and sarcoidosis) of a group of patients consuming >28 grams of ethanol per day, during a minimum of 10 years, compared with a control group (including persons drinking <100 grams per month). Similar changes in magnetic resonance imaging are observed when the content of fat molecules in the cell is increased. (26) Matyas and al. observed heart steatosis in the mice exposed to ethanol compared with the control group receiving a calorie-adjusted diet but without ethanol exposure. (40)

In images recorded by positron emission tomography with carbon 11-labeled acetate, the decreased metabolic activity of the myocardium has been observed in chronic alcohol overusers (26 years on average) consuming high alcohol doses (167 grams of pure ethanol per day) compared with patients drinking for a similar period a lower amount of alcohol (50 grams per day), which suggests a decrease in mitochondrial function after chronic alcohol exposure. (26)

The threshold of myocardial vulnerability to alcohol varies from person to person and has not been clearly defined. The literature suggests that the sensitivity can be also determined by genes. It is estimated that the genetic background of susceptibility is present in 20% to 37% of dilated cardiomyopathy cases. Currently, the possible mutations related to alcohol cardiomyopathy occurrence are identified in over 50 genes, (41) the most common encoding proteins being titin, posterophyllin - 2, myosin - binding protein C, desmoplakin, ryanodine - 2 receptor, desmokolin - 2, desmoglein- 2 and SCN5A. (42) Ware and co-authors assessed the effect of the presence of genes related to the occurrence of dilated cardiomyopathy on cardiac function in patients consuming alcohol. The group consisted of 715 patients aged 55 ± 14 years and included 70% men. In the subgroup with the titin mutation (titin is the largest human protein, crucial for the molecular basis of diastolic function), drinking excessive amounts of alcohol (>21 AU/week in men or >14 AU/week in women) resulted in an 8.7% reduction of left ventricular ejection fraction, LVEF (95%CI 2.3% - 15.1%; p =0.007), compared with patients without this mutation. (43) The titin-encoding gene variants associated with the development of dilated cardiomyopathy were more prevalent in the alcoholic cardiomyopathy group compared with the control group. In the group of patients with alcoholic cardiomyopathy, a relationship between the amount of alcohol consumption and a decrease in LVEF was observed. This means that in sensitive individuals, alcohol can also be a trigger in the dilated cardiomyopathy development process. In addition, the finding of a greater prevalence of titin gene mutations in the group with alcoholic cardiomyopathy indicates the need for the active search of cardiomyopathy signs and symptoms among the relatives of patients with this diagnosis. (44)

The toxic effect of alcohol metabolites on the heart results in left and right ventricular muscle remodeling, atrium enlargement, and secondary mitral and tricuspid valve regurgitation. (11) Based on the literature, it is postulated that the diastolic dysfunction occurs first, followed by left ventricular wall hypertrophy comparable to that observed in arterial hypertension. Further, left ventricular systolic diameter (LVSD) and the left ventricular diastolic diameter (LVDD) increase is observed, which parallels LVEF reduction. (11,25,33,45,46)

Current available data suggest that chronic alcohol exposure also damages the right ventricle. (47) In a study of the cardiac effects of a single exposure to alcohol, Cameli and co-authors observed a group of 64 volunteers (mean age 25 ± 4 years, 29 women) before and 60 minutes after 0.5 gram per kg alcohol consumption, and compared it with a control group. TAPSE (tricuspid annulus plane excursion) was 22.1 ± 3.3 mm in the studied group vs. 24.0 ± 3.1 mm in controls, p = 0.003; and pulmonary artery systolic pressure (PASP) amounted to 23.7 ± 3.2 mmHg in the exposed group vs. 20.2 ± 4.9 mmHg in controls, p = 0.0002. (48)

This influence of alcohol on right ventricular hemodynamic function can be related to increased pulmonary artery resistance due to vasoconstriction

caused by leukotrienes released from leukocytes after alcohol exposure. (49)

Guzzo-Merello and co-authors postulated that the lack of β-blocker treatment, the occurrence of atrial fibrillation and the widening of the QRS complex are independent predictors of worse prognosis in alcoholic cardiomyopathy, with an increased incidence of cardiac death and heart transplantation. In patients who reduced their alcohol intake below 80 grams per day, the 59 - month risk of cardiac death or heart transplantation was reduced to a level comparable with that of the general population. (23) The lack of abstinence in patients with alcohol-related dilated cardiomyopathy resulted in very high mortality, reaching 50% within 4 years, which poses alcoholic cardiomyopathy near to patients with cancer diagnosis. (50) The pleiotropic effects of alcohol on the heart are schematically shown in Figure 3.

Since the key issue related to early diagnosis of alcohol related cardiomyopathy may be the usage of adequate diagnostic methods, it is worth mentioning the still underused potential of the adapted protocols of stress echocardiography in the early detection of diastolic dysfunction as well as pulmonary hypertension. (51) Vriz and co-authors performed exercise Doppler echocardiography in a group of 155 hypertensive patients and in 145 healthy subjects, and documented that TAPSE during exercise was lower in the hypertensive group, whereas PASP as well as its value indexed to the cardiac output achieved during exercise was higher. (52)

In a recently published analysis of our group, the median and interquartile range (IQR) of left ventricular mass index was 119 (91—155) g/m^2 in patients drinking alcohol (median 30 (12–51) AU per week) vs. 93 (75–110) g/m^2 in a control group (drinking up to 2 AU per week), p = 0.008; and the relative wall thickness in the alcohol group was 0.5 (0.4–0.6) vs. 0.4 (0.4–0.4) in controls, p = 0.001. In the same study, global longitudinal strain (GLS) and layer strains showed lower absolute values in alcohol overusers as compared to controls. All abnormal strain parameters were associated with a more frequent composite endpoint occurrence (higher clinical risk of death or cardiovascular hospitalization). The best absolute cut-off values for outcome prediction were: GLS <18%, layer endocardial strain <19%, and layer epicardial strain <15%. (53)

Alcohol related arrhythmias

Atrial fibrillation (AF) is the most common arrhythmia observed among alcohol abusers. Larsson and al. proved that during chronic alcohol exposure, an increase in consumption of one AU per day increases the risk of AF by 8%. (54) Most often, arrhythmias are observed as a consequence of a single high alcohol dose intake in a short time and numerous authors have mentioned this as “holiday heart syndrome”. This syndrome was first reported in 1978 by Ettinger et al. (55,56) Chronic alcohol consumption is positively associated with increasing risk of AF in the long-term follow-up. In the study performed by Larson and al. (12 years of follow-up), AF RR (95%CI) for 7-14 AU/week was 1.12 (1.02 – 1.23), and for >21 AU/week, 1.43 (1.25 – 1.65) compared with controls. (54) Arrhythmias are more often observed in patients diagnosed with cardiomyopathy than in those without structural abnormalities. Moreover, episodes of abstinence may be triggers of arrhythmia in chronically alcohol overusing patients, due to the increased adrenergic activity observed at the beginning of abstinence and the coexisting deficiencies of macro and micronutrients (sodium, potassium, magnesium, calcium, phosphorus, selenium) and vitamins (thiamine) associated with previous alcohol abuse. (33,57,58)

Cirrhotic Cardiomyopathy

The disorders observed in the hepato-cardiac syndrome may also contribute to the pathogenesis of alcoholic cardiomyopathy. (59) Systolic function is decreased both at rest and during stress, the impairment associated with a decrease in the activity of β1-receptors through a reduction in G protein expression in the cytosol, related to liver impairment. (59-61) In parallel, diastolic dysfunction is observed, associated with left ventricular hypertrophy, fibrosis, and endothelial dysfunction. (59,62) These factors lead to secondary higher heart rate and increased cardiac output, which result in a hyperkinetic cardiomyopathy. Diagnostic criteria of Cirrhotic Cardiomyopathy have been established in 2005 during the World Congress of Gastroenterology and are displayed in Table 1. (59,63)

Summary

The recent data show that chronic overuse of alcohol may lead to cardiovascular dysfunction, starting from traditionally judged as low ethanol doses, since the burden of arrhythmias, including atrial fibrillation, increases even in moderate alcohol consumers. The other common mechanisms of the disadvantageous impact of ethanol are related to the development of hypertension and its direct aftermath, hypertrophy, fibrosis, and diastolic dysfunction.

Since the chance of the reversibility of cardiac remodeling depends on the early diagnosis of cardiac dysfunction, the wider application of novel and sensitive methods of myocardial function assessment, including longitudinal strain of the left and right ventricles, as well as the adapted protocols for stress echocardiography, should be recommended.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

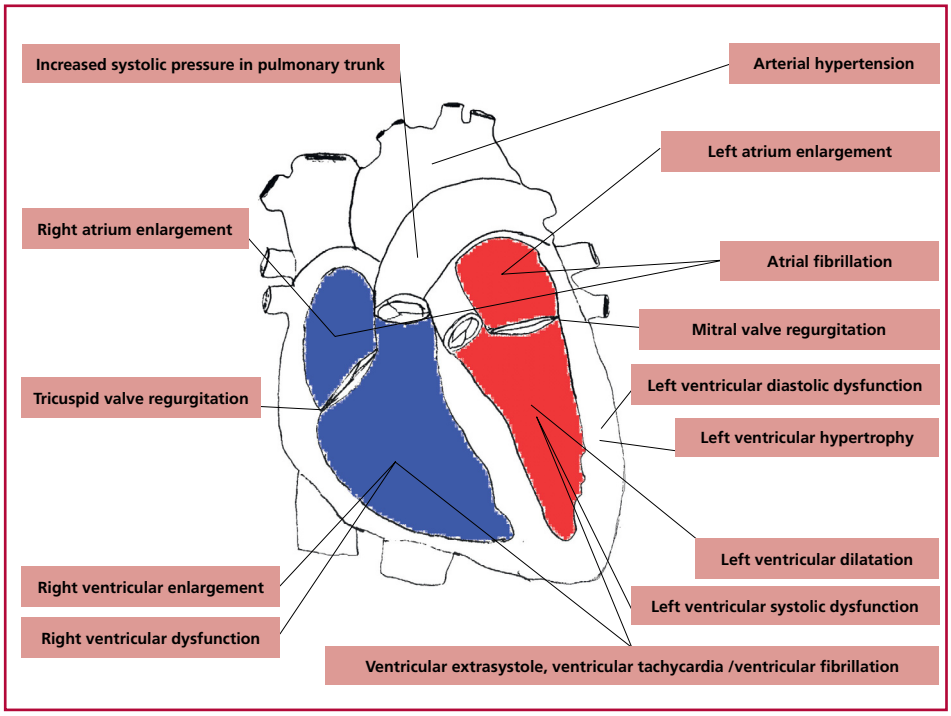

Fig. 1. D-dimer boxplot between patients undergoing computed tomography pulmonary angiography diagnosed with (1) or without (0) pulmonary embolism. a) pre-COVID-19 phase, b) COVID-19 phase

Table 1. Diagnostic criteria of Cirrhotic Cardiomyopathy – World Congress of Gastroenterology, Montreal 2005.

Definition: A cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease	
Systolic dysfunction (one with above)	- blunted increase in cardiac output with exercise, volume challenge or pharmacological stimuli (in ex. dobutamine) - resting LVEF <55%
Diastolic dysfunction (one with above)	- E/A ratio <1.0 (age - corrected) - Prolonged deceleration time (>200 msec) - Prolonged isovolumetric relaxation time (>80 msec) (14)
Supportive criterias	- inadequate chronotropic reaction to exercise, assessed during tilt-test as heart rate increases over 22% in patients in B Child's – Pugh's class and over 17% in patients in C Child's – Pugh's class (64) - prolongated QTc interval - enlarged left atrium - increased myocardial mass - increased BNP and pro-BNP levels - increased troponin I level

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SPECIAL ARTICLE

Dimensions of Truth in Cardiology Consultation

Las dimensiones de la verdad en la consulta cardiológica

CARLOS D. TAJER[1, MTSAC, FACC, FESC,]

The clinical practice of consultation requires an interpretation of the conditions reported by the patients, their diagnostic characterization, eventual therapeutic indications and an explanation of what can be expected and what should be done. My intention is to propose a reflection on the dimensions of truth in each of these steps of the consultation and to what extent each of them is guided by a solid scientific support that legitimizes our practice.

How close can we get to the truth about the real suffering of patients? I report a case. An 83-year-old female patient, whom I have been treating for many years for easily controlled high blood pressure, referred to me multiple recent symptoms: dyspnea on exertion, nocturnal palpitations, and frequent sighs.

- Do I have an enlarged heart? At my age there are many people who have enlarged hearts. With my age and all that happens to me, it seems to me that something is going to happen to me, I have little life left.

From a phrase from her husband present at the consultation, she hinted that he suffers from cognitive problems, an initial Alzheimer.

I examined her, initially ruling out cardiac problems that would explain her symptoms, and I was encouraged to say:

- I am not a psychoanalyst, but it seems to me that all these comments about an enlarged heart, the arrhythmias, the sighs, the fear of death, perhaps hide the desire to get sick and not have to suffer what you see as a nightmarish future.

Table. Dimensions and questions about the truth in the doctor's office

- About the real suffering of my patients
- About the disease that I can diagnose
- About the benefits that my treatments or recommendations will exert
- About what we communicate about the disease and the future scenario

- Don't think I haven´t thought about it, doctor.

The fear of death is a frequent reference in cardiology consultations. The book *Staring at the Sun* by Irvin Yalom, (1) a psychotherapist with experience in terminally ill patients, proposes this metaphor about thinking of death: you can stare at the sun for brief moments, but holding your gaze burns your eyes. The main conclusion of the book is that this fear indicates a lack of perspective of personal developments, a scenario in which it is difficult to imagine future pleasant contexts, as reflected in this patient.

This is a close-up of the truth, the relationship between the symptom and an eventual disease that must be distinguished from what we could call life ailments, symptoms that inform us of particular emotional moments. A very arduous task in the cardiology office, both in healthy people and in patients with known diseases. Thus, a patient who underwent heart surgery can also consult for pain, palpitations or dyspnea, and we must explore what is really happening in his/her life.

About the disease that I can diagnose

This field is closer to the "scientific truth", with the help of diagnostic methods, a relevant part of cardiology science. We know their sensitivity, specificity and predictive value, and we apply them on a daily basis. In Figure 1 we exemplify an excellent method, with 90% sensitivity and specificity, applied in a check-up to an asymptomatic person (1% prevalence). When it is positive, most people are healthy, they are false positives.

Here lies the clinical capacity to listen and define symptoms and risk, to detect candidates for studies in which they yield the best benefit, and in the common uselessness of indiscriminate check-ups applied to healthy people. When we start from a suspected probability of 40% with the same method, most of the positives are true and false positives are greatly reduced.

This selection is essential; it implies approaching the disease through the symptom and the epidemiological context. The complexity is even greater; the disease does not always justify the symptom: patients

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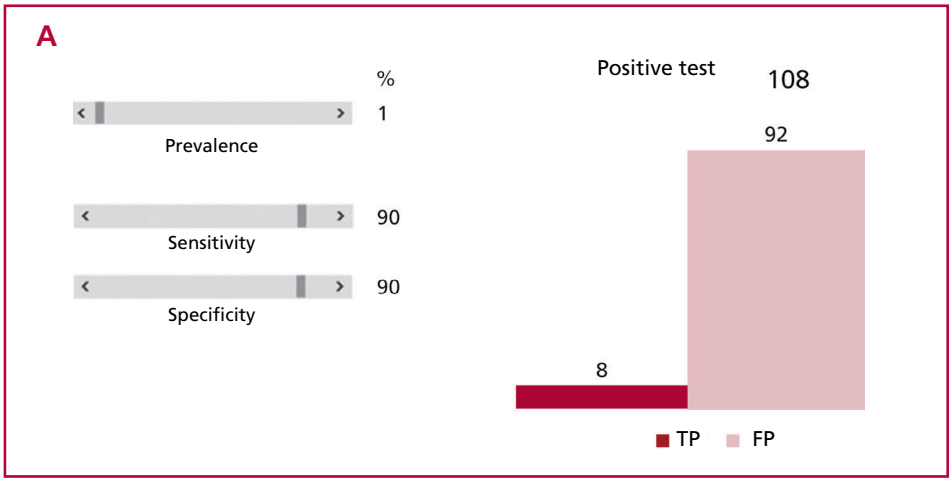
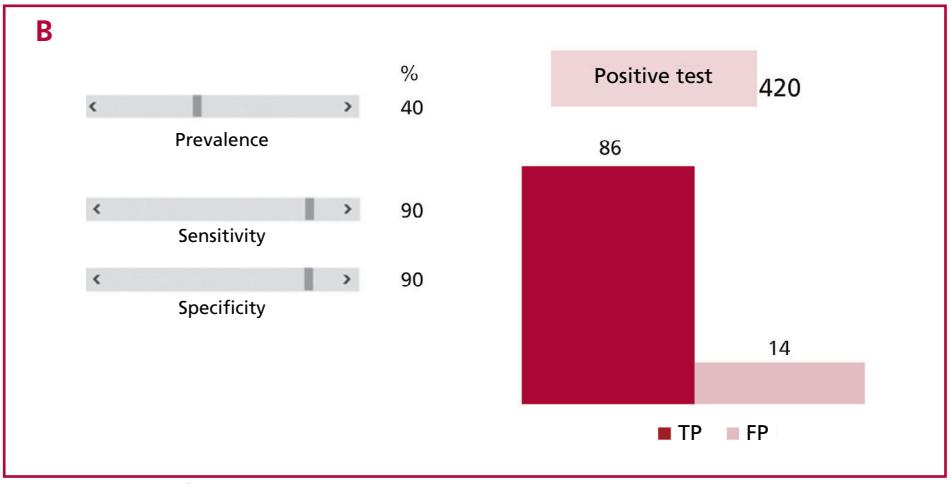
[1] This article initially arose from a first conference at the Academy of Medicine on June 17, 2021 at the Virtual Seminar on Scientific Truth in the Post-truth Era, and a second on October 22, 2022 at the 48th Argentine Congress of Cardiology.



TP: true positive. FP: false positive.



TP: true positive. FP: false positive.

Fig. 1. 1A. In a population of 1000 people with a low prevalence of disease (1%), a method with 90% sensitivity and specificity, when it is positive, results in a rate of 8% true positives and 92% false positives. **1B.** The same method applied to a population of 1000 people with a disease prevalence of 40%, when it is positive, raises the rate of true positives to 86% and the rate of false positives to 14%.

with coronary heart disease have chest pain from any other cause. Or an elderly person with aortic stenosis who is breathless when climbing a flight of stairs, but perhaps due to lack of exercise the dyspnea is not related to the disease, with the serious implications the symptoms have that could lead to a surgical indication.

As a summary, these first two reflections on true diagnoses and the level of truth that we can achieve through careful listening and diagnostic methods show us a very complex task, which requires distinguishing the ailments of life from a serious symptom, where a mistake can be catastrophic. It is possibly the most relevant role of clinical experience.

About the benefits that my treatments or recommendations will exert

There is solid scientific data to decide treatments in different clinical contexts, the powerful arsenal of evidence-based medicine. Large clinical trials are in many scenarios undisputed scientific evidence that leads us to a more comfortable perspective that is approached with confidence. As explained in Figure 2, with the same degree of conviction as Tulp in body mechanics and clockwork, we trust the probabilistic approach and the significant p-value for therapeutic evaluation. (2)

As an example, we will consider the EMPEROR-Preserved study (3) (Figure 3) which reduced the composite event by 21%, with a highly significant p. This finding guarantees us that empagliflozin is better than placebo, and we feel confident with its indication. How do we interpret this information for decision-making in the individual patient? In the first place, the benefit in a large study will be reflected in the guidelines as an indication with Class I recommendation, so we start from a strong conviction of its usefulness.

Evidence-based medicine has been of great importance in the professional life of a cardiologist my age. In my first years of residence, after an uncomplicated heart attack, a patient was discharged with recommendations for rest and diet, without any additional treatment. Today patients are discharged with at least four medications that reduce mortality by 80% and

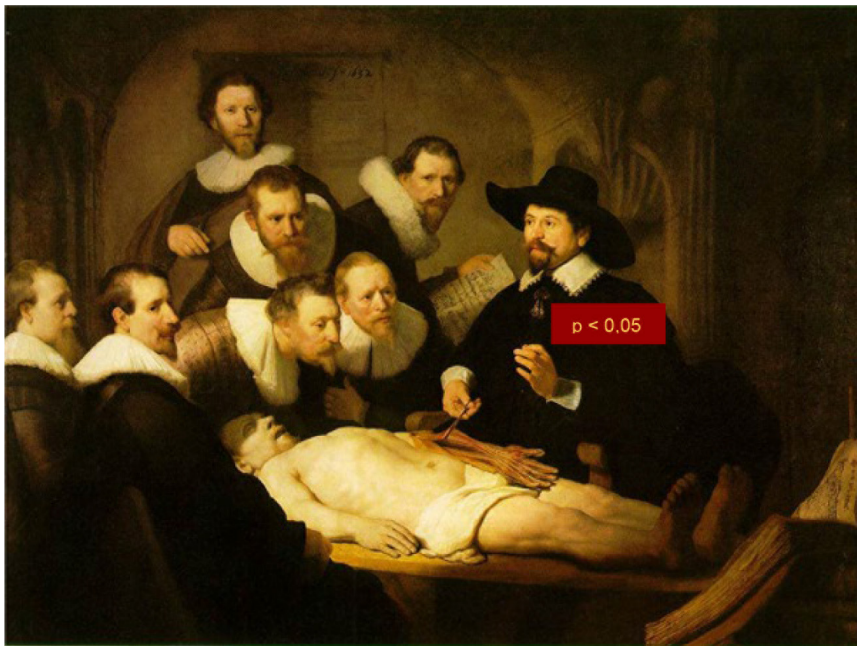


Fig. 2. Rembrandt's painting, Doctor Tulp's Anatomy Lesson. Dr. Tulp pulls an arm tendon with the forceps and with his left hand he moves the finger. The message is clear: I understand the mechanics of the human body, I know that pulling this tendon will move this finger. We added our new conviction at the p level.

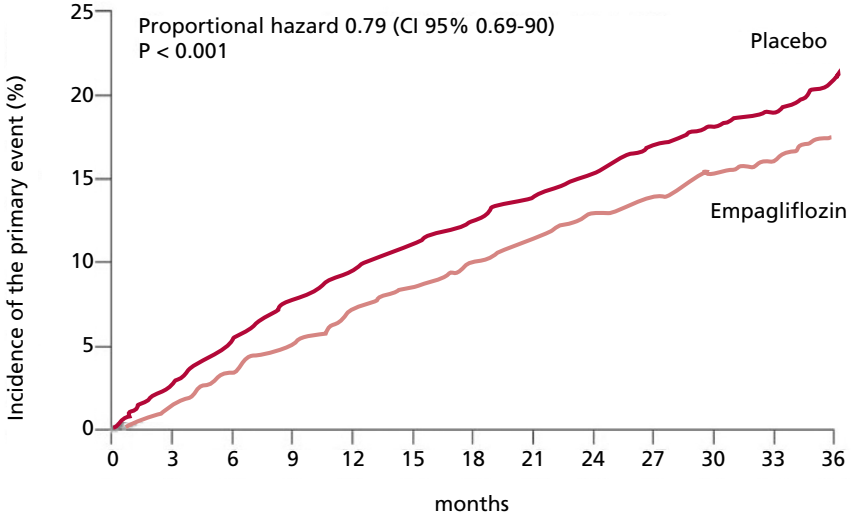


Fig. 3. EMPEROR study. Empaglifozin in heart failure with preserved systolic function. A reduction in the cumulative incidence of major events is observed with a highly significant p. The incidence of the event was 13.8% vs. 17.1% in favor of the drug.

prolong life for many years, (4) and we clearly perceive this improvement in the outcome of our patients.

But even with this strength of evidence, the problem is the dimension of truth to apply to an individual patient.

The empaglifozin trial lowered the incidence of the main event from 17.1 to 13.8%, an absolute reduction of 3.3% compared with placebo, a highly statistically significant reduction. What does this reduction mean in terms of what we now call population medicine? If 100 people with this disease consulted us, 17 would be hospitalized or have cardiovascular death in the next 26 months, and when we applied empagliflozin we would reduce this risk to 14.

It is clear that 97 of those 100 patients who consulted us will not change their outcome with the treatment. No complications will occur in 83 patients, 14 will develop complications despite the treatment and we will change the course of 3. (Figure 4)

Does that give us authority to say that we should prescribe empagliflozin to all patients with this same problem? Is this true? The Handbook of the Philosophy of Medicine, (5) dedicates a juicy chapter to evidence-based medicine. I will only take the epistemological critique regarding the validity of our demonstration of the truth and its application to the individual patient.

Do clinical trials, on which evidence-based medicine stands, prove causality? We believe so, without any doubt. In other words, if we evaluate a comparative treatment in two groups, and the two groups are the same except for the treatment and this is associated with lower mortality, this effect is causal.

A first objection that is raised is that causality does not prove a mechanism. We know that aspirin administered in the first hours of an infarct reduces mortality, but we do not know why it does so, or whether we can extend this beneficial effect to other drugs with similar mechanisms. But a more complex and relevant aspect is whether the evidence from a controlled trial can assure me that if I prescribe this treatment to a patient, it will be beneficial for him.

With the same conceptual line, the philosopher Nancy Cartwright published in The Lancet a critique of the truth of randomized clinical trials. (6) She claims that the logic of clinical trials assumes a first premise, that the probabilistic effect in favor of a treatment requires a causal explanation. That is, if I reduce mortality probabilistically, that is caused by the intervention. Why? Because the second premise tells us that the out-of-treatment parameters are the same, since the treatment assignment was random and the groups were equal. The only possible logical explanation for the result of the treatment is the change of outcome in some members of the group. This is very clear. But this statement brings us a great difficulty: it changed the outcome of the group by changing the outcome of some of its members.

How do we translate this knowledge that a proven treatment in the final result of a clinical trial is proof that it will cause this result in our patient? The result of the trial is only part of an evidentiary argument. We can tell the patient: this drug empagliflozin is very good; I'm going to indicate it to you because it is generally beneficial for the health, but it doesn't do anything to some and it is probably harmful for others. We do not have a hard truth in that regard. We start from an argumentative basis for decision making, but it is very difficult to go from these probabilistic results supported by clinical trials to the detailed and particular knowledge that we require in the clinical context for an individual person.

We know that it is feasible to reproduce these positive results in some of our patients. Could we step up and try to identify those participants who will benefit? What methods do we have?

From subgroup analysis to precision medicine

One tool is subgroup analysis. In the empagliflozin study, it was observed that patients with left ventricular ejection fraction more than 60% and those under 70 years of age obtained less benefit than the others. But this observation arouses immediate mistrust in us, at least in cardiologists of my generation, due to the memory of the ISIS II study. (7) The Lancet required them to publish effects on subgroups, and researchers who did not wish to do so introduced a misleading analysis. Aspirin lowered mortality by 20% in the general population; grouped according to the zodiac signs, Gemini and Libra patients had a 9% increase in mortality and patients with other zodiac signs had a 28% reduction. (8) The message was very clear: it is fun to analyze subgroups, but do not believe what it looks like, it is almost always fictitious. This knowledge left us with a positive methodological mark, not believing or mistrusting the subgroups, but on the other hand it increased our uncertainty because each

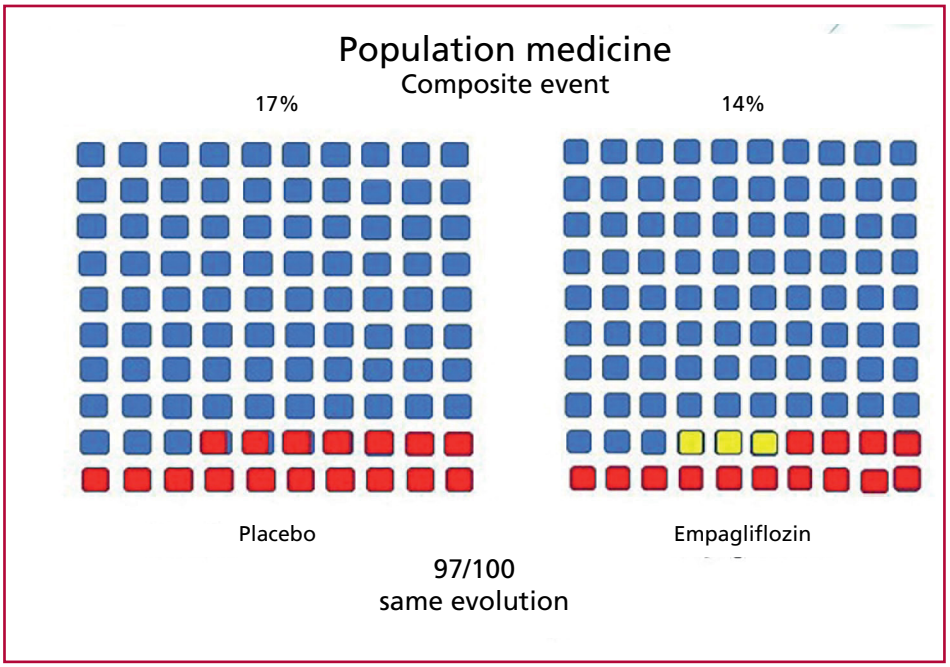


Fig. 4. Conceptual diagram of the impact of population medicine. On the left, in the placebo group, 100 patients are represented, 83 with blue boxes that will not undergo hospitalization or cardiovascular death, and 17 with red boxes, who will have this composite event. On the right, the three patients who modified their course with empagliflozin and avoided the event are seen with yellow boxes.

patient has a particular age, gender and history, that is, each patient belongs to certain subgroups.

In an analysis scheme on the sources of evidence in relation to the individual case, Upshur (9) proposed dividing into qualitative aspects that require what we call medical humanism, the quantitative population aspects, which can be sustained on evidence-based medicine, and the quantitative personal ones, which we could identify today with precision medicine (Figure 5).

Could we build precision medicine in cardiology? (10) This approach tends to recognize that we can resort to immense information in the individual case, from the genome, transcriptome, proteome, metabolome, exposome, concentrate millions of data, do stratified analyses and conclude that aspirin will be beneficial for this person.

The application of genetic markers has had an important development in oncology, since they condition the natural evolution and responses to treatments. In cardiology the development is lower and for now without any practical application. (11) An implicit limitation is the magnitude of the information: in order to process, analyze and decide with this future approach, we will need another way of practicing medicine, supported by artificial intelligence or even robotic medicine. The analysis of this magnitude of information for the individual case is beyond the reach of our brain.

To summarize this third reflective step on the truth in the office in front of an individual case, evidence-based medicine gives us confidence to adopt behaviors, scientific truths that are population and general truths. But there is a limited amount of evidence for many more problems that are not studied, and in turn we have the limitation that we practice population medicine; we do not know what will happen to this person with this new treatment.

Here I allow myself a small digression on the recommendations that I try to avoid in the office. It is common that after a heart attack the patient is told: from now on you have to eat without salt, eat less fat, change your diet; if you have low vitamin D you should receive a supplement and you have to lose those extra kilos even if you are not obese. Since each one lacks evidence or has evidence against it, I do not make these recommendations; at least I prefer not to tell lies or add unnecessary care.

About what we communicate concerning the disease and the future scenario

This last reflection is aimed at exploring the dimension of the truth of what we communicate about the disease and future prospects. We are entering a different terrain, that of discourses and metaphors. Lakoff and other authors brought a revolutionary change in the understanding of metaphors as essential resources of thought. (12) We cannot think about complex aspects of life without metaphors, and what is most exciting is the definition that "we inhabit our metaphors". As an example, we can ask ourselves what medicine is and what are we doctors: Artists? Priests? Warriors against disease? Mechanics that repair malfunctioning organs?

If I inhabit the metaphor of medicine as art, I live the relationship with patients in that way. As an exaggeration, I am the artist and the patient is a canvas on which I paint my work. We inhabit different metaphors as ways of dealing with the relationship with patients and relatives from a medical perspective.

What role does the metaphor play? It allows us to understand one aspect of one domain through a dif-

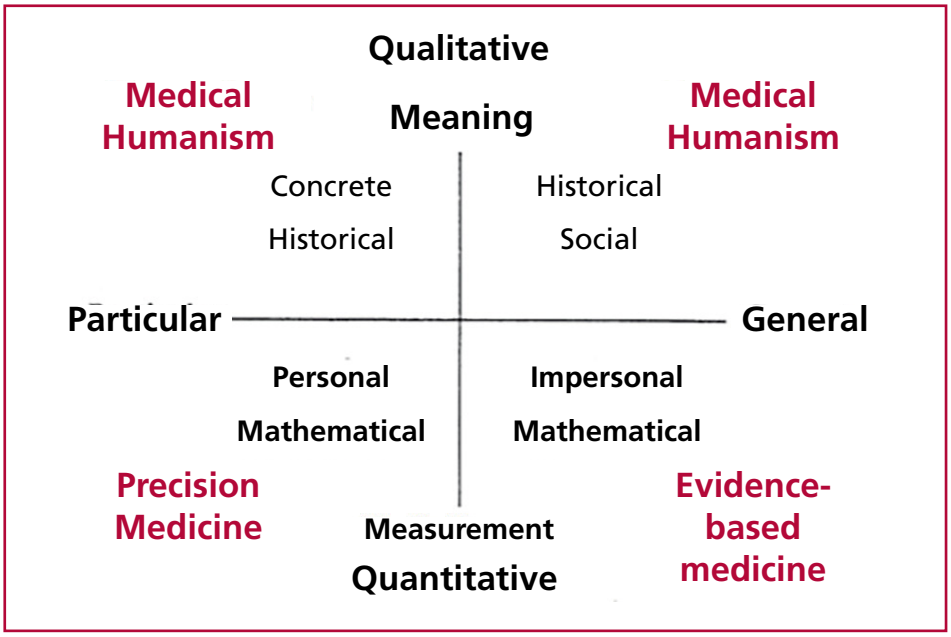


Fig. 5. Dimensions of the sources of evidence. Upshur (9).

ferent domain. If I state that *the paths of life take us here or there, that this journey that we have begun together will take us wherever it leads*, I describe life as a journey. I use the conceptual metaphor *life is a journey* through multiple expressions. When I inhabit the metaphor of *life is a journey*, just as when I selected to inhabit medicine with the metaphor of the artist, correspondences are generated that stick from one domain to another. If life is a journey, it has meaning, destiny, speed, obstacles, risks, crossroads. Anything that a journey has can be referred to as a metaphor of life. But life cannot be summarized only as a journey, it can admit many other metaphors, which is usual for complex subjects.

Metaphors are very relevant to interpret the patient's story and communication, to recognize how he explains his condition, his illness and his future scenario.

In turn, metaphors are a very relevant resource for medical rhetoric, that is, the discourses that we elaborate a priori, or often improvise, in order to address the questions and concerns of patients and family members.

It is a challenge to become aware of the possibility of building more appropriate metaphors to explain diseases and treatments, which contribute to generating a more pleasant life and better adherence.

I am going to read you a brief story from a book by Juan Forn, *I will remember for you*. (13)

"He came to see doctors for an ailment that did not leave him. It was a terminal cancer, but no one dared to tell him. They had admitted him to Hospital de Clínicas with an outpatient permit, while they made him believe that they were submitting him to studies and preparing him for an operation. One day wandering through the basement of the hospital, Horacio Quiroga found a patient named Batistessa. They had him hidden there because of his physical appearance, caused by a neurofibromatosis known as elephantiasis. Quiroga demanded that Batistessa be taken out of the basement and transfered to his room, and in idle hours he told him stories of the jungle. One day Batistessa heard the doctors talking and went to tell Quiroga that the supposed operation they had promised him was actually a simple and painful postponement of death. Quiroga said that he was going for a walk, went to a hardware store to buy cyanide, returned to the hospital, mixed the powder in a glass with whiskey and swallowed it."

Tell the truth.

In medical ethics it implies the moral duty to be honest with patients about health conditions, medications, procedures and risks, and this can often be unpleasant, but it is usually necessary.

How do we say it's true? How do we raise it? How do we empathize with patients?

What is the future scenario that we project to the patient and his family?

Everything we communicate about the disease and the future scenario must be true. Hiding implies a metaphor for the horrendous, the ineffable, what cannot be said or spoken. It is counterfactual, but they could have informed Horacio Quiroga better, helped him to a better death or perhaps a last story that would have brightened our lives.

How do we cultivate this subject? One possibility is to generate metaphorical scenarios through research. The metaphor menu for people living with cancer is a contribution from linguists that proposes 17 metaphorical scenarios as opposed to the usual metaphor of the war against cancer. (14)

We can choose from the menu a metaphor according to what we perceive in the patients. Living with cancer can be a stone in your shoe: you will have a stone all the time that will bother you, but it will not prevent you from walking. Or a difficult path, with obstacles, slopes, crossroads and deviations. Or a roller coaster: you will have a moment of chemotherapy or perhaps surgery, have dizzying ups and downs, but we will always be here waiting for you to give you a hand.

These are possible metaphors in cancer communication. We have a lot of evidence in everyday medicine about the power of language and narrative to heal, but it can also harm. (15) Words and metaphors are more prone to harm when we do not have narrative competence, when we say it wrong. I had the evil of collecting some medical verbal abuse, (16) hundreds of terrifying phrases that all doctors say, unfortunately, including myself.

How do we acquire narrative competence?

The first step is to approach the subject with humility, recognizing that we have deficiencies in this sense, and supplying them with training in reading, writing, and group reflection workshops. With a group of colleagues in July 2022 we founded the Society for Narrative Medicine and we are hopeful that it will grow as a discipline in the coming years. (17)

What is the truth and what is the source of legitimacy of medical practice?

Throughout the article I referred to the truth, without trying to define it. It is a key question of philosophical thought. We can resort to one of Aristotle's definitions: *"to say of what is that it is not, or of what is not that it is, is false. To say of what is that it is and of what is not that it is not, is true."* The truth is a correspondence between what we say and an objective reality that we know. The conception of truth has had an infinite number of questions and approaches. One of Nietzsche's famous phrases there are no facts, only interpretations accompanies the synthesis that Darío Sztajnszrajber makes of his conception: *What is truth? The most efficient lie*. (18) Truth is thus a cultural, temporary and relative construction.

As a final thought

It is not easy to reach a firm conviction about our access to the truth in the four dimensions raised with

the limitations that I have tried to point out, to which is added the great philosophical complexity of the subject. In the consultation practice, we try to find the truth and thus reach the most solid scenario, but we go through slippery terrain, from the uncertainty in the interpretation of the symptoms, in the indications, in the interpretation of the patients' speech and in the elaboration of our medical rhetoric. This fragility may question whether we practice true and valuable medicine.

I will resort to the help of another contemporary philosopher, Fredriksen, (19) who in his article *Diseases are Invisible*, explains that medicine is not a positive science, based on unquestionable facts, but rather a normative science, a practice with values. *Values such as care, compassion and solidarity guide and legitimize medicine, not precision or truth as such*.

I move on to a last metaphorical scenario, medicine for Pérez Tamayo, which is the one I try to inhabit. (20) *Medicine is a space for the encounter between a being that suffers and another that tries to alleviate it*. This relief comes from a practice with the greatest dimension of scientific and technical truth, based on the values of care, compassion and solidarity that legitimize it.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

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OPINION ARTICLE

Is Fluid Dynamics Assessment the New Stage of Cardiovascular Imaging Diagnosis?

¿Es la evaluación de dinámica de fluidos la nueva etapa del diagnóstico por imágenes cardiovascular?

OMAR PRIETO[MTSAC, FACC, FASE], FEDERICO STARICCO

Echocardiography, as well as the different cardiac imaging techniques, has significantly evolved in the last decades.

Ultrasound machines and software continue to amaze us both in the medical setting as in biomedical engineering.

For a long time we dedicated our attention to the study of the cardiac structure and its impact on velocities, pressures and gradients. We were able to assess myocardial deformation and early predict the involvement of the left ventricular pump function, and numerous scientific studies were published correlating anatomo-functional disorders with clinical scenarios.

At present, we have the immense possibility of evaluating the inverse relationship. That is, what happens to our heart when fluid dynamics are altered and the energy this generates. Although this type of evaluations can be performed with 3D resonance imaging, this is not always available for routine practice. On the other hand, there are similar methods of intracardiac fluid analysis, but they require the use of contrast material, are dependent on the angle or can only be used with transesophageal echocardiography. (1)

Until recently, the evaluation of fluid dynamics with conventional ultrasound machines was done with spectral and color Doppler tools. However, these methods present the limitation of velocity analysis only parallel to the direction of the ultrasound beam, and the rest of the components of the complex intracavitary flow analysis could not be evaluated through this modality. (1)

In order to understand this technology, it is useful to perform a review of some concepts related to fluid dynamics, and vector and scalar fields.

Upon making a closer evaluation of intracardiac flows by echocardiographic assessment with transthoracic transducer, we can incorporate a blood flow vector map and observe that within the cardiac chamber it runs in more than one direction.

As can be seen in Figure 1, the blood that passes through the mitral valve to enter the left ventricle generates a ring of vortices which, if selected and analyzed in the bidimensional plane, show that some rotate in a clockwise and others in a counterclockwise direction. (1)

In the case described, vortices rotate in a counterclockwise direction in the space between the posterior leaflet of the mitral valve and the left ventricular posterior wall. On the other hand, at the left ventricular outflow tract higher magnitude vortices rotate in a clockwise direction.

To understand this phenomenon, we believe it is adequate to define some central concepts

Vortices: physical magnitude used in fluid mechanics to quantify rotation, given by a rotational vector. (2)

Direction of rotation and angular velocity: If an object is rotating in two dimensions, it is possible to completely describe the rotation with angular velocity. A positive angular velocity indicates that the rotation is counterclockwise, whereas a negative value indicates that the rotation is clockwise. (2)

However, the situation is somewhat more complex for intracardiac flow. It is necessary to represent both the angular velocity as the three-dimensional space direction in which the cardiac flow is rotating. To achieve this, the rotation in three dimensions is normally described using a rotational vector where both the vortex magnitude and direction are represented. To evaluate the vortex direction in a simple way, the "right-hand rule" is used. What does it consist of? The right-hand fingers are curled in the direction of the rotation and the thumb is extended. The vector that represents this rotation in three dimensions is, by definition, oriented in the direction of this finger. (2)

Another important point to consider is how a velocity vector map is generated. This technique is derived from the use of two modes, which have been very useful in echocardiographic assessment in the last years: color Doppler and left ventricular deformation assessment by speckle tracking. As previously mentioned, color Doppler only provides the velocity parallel to the

ultrasound axes and, on the other hand, it is possible to obtain the transverse velocities of the left ventricular myocardium by speckle tracking. (3)

This means that blood velocity and trajectory within the left ventricle can be represented by means of myocardial transverse velocity vectors as blood flow longitudinal velocity through the color mode.

As seen in Figure 2, another point to emphasize is that having the information of the flow velocity vectors, it is also possible to represent through a parametrization map, the magnitude and direction of vortices generated in a cardiac cycle by means of a color map. (4) By convention, in this map, the vortices that rotate in a clockwise direction are represented in blue, and those that rotate in the opposite direction, in red

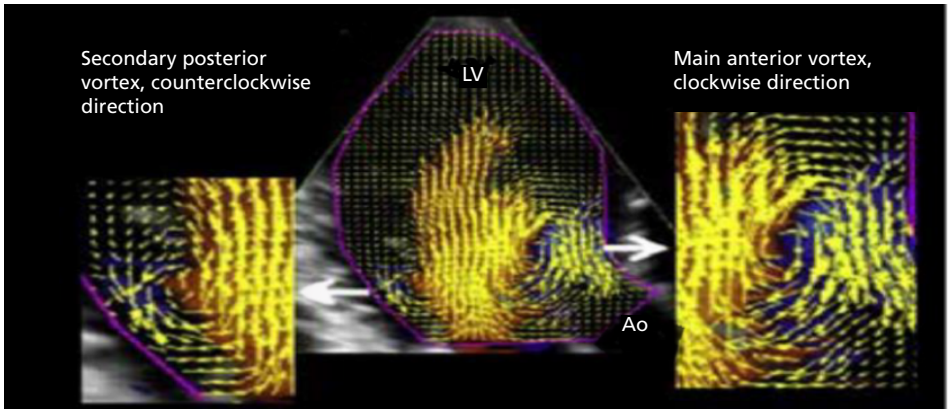
In addition, thanks to fluid velocity vectors and blood density and viscosity values, it is possible to represent a third map of kinetic energy to study the higher levels of energy generated in the left ventricle denoted in red. In a healthy patient, the highest levels of energy directly proportional to velocity variations are in the left ventricular outflow tract. In dilated cardiomyopathy, the kinetic energy analysis shows that the highest levels of energy are far from the left ventricular outflow tract, at the ventricular apical level. Then, by knowing the kinetic energy, it is possible to assess energy dissipation. This variable has been very useful to monitor healthy and ill persons, and it has been shown that patients with dilated cardiomyopathy present lower values of energy loss compared with healthy individuals (Figure 3). (4)

Possibly, the greatest clinical experience with this technique is in left ventricular systolic function impairment.

An interesting work presented by the group of the University of Padua led by Dr. Donato Mele could show the differences present in the dynamics of intracavitary flow among healthy individuals and patients with heart failure. (5) It was seen that the study was feasible and the differences present in the different evaluation parameters of intracavitary flow dynamics were reproducible, therefore providing relevant scientific support to consider it as a highly useful tool.

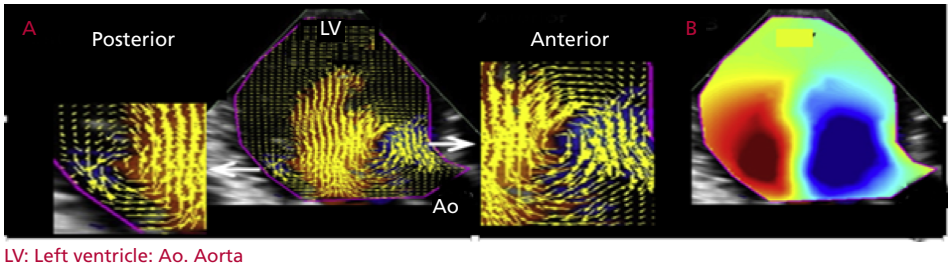
The diverse clinical scenarios in which the anatomical geometry can be affected probably impact on fluid dynamics. An example is supplied by coronary heart disease and transmural acute myocardial infarction: here the extent of infarction and left ventricular systolic function can be considered. Consequently, with this variable, it has been possible to demonstrate the relationship between the extent of the ischemic event, regional dysfunction and left ventricular systolic function with intraventricular turbulence and the fluctuation and dissipation of kinetic energy, a phenomenon that makes a significant difference in the analysis and interpretation of the consequences and implications of these events. (6)

Heart valve disease as well as valve replacement have also been evaluated with this technology, and changes have been shown in the sense of vortex rotation in dual-leaflet mechanical valves. The kinetic energy dissipation parameters are greater in patients with valve replacement compared with healthy ones. (7)



LV: Left ventricle. Ao: Aorta

Fig. 1. Vector mapping illustrating the different rotational behavior of anterior and posterior vortices.



LV: Left ventricle: Ao. Aorta

Fig. 2. To the left (**A**), vortices' vectorial field map generated in the left ventricle. To the right (**B**), vortices' magnitude and direction parametrization map

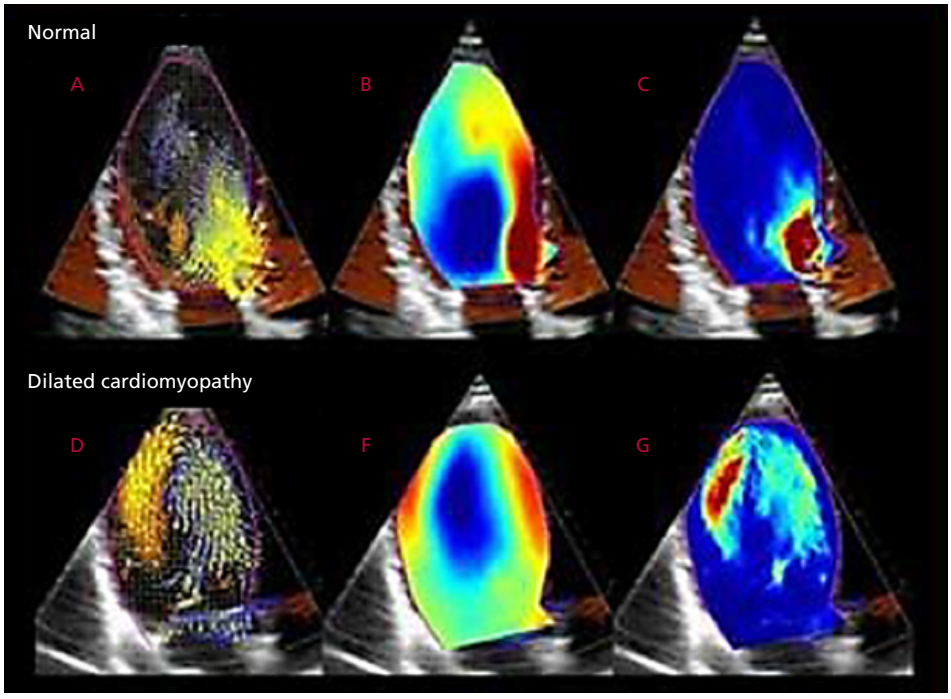


Fig. 3. Panels **A** and **D** exemplify the representation of the flow velocity vector data map, in which a 2D velocity vector field is represented as overlaid vectors in the traditional CFM (Color Flow Mode). Panels **B** and **E** show a circulation parametric map, in which vortices are represented as compact regions colored in blue (clockwise vortex rotation) or red (counterclockwise vortex rotation): Panels **C** and **F** provide representations of kinetic energy maps.

Cardiac resynchronization therapy (8) hypertrophic cardiomyopathy, (9-11) atrial fibrillation (12) and the detection of apical thrombi (6) have also been analyzed with this technology, which offers a novel aspect in the anatomo-physiological explanation of cardiovascular disease.

Once again, the association of technological and cardiology progress demonstrates that joint work defines a course where the goal is the optimization of patient diagnosis.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

Ethical considerations

Not applicable.

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The Chylous Vessels. Depart Without Liver, Wayfarer!

Los vasos quilíferos. ¡Vete de aquí, sin hígado, caminante!

JORGE C. TRAININI[MTSAC]

In ancient times, there was some reference to chylous vessels by Herophilus of Chalcedon and Erasistratus of Ceos, both belonging to the school of Alexandria in the 3rd century BC. It was only until the Renaissance that the topic was mentioned. Gabriele Falloppio (also Gabrielle Fallopia) (Modena, 1523-1562) and Bartolomeo Eustacchio (also Eustachio) (Rome, 1520-1574) were the first to introduce a vague reference on the topic. Eustacchio, a staunch supporter of Greek medicine, described the thoracic duct in his work "*De vena azygos*". He also described the valve at the junction of the inferior vena cava and the right atrium, which was named after him.

Notwithstanding this background, the presentation of chylous vessels as a system is due to Gaspare Aselli (also Asello) (Cremona, 1581-circa 1626). On July 23, 1662, Aselli discovered the chylous vessels in a dog. The finding was purely incidental. In the vivisection of a recently-fed dog, while observing the recurrent nerves —together with his friends A. Tadino and S. Settala—, Aselli found some white cords, which he immediately assumed to be a novel finding. However, when the experiment was repeated on a fasting animal the following day, the presence of chylous vessels was not confirmed. Aselli immediately realized that the finding was associated with the postprandial period. Therefore, by reproducing the first experience he confirmed his assumption, and called them "*lacteals*". Aselli, who was a professor at the University of Pavia, left a manuscript on the subject, "*Lectiones de Venis Lacteis*", in which he also described the venous valves of the chylous vessels, which he called "*quartun vasorum genus*"; this research study, "*De lactibus, sive lactis venis, quarto vasorum mesaraicorum genere novo invento*", was published posthumously by his friends A. Tadino and S. Settala in Milan in 1627, and included the first illustrations published in color.

However, Aselli, in line with Galen's theory, thought that the outflow of chylous vessels occurred in the liver, which is essential for blood formation. This work, launched a year before the stunning publication of William Harvey's "*De Motu Cordis*", was criticized by Harvey (did the brilliant Englishman consider his theory of blood circulation threatened?) and by Gaspar Hoffmann, a great connoisseur of Galen, and author of "*Comment in Galen de Usu Partium*" (1625).

Later on, Jean Riolano (1577-1657) confirmed the description of chylous vessels, but also in animals. The discovery in human beings was made by an anatomy enthusiast, Fabrice de Peiresc (French, 1580-1637) around 1634. In that same year, Johann Vesling (1598-1649), a famous professor in Padua, confirmed the previous experience, but still repeating Galen's errors regarding the central role of the liver. Nicolaes Pietersz Tulp (Dutch, 1593-1678) was also one of the first to describe the chylous vessels. His figure was immortalized by Rembrandt (Dutch, 1606-1669) in his famous painting "*The Anatomy Lesson of Dr. Nicolaes Tulp*".

Jean Pecquet discovered the thoracic duct; he was born in Dieppe in 1622 and died in Paris in 1674. He wrote "Experimenta nova" in 1651. In 1647, not yet qualified as a physician, while dissecting a dog, Pecquet found by chance the termination of the thoracic duct at the place where it opens into the subclavian vein; by following its course, he described the chyle cistern that would later be named after him. In his own words: "*I had removed the heart of a dog and placed it on a table. I was thinking of nothing but counting the systoles and diastoles which the last efforts of its spirit produced, when I perceived a white substance like milk flowing from the ascending vena cava into the pericardium, at the point already occupied by the right ventricle of the heart. I found that this substance —which, by taste, odor, color and consistency, could be compared to the milk or chyle I had seen flowing out of the lacteal veins— came from the subclavian branches in which I found, a little above the jugular veins, the orifices through which this milky fluid penetrated into the vena cava.*"

Thus, by demonstrating the actual path of the chyle, the liver was dethroned as the essential organ of blood formation, a fact that was hailed by the Danish Thomas Bartholin (1616-1680) with an epitaph that read: "*Stay, wayfarer. Enclosed in this tomb is one who hath entombed very many, the liver, known to the ages, but unknown to nature... So long he digested, until with his bloody tyranny himself, he digested away. Depart without liver, wayfarer! And concede bile to the liver, that without bile will thou wayst digest for thyself. Pray for him.*" The description of the thoracic duct in human beings was carried out by Jan van Horne (Dutch, 1621-1770), which was published with illustrations.

Cardiac Autotransplantation as Treatment Strategy for Malignant Heart Tumors

Primary malignant cardiac tumors, usually sarcomas, represent an infrequent subgroup among cardiac masses. However, they constitute processes with poor prognosis, and surgical treatment is the most favorable therapeutic alternative in terms of survival.

The literature regarding left-sided cardiac sarcomas reveals that patients are subjected to reinterventions for local recurrence, generally related to incomplete resections, probably due to a suboptimal anatomical exposure during surgery, which conditions inadequate resections and technically difficult reconstructions.

Sometimes, to fulfill the objectives of a radical oncological resection and facilitate the reconstruction of the resected cardiac structures, it is necessary to explant the heart in order to resect the tumor with adequate margins and reconstruct the cavities or involved structures, finally reimplanting the heart in bench surgery (cardiac autotransplantation).

This is the case is a female 73-year-old patient, without relevant clinical history who was admitted to hospital due to progressive dyspnea and anemia. In the diagnostic algorithm, the transthoracic echocardiogram showed a dilated left atrium occupied by a 4.8 cm × 2.8 cm immobile, heterogeneous mass, intimately associated with the mitral annulus, which completely filled the left atrial appendage, and severe mitral valve insufficiency with central jet.

A cardiac magnetic resonance performed to complete the mass evaluation revealed the mentioned heterogeneous tumor in weighted T1 and T2 sequences, before and after contrast, as well as in perfusion and late enhancement sequences. No contrast capture was evidenced in the tumor sector protruding to the left atrium, which was interpreted as an added thrombotic component (Figure 1). The same study showed absence of pericardial and pulmonary vein involvement. Prophylactic anticoagulation was started, and a positron-emission computed tomography (PET-CT) of the whole body was performed for local evaluation and search of eventual metastasis.

The PET study showed a hypermetabolic mass of 5.9 cm × 3.4 cm × 2.4 cm (SUV 8.5) in the already known location, focal liver lesions compatible with hemosiderosis and absence of secondaries.

A surgical treatment was decided due to the condition and clinical characteristics of the patient, disease staging and prognosis without resection. Owing to the location of the lesion to resect, in close contact with the mitral annulus, the circumflex artery and the coronary sinus, it was inferred that to perform an adequate oncological resection, the heart should be explanted and reconstructed in bench surgery (ex situ) with subsequent autotransplantation.

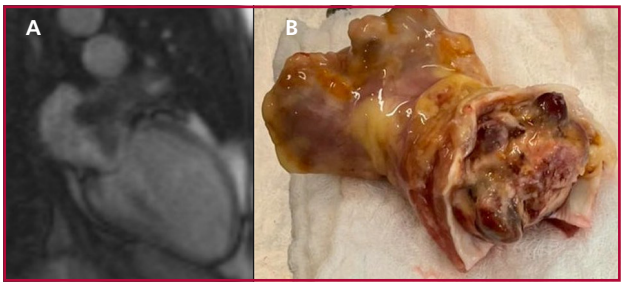

Fig. 1. A. Nuclear magnetic resonance: left atrial sarcoma located in the left atrial appendage. **B.** Surgical specimen with complete lesion resection. The resection margins are evidenced on tissue not affected by the tumor.

Surgery was performed with midline sternotomy and cannulation of both venae cava and aorta

The tumor was explored entering the left atrium by the interatrial sulcus as usually performed for a mitral valve procedure. Absence of pulmonary vein involvement and tumor growth up to the vicinity of the mitral annulus were verified.

Considering that the oncological resection would involve resecting the mitral annulus and part of the mitral valve, and faced with the difficulty to define, through the mentioned approach, the external margin of the resection in relation to the interventricular sulcus structures, it was decided to explant the heart and perform a bench tumor resection.

The venae cava, aorta and pulmonary artery were sectioned and the atriotomy was extended leaving a hood that contained the pulmonary veins. The tumor was resected ex situ (bench surgery), which implied resecting a section of the mitral annulus at the P1 level exposing the atrioventricular sulcus vessels and the ventricular myocardium. The mitral annulus and the left atrium were reconstructed with a bovine pericardial patch and the mitral valve was replaced with a #25 porcine biological prosthesis.

The organ was reimplanted with autotransplantation technique (Figure 2).

Extracorporeal circulation time was 232 min and cross-clamping time 175 min. The postoperative course was in accordance with the magnitude of the procedure, requiring inotropic support for 72 h. Among other events, the patient presented an episode of atrial flutter which was controlled with amiodarone and isolated subfebrile records with negative cultures.

Anatomical pathology reported a grade III undifferentiated pleomorphic sarcoma, which implies a maximum level of malignancy and undifferentiation.

The prevalence of primary cardiac tumors in autopsy series is 0.02%. Among them, 25 % are malignant and 75 % of these are sarcomas. (1) Median survival in published series ranges between 9 and 33 months. (2) Most are clinically silent until a very ad-

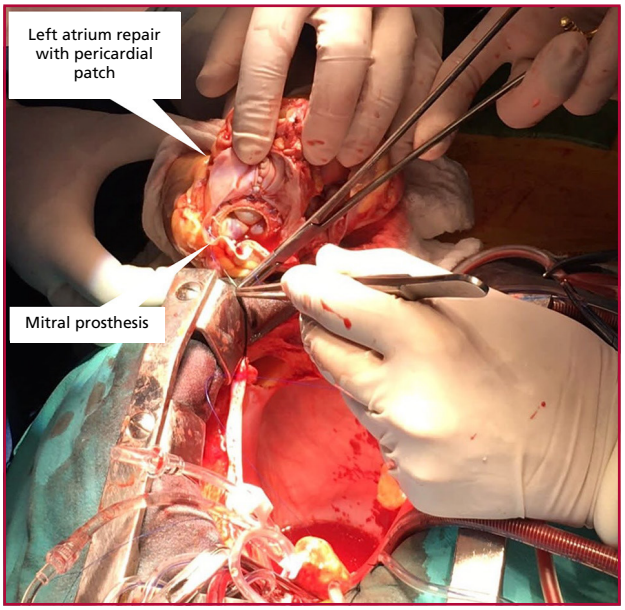

Fig. 2. Cardiac autotransplantation showing the left atrium repaired with bovine pericardium and mitral prosthesis.

vanced stage and are often considered nonresectable due to the proximity to critical structures. However, surgical and imaging techniques have improved allowing more aggressive interventions, which aim to achieve a microscopically negative resection (R0), a situation in which there is clear benefit of survival. (3)

Cardiac autotransplantation is a procedure described many years ago for the resection of tumors with difficult approach or complex intraoperative management. (4)

Along time, the technique was reproduced for the management of this pathology in numerous patients, (5) and the initial results improved in terms of quality of the oncological resection and survival. (6)

With adequate surgical training the technique is reproducible and should be considered a valuable alternative in the therapeutic arsenal to offer opportunities to patients with severe oncological disease and poor prognosis without surgery.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

Ethical considerations

Not applicable.

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Compressive Mass in the Anterior Pericardium: Difficulty of the Differential Diagnosis

We report the case of a 79-year-old male patient, smoker, with hypertension, type 2 diabetes, coronary artery bypass surgery in 2009 due to chronic coronary syndrome, and prostatic adenocarcinoma actively followed-up by the Urology Department. The patient was referred to the Emergency Room due to dyspnea on moderate exertion for three weeks and right pleural effusion seen in a chest X-ray. Upon arrival, the patient was hemodynamically stable (blood pressure 153/93 mmHg, heart rate 99 bpm), and oxygen saturation at room air of 89%, with no tachypnea at rest. Physical examination revealed jugular venous distention up to the middle third of the sternocleidomastoid muscle, abolition of the vesicular murmur in the right lung base, and bilateral pitting edema up to both knees.

ECG showed sinus rhythm (89 bpm) with negative T-waves in V1-V4, already present in previous studies. Blood screening showed normal renal function (urea 31 mg/dL, creatinine 0.77 mg/dL, glomerular filtration rate 86 ml/min/1.73 m^2) with all ions in range, C-reactive protein 25.98 mg/L, lactate dehydrogenase 950 U/L, creatinine kinase 55 U/L, NT-proBNP 950 pg. /mL, ultrasensitive troponin T 25 ng/L, hemoglobin 11.2 g/dL, platelets 335000/mm^3, white blood cells 11430/mm^3, and D-dimer 4860 ng/mL. To complete the diagnosis, the unsynchronized computed tomography (CT) scan revealed a hypodense lesion over the right cardiac chambers (Figure 1). Neoplasia or hemopericardium due to cardiac rupture or bypass dehiscence were suggested as first possible diagnosis. In view of

these findings, evaluation by the Cardiology Department was requested. Transthoracic echocardiography (TTE) showed a heterogeneous, solid mass in the anterior pericardial sac, with adhesions in the right chambers and compression of the right atrioventricular sulcus, which did not capture echocardiographic contrast (Figure 2). The picture did not suggest a cardiac rupture, not only because of the echocardiographic findings, but also because the patient did not experience chest pain and was hemodynamically stable, and ECG did not show abnormalities suggestive of acute ischemia, making bypass dehiscence unlikely.

Given the discrepancies, a synchronized CT scan was performed for better characterization of the lesion, which showed an 8.5 x 10 cm right precardiac mass, apparently depending on the pericardium, and showing enhancement after intravenous contrast (Figure 1). These findings raised the differential diagnosis of metastasis or primary pericardial neoplasia.

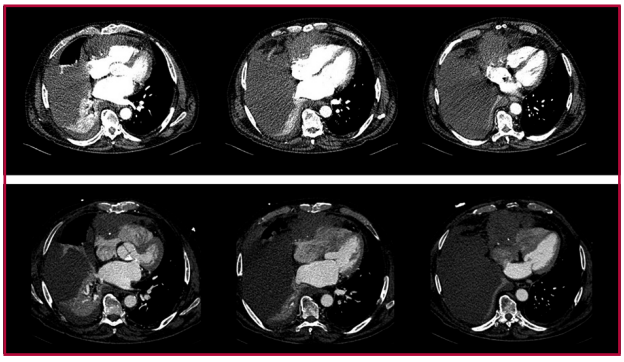

Fig. 1. CT scan. *Top*: Unsynchronized CT scan, with a hypodense lesion over the right cardiac chambers and severe right pleural effusion with associated collapse. *Bottom*: Synchronized CT scan, with a right precardiac mass of 8.5 x 10 cm, enhanced after contrast injection. The tumor exerts mass effect and possibly infiltrates the right atrium, in contact with anterior chest wall and possible infiltration of the right ventricle.

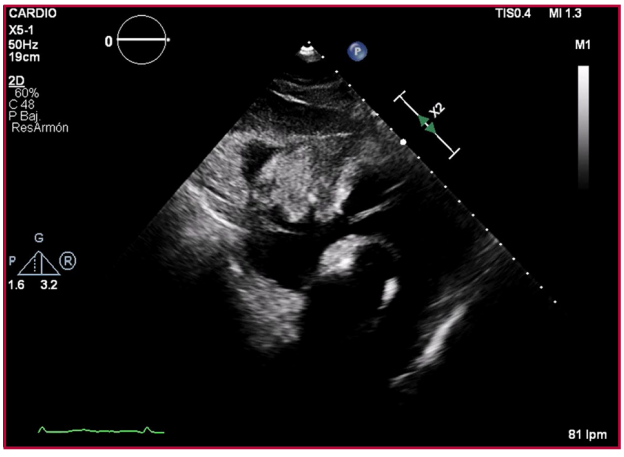

Fig. 1. Transthoracic echocardiography, subcostal access. Heterogeneous, solid mass in the anterior pericardial sac, compressing the atrioventricular groove and appearing to adhere to the ventricular wall.

The differential diagnosis of mediastinal masses is primarily based on the location of the mass, its composition and the age of the patient. (1) Different radiological techniques, including CT scan and cardiac magnetic resonance (CMR), are of significant diagnostic value. Considering that the lesion was located in the anterior wall of the heart, in contact with the anterior chest wall, a broad differential diagnosis including the different lesions at the level of the anterior mediastinum and the tissue-dependent masses in the pericardium was proposed.

Unlike in our patient, thymomas appear as an oval, homogeneous mass, with well-defined contours in CT scan. Calcifications and cystic areas are usually present in thyroid goiters and teratomas, (1-2) and considering that CT findings showed no calcifications in our patient, these two entities seemed unlikely. Lymphomas account for 20% of mediastinal tumors in adults, and Hodgkin's lymphomas are the most common subtype. (1-3) Within this subtype, mediastinal large B-cell lymphoma constitutes an independent entity within the classification of malignant lymphoid neoplasms, with a frequency estimated at 2-3% of non-Hodgkin's lymphomas and between 6-10% of large B-cell lymphomas. This tumor usually occurs as a rapidly expanding mediastinal mass and may be associated with pleural or pericardial effusion. (4, 5)

The patient was admitted to the Cardiology Department to complete assessment. An ultrasound-guided thoracentesis of the pleural effusion was performed, and a serosanguineous fluid consistent with an exudate (Light's criteria) was obtained, showing a hypercellular area in the cytological examination, with characteristics indicative of a B lymphoproliferative process. To complete the study, a core biopsy of the mediastinal mass was performed, confirming the diagnosis of primary mediastinal large B-cell lymphoma. Finally, the first cycle of chemotherapy was started with rituximab, cyclophosphamide, non-pegylated liposomal doxorubicin, vincristine, and prednisolone. He is still on treatment.

Conflicts of interest

None declared.

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Ethical considerations

Not applicable.

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Native Tricuspid Valve Infective Endocarditis

Right-sided infective endocarditis is a rare but potentially fatal disease. It comprises 5-10% of the total number of infective endocarditis events. It is most frequently associated with intravenous drug use, and occurs less frequently in patients with venous access, intravascular devices or underlying congenital heart disease, and exceptionally in non-addict patients or in patients without cardiac malformations. (1)

We report the case of a 58-year-old male patient with hypertension, dyslipidemia, and a history of aortic valve replacement with mechanical prosthesis due to aortic stenosis in 2019.

He is admitted to the general ward for febrile syndrome under study. Cardiac physical examination reveals neither changes in heart sounds nor signs of congestive heart failure. ECG shows sinus tachycardia and first-degree atrioventricular block (PR interval 220 msec).

Blood screening on admission shows white blood cells 31 840/mm^3 (neutrophils 96%, lymphocytes 1.7%), C-reactive protein 58.9 mg/L (normal range 0-5), procalcitonin 4.55 ng/mL (normal range 0-0.1), total bilirubin 1.33 mg/dL, indirect bilirubin 0.83 mg/dL, and direct bilirubin 0.50 mg/dL.

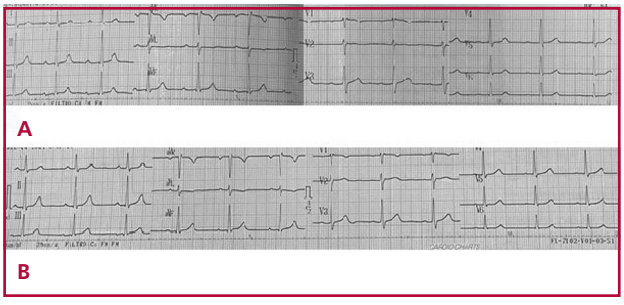

Fig. 1. A. ECG: Prolonged PR interval (270 msec). **B.** ECG: Normal PR interval (200 msec).

During hospitalization, methicillin-susceptible *Staphylococcus aureus* is detected in blood cultures. Due to suspicion of infective endocarditis, a transesophageal echocardiogram is performed, that detects no vegetations, and normal mechanical valve function. On the fourth day of antibiotics, further blood cultures detect no bacterial growth; on the tenth day, transesophageal echocardiography shows no vegetations in the heart valves, ruling out infective endocarditis. After receiving intravenous antibiotics during 14 days, patient is discharged.

A week later, he is readmitted for fever and general malaise; ECG reveals further PR interval prolongation (270 msec) (Figure 1A). Blood screening shows white blood cells 11 870/mm^3 (neutrophils 87%, lymphocytes 4.7%), C-reactive protein 25.6 mg/L, procalcitonin 0.19 ng/mL, erythrocyte sedimentation rate 32 mm/h. Methicillin-susceptible *Staphylococcus aureus* is isolated in follow-up blood cultures. Transthoracic echocardiography reveas a 0.6 cm x 0.6 cm mobile image at the tricuspid valve level. Transesophageal echocardiography (TEE) confirms 0.9 x 0.6 cm vegetation at the level of the septal leaflet, mild tricuspid regurgitation, and normal prosthetic valve function (Figure 2).

A conservative approach with intravenous cefazolin for 6 weeks is followed. First-degree AV block improves by the fifth week of antibiotic treatment (Figure 1B). Follow-up transthoracic echocardiograms on the second and sixth weeks of treatment show no evidence of tricuspid vegetation.

Outpatient positron-emission tomography/computed tomography (PET/CT) for suspected prosthetic valve involvement reveals moderate diffuse radiotracer uptake at the level of the replaced aortic valve, suggesting the absence of an active infectious process, given the absence of a dominant focus with increased concentration of the contrast material and SUVmax 3.5 (Figure 3).

Right-sided infective endocarditis is common in injecting drug addicts and in patients with cardiac malformations; it is a potentially serious condition, with a mortality rate between 23 and 31%. Simultaneous left and right-sided endocarditis comprises 13% of the cases, whereas right-sided endocarditis alone affects 10%. (1, 2)

Isolated native tricuspid valve endocarditis (NTVE) usually occurs spontaneously, without evident history of dental or surgical procedures; however, the skin is usually the most common portal of entry (particularly in the case of *S. Aureus*). In this clinical case, the predisposing factor could not be identified. *Staphylococcus aureus* is the most commonly isolated infectious agent (70% of cases), followed by *Streptococcus* and *Enterococcus*. (3)

The clinical presentation invariably consists of persistent fever associated to pulmonary events, anemia and microscopic hematuria (tricuspid syndrome of Nandakumar and Raju). The absence of peripheral stigmata of endocarditis or relevant murmurs in most cases is noteworthy. (4)

If fever is persistent (if it remains after a 2-week course of antibiotics) it is usually associated with perivalvular extension of infection, new septic emboli or superimposed nosocomial infection. The clinical picture, positive findings on blood culture and echocardiography are the main diagnostic tools in NTVE. (4)

The usefulness of PET/CT is significantly greater for prosthetic valve endocarditis than for native valve infective endocarditis and is an excellent alternative in case of negative or doubtful ultrasound scans. Integrating PET/CT as a diagnostic tool in endocarditis allows for reclassification of 76% of patients with prosthetic-valve infective endocarditis from "possible" to "definite". (5)

Eighty percent of isolated NTVE patients are successfully treated with medical therapy. However, surgery is recommended in uncontrolled infection or right heart failure with tricuspid regurgitation refractory to treatment. Surgical treatment repairs the valve dysfunction and eliminates the infectious focus, thus contributing to reduce mortality associated with heart failure. (6)

Regarding prognosis, a high success rate is achieved with medical treatment (antibiotics), the development of heart failure is uncommon, and only 25% of cases require valve replacement or surgery. (1) Mortality associated with isolated NTVE is lower than that reported for endocarditis with a predisposing condition. (6)

This case suggests the need to consider isolated NTVE, its clinical presentation, treatment, and prognosis, as well as the usefulness of PET/CT to confirm prosthetic valve involvement.

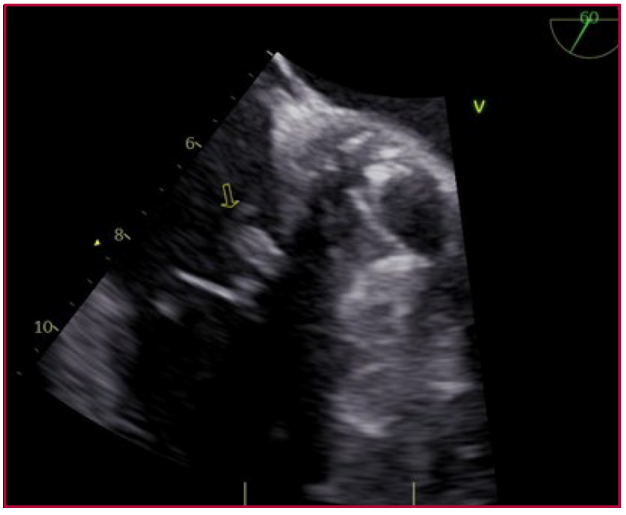

Fig. 2. TEE: View at 60°. Tricuspid septal leaflet vegetation is observed.

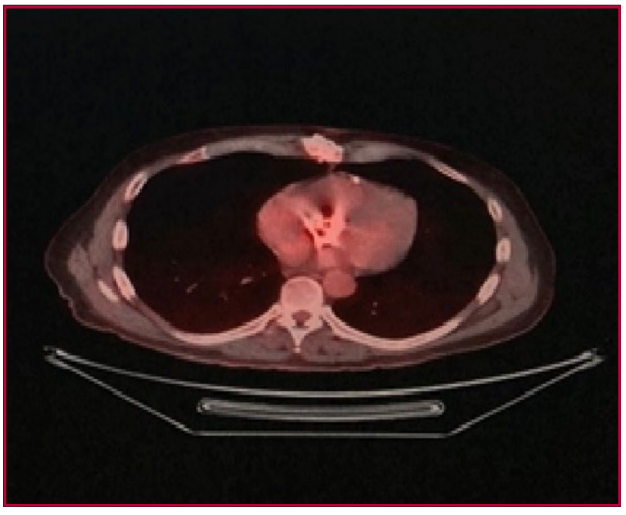

Fig. 3. PET/CT with fluorine-18 deoxyglucose: transverse projection. Diffuse uptake in the aortic prosthesis is observed.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material).

Ethical considerations

Not applicable.

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JORGE THIERER[MTSAC]

A meta-analysis confirms the effects of walking on cardiovascular prognosis

Paluch AE, Bajpai S, Ballin M, Bassett DR, Buford TW, Carnethon MR, et al. Prospective Association of Daily Steps With Cardiovascular Disease: A Harmonized Meta-Analysis. **Circulation 2023;147:122-31. https://doi.org/10.1161/CIRCULATIONAHA.122.061288.**

Countless observational studies have associated physical activity with improved vital prognosis and a reduced risk of diabetes mellitus, malignancies, and cardiovascular disease, among others. In fact, clinical practice guidelines for cardiovascular prevention recommend vigorous physical activity or moderate activity for at least 75 minutes a week or 150 minutes a week, respectively. Walking is certainly the most accessible, manageable, and simple form of physical activity. It is widely acknowledged that 10 000 daily steps are the target to improve life expectancy in terms of both quantity and quality. In 2022, Paluch et al. published a meta-analysis of 15 observational studies in 47 471 adults with a median follow-up of 7.1 years. The population was divided into quartiles according to the daily number of steps, with a median of 3553, 5801, 7842, and 10 901 for the first, second, third and fourth quartiles, respectively. As compared to the lowest quartile, the hazard ratio (HR) adjusted for all-cause mortality was 0.60 (95% CI [confidence interval] 0.51-0.71) for the second quartile, 0.55 (95% CI 0.49-0.62) for the third quartile, and 0.47 (95% CI 0.39-0.57) for the fourth quartile. The mortality risk was gradually reduced in ≥60-year adults with an increasing number of up to 6000-8000 steps a day, and in <60-year-olds with up to 8000-10 000 daily steps. When adjusting for the daily number of steps, the association between a higher frequency of steps and mortality diminished, though still remarkable for a daily walk reaching 30 minutes and 60 minutes; however, there was no significant association between the time spent walking at 40 steps/min or faster, or 100 steps/min or faster.

The same group of authors has now published a meta-analysis focused on defining the relationship between a daily walk and cardiovascular risk, including 8 studies of 20 152 participants (mean age 63.2±12.4 years; 52% females) followed for a mean of 6.2 years (range 2.8 to 12.6 years). Seven of these studies are also part of the previous meta-analysis. Each of the studies used a device (pedometer, accelerometer) to prospectively measure the number of daily steps for 3 to 7 days, according to the study, and this was averaged to define the daily number of steps. The incidence of fatal or non-fatal cardiovascular events was reported in every case. A cardiovascular event was any cardiac episode, a stroke, or heart failure (HF).

Among participants aged ≥60 years old (7 studies, 12 741 participants), the median number of daily steps was 4323. When divided into quartiles, the median number of steps was 1811 for the lowest quartile, and 3823, 5520 and 9259 for the second, third and fourth quartiles, respectively. The annual incidence of cardiovascular events was 1.93%. In a multivariate analysis including age, sex, time spent using the device, race/ethnic group, education or income, body mass index, as well as lifestyle-specific variables (e.g., smoking, alcohol), hypertension, diabetes mellitus, dyslipidemia, chronic conditions, and general medical condition, there was a significant association with a higher number of steps leading to better cardiovascular prognosis. Relative to the first quartile, the HR (95% CI) for cardiovascular events was 0.80 (0.69-0.93) for the second quartile, 0.62 (0.52-0.74) for the third quartile, and 0.51 (0.41-0.63) for the fourth quartile. There was a curvilinear relationship between the number of steps and risk reduction, with a steeper slope for steps 2000 to 6000 that was later attenuated.

For those aged <60 (4 studies, 7411 participants), the median of daily steps was 6911, and 3128, 5464, 7857, and 11,463 for the first to fourth quartiles, respectively. The annual incidence of cardiovascular events was 0.51%. The multivariate model showed no significant incidence of the number of steps on cardiovascular prognosis for the second, third or fourth quartiles versus the lowest quartile.

In the overall population, the HR (95% CI) for females in the final adjusted model was 0.81 (0.62-1.04) in the second quartile, 0.68 (0.48-0.97) in the third quartile, and 0.51 (0.35-0.76) in the fourth quartile, as compared to the first. For males, values were 0.76 (0.63-0.90), 0.63 (0.52-0.76), and 0.68 (0.51-0.89). For both males and females, there was a curvilinear relationship between the number of steps and cardiovascular prognosis, with a steeper slope of risk reduction of up to 8000 steps that was then attenuated.

An important aspect of this publication is the curvilinear association between the distance walked and the effect on events reduction. Particularly in those aged 60 or older, increasing the walk from 2000 to 6000 steps provides many advantages, and a median of about 9000 steps reduces cardiovascular risk to a half. Therefore, an initial increase is highly beneficial, while persistence and increased exercise help to reinforce and improve results. There is no need to achieve 10 000 steps to gain any benefits! Why does the effect become less evident in younger individuals? Probably

because incidence of cardiovascular disease is much lower in this population (4 times lower than annual incidence in this meta-analysis), and therefore, the time needed to experience some kind of effect must be much longer. Evaluating the effect on body weight, or emergence of hypertension or diabetes mellitus may evidence a very much suspected effect. It is worth noting that the effect of steps in this meta-analysis using devices is more powerful to determine the effort made than in analyses based on self-reporting, possibly since the former tend to be more objective. As with every observational study, there are limitations. Is the effect of walking due to the activity itself (with the whole array of favorable consequences, such as reduced endothelial dysfunction, reduced neurohormonal and inflammatory activation, and improved cardiopulmonary capacity)? Or is walking an expression of lower rates of baseline disease (whether cardiovascular or not) and part of a healthier lifestyle including more self-care and better eating habits, etc.? There is always a risk of residual confounding. This meta-analysis is also limited by lack of individual data and a distinction of the effects on each of the components of the cardiovascular compound. In any case, walking only require time, proper outfit, and footwear, and most of all, being willing to walk. The cost-benefit ratio has rarely been clearer. So, let's walk!

Cardiovascular rehabilitation and the effects on secondary prevention of coronary events. A meta-analysis

Dibben GO, Faulkner J, Oldridge N, Rees K, Thompson DR, Zwisler AD et al. Exercise-based cardiac rehabilitation for coronary heart disease: a meta-analysis. **Lancet 2022;400:1417-25. Eur Heart J 2023;44:452-69. https://doi.org/10.1093/eurheartj/ehac747.**

Cardiovascular rehabilitation (CR) has a Class I indication in the international guidelines for coronary disease management. Recently, an updated meta-analysis was published; this analysis was conducted according to the Cochrane Collaboration guidelines to evaluate the effect of exercise-based CR for patients with coronary artery disease on overall and cardiovascular mortality, events, quality of life, and cost-effectiveness. The Cochrane meta-analysis, released in 2016, had included 63 randomized trials until June 2014. This update added 22 studies published from 2016 to September 2020. There are 85 studies in 23 430 patients with a history of acute myocardial infarction (AMI), coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA), angina or coronary angiography with significant injuries who were randomized to exercise-based CR alone (45% of studies) or who had received some additional psychosocial or educational intervention (the remaining 55%), or control (no exercise, or routine care), and monitoring for at least 6 months. The endpoints were all-cause mortality and cardiovascular death, AMI, CABG, PTCA, and all-cause and cardiovascular hospitalization.

The median age of participants was 56; the median length of intervention was 6 months, with a median follow-up of 12 months. The frequency of intervention in the studies ranged from 1 to 7 times a week; sessions lasted 20 to 90 minutes, intensity went from 50% to 90% of the highest heart rate and 50% to 95% of aerobic capacity. Exercise was done at home in 21 studies. The effect of the intervention was reported at the longest follow-up as the continuous mean, and it was classified after 6-12 months, 12-36 months, and >36 months. According to Cochrane classification, the risk of bias (matters relative to deficits in randomization, follow-up, blinded events, selective report) was generally low or uncertain. Based on GRADE, a reference framework to assess the quality of evidence, during 6-12 months of follow-up (the most commonly reported period), it was moderate for all endpoints, except for CABG (high) and cardiovascular hospitalization (low).

CR did not affect all-cause mortality (reported in 60 studies) in none of the follow-up periods. Out of 33 studies reporting cardiovascular mortality, events occurred in 26 trials, where CR was associated with a relative risk (RR) of 0.74, a 95% CI 0.64–0.86 in the longest follow-up, and a number needed to treat (NNT) of 37. However, 6-12 months of follow-up showed no significant difference.

The incidence of AMI was reported in 42 studies, and events were experienced in 39 of these. CR was associated with a RR (95% CI) of 0.82 (0.70–0.96), and a NNT of 100. This reduction was due to the decrease observed after 6 to 12 months (RR 0.72) and >36 months (RR 0.67), while no difference was noted after 12-36 months. There was no difference as regards the incidence of CABG or PTCA, with or without CR. Twenty-two studies reported incidence of all-cause hospitalization, and 21 studies had events, where CR was shown with a RR (95% CI) of 0.77 (0.67-0.89) and a NNT of 37. There were no effects on cardiovascular mortality. Six studies evaluating the effect on SF-36 questionary, and 20 out of 32 trials including other methods of measurement reported improved quality of life. The difference in costs versus traditional care was heterogeneous in 8 cost studies, and a significant difference was found in one of them. Only 3 studies reported an acceptable cost-effectiveness ratio.

The relevance of this meta-analysis lies in the number of patients enrolled and its contemporaneous nature, making it possible to extend evidence to CR in the setting of the latest pharmacologic treatment. Another advantage is the inclusion of 21 studies in low to moderate income countries, where the effect of the intervention was no different from that in high-income nations. Results are generally reliable and confirm reduced cardiovascular mortality and AMI incidence, as well as all-cause hospitalization. However, they are not very clear concerning cost-effectiveness, and the effect

on quality-of-life scores, though significant in many trials, is not always clinically relevant. The heterogeneous population, the background heart condition, schedules, the amount of exercise, etc. may impact on a lack of uniform results. In addition, in half of the cases, follow-up lasted less than 12 months. As above stated, the effects of CR cannot be ascribed only to the physical activity it entails, unless we consider that taking part in a CR program also involves closer contact with the healthcare system, and a higher possibility of identifying manageable impairments, and that in more than half of the studies, CR involved psychosocial or educational support as well. Anyway, CR appears to be a positive intervention for secondary prevention of coronary artery disease, and it seems increasingly wrong to leave it out, at least when deciding treatment for many of our patients.

High-sensitive troponin T and NT-proBNP in SPRINT study: it is not always as expected

Berry JD, Chen H, Nambi V, Ambrosius WT, Ascher SB, Shlipak MG et al. Effect of Intensive Blood Pressure Control on Troponin and Natriuretic Peptide Levels: Findings From SPRINT. **Circulation 2023;147:310-23. https://doi.org/10.1161/CIRCULATIONAHA.122.059960.**

The use of biomarkers in cardiovascular disease is here to stay. The two biomarkers most commonly used in daily practice and in the context of interventional studies are undoubtedly high-sensitive troponin, T or I, and natriuretic peptides, BNP or NT-proBNP. Troponin expresses myocardial injury; it is an essential part of the diagnosis of acute coronary syndromes, but, in addition, its acute or chronic elevation indicates worse prognosis in a variety of conditions, from peripheral artery disease to atrial fibrillation, in respiratory diseases or in the non-cardiac surgery postoperative period. Natriuretic peptides are elevated as an expression of increased wall stress in both ventricles; they are usually associated with elevated filling pressures, but they also increase in the context of renal dysfunction, general cardiovascular involvement, and activation of inflammatory events. They are used in the differential diagnosis of dyspnea of cardiac versus respiratory origin in acute conditions, in the characterization and follow-up of the response to treatment of chronic heart failure, in determining the severity of valvular heart disease, and so on. A generalized concept is that the increase in any of both biomarkers implies greater cardiovascular involvement and is associated with worse outcome. Another concept is that treatments that improve cardiovascular prognosis should generate a reduction in both biomarker values, or at least not increase them.

Despite all the uses above mentioned, the use of troponin or natriuretic peptides in the context of arterial hypertension is infrequent, and information on their usefulness in this condition is scarce. A subanalysis of the SPRINT study challenges some of the assumptions that have been made. As we all know, the SPRINT study was a randomized, open-label, controlled study that compared two strategies in hypertensive patients: to achieve a systolic blood pressure (SBP) <140 mmHg (standard treatment, ST) or <120 mmHg (intensive treatment, IT). It included patients with SBP between 130 and 180 mmHg, >50 years old and with at least one cardiovascular risk criterion: previous clinical or subclinical cardiovascular disease, except stroke; 10-year event risk according to the Framingham score of at least 15%; glomerular filtration rate between 20 and 59 mL/min/1.73 m2; ≥75 years old. Patients with diabetes were excluded. The primary endpoint was a composite of acute myocardial infarction (AMI), other acute coronary syndromes, stroke, acute decompensated heart failure (HF), and cardiovascular death. A total of 9361 patients were enrolled, with a mean follow-up of 3.26 years. The annual incidence of primary endpoint was 1.65% in the IT arm and 2.19% in the ST arm (HR 0.75, 95% CI 0.64-0.89), with no significant difference in the incidence of AMI or stroke, but significant differences in the incidence of acute HF (HR 0.62, 95% CI 0.45-0.84), cardiovascular death (HR 0.57, 95% CI 0.38-0.85) and all-cause death (1.03% vs. 1.40% per year, HR 0.73, 95% CI: 0.60-0.90).

A substudy of SPRINT including patients with baseline and 1-year measurements of high-sensitive troponin T (hsTnT) and NT-proBNP has just been published. The study aimed to evaluate the relationship of the changes in both biomarkers (1-year minus baseline) with the primary endpoint of all-cause death and incidence of HF, and the secondary endpoint of the other cardiovascular events. Such change was analyzed as a continuous variable and as a categorical variable. In each case, the analysis was stratified based on the baseline value. The minimum detection value for hsTnT was 6 ng/L. Participants with undetectable hsTnT at baseline (<6 ng/L), were classified at follow-up as patients with incident hsTnT elevation (≥6 ng/L at 1 year) or patients with no change (<6 ng/L). Participants with baseline levels ≥6 ng/L, were classified at follow-up they into 3 mutually exclusive categories: decrease (decrease ≥50%), increase (increase ≥50%), or no change (change <50% from baseline). The minimum NT-proBNP detection value was 5 pg/mL, but the cutoff value for the analysis was 125 pg/mL, as it is considered the one that in clinical practice divides normal from elevated values. For patients with baseline NT-proBNP values <125 pg/mL, changes were classified as increase (increase ≥50% up to a value ≥125 pg/mL), decrease (decrease ≥50%), or no change (change <50% in either direction). For those with baseline NT-proBNP values ≥125 pg/mL, changes were also classified as increase (increase ≥50%), decrease (decrease ≥50% up to a value <125 pg/mL), or no change (change <50 %).

Regarding hsTnT, out of 9361 patients, 8828 and

8027 had baseline (median 9.4 ng/L and 99th percentile 48.6 ng/L) and 1-year (median 9.5 ng/L and 99th percentile 53 ng/L) measurements, respectively. A total of 21.2% of patients had undetectable hsTnT value at baseline; of these, 20.3% had a value ≥6 ng/L at 1 year. Among the 78.8 % of patients with hsTnT ≥6 ng/L at baseline, there was no significant change in 89.4%, decrease in 6.1% and increase in 4.5%. Increased hs-TnT was associated with male sex, older age, higher baseline SBP, and worse renal function. In patients with increased hsTnT, the mean annual change in glomerular filtration rate was -8.9 mL/min/1.73m², compared to an increase of 1.7 mL/min/1.73m² in those with decreased hsTnT. There was no variation in diuretic use throughout follow-up in those patients with decreased hsTnT. Belonging to the IT arm was more frequent in those in whom hsTnT increased (60.8%) than in those in whom it decreased (43.7%). In multivariate analysis, when considering clinical characteristics and the initial value of hsTnT, IT was associated with a significant 3% increase in biomarker values, but when considering the change in glomerular filtration rate, the difference between IT and ST disappeared. In mediation analysis, 96% of the effect of IT with respect to the increase in hsTnT was explained by the change in glomerular filtration rate.

Regarding NT-proBNP, 8836 had baseline measurements (median of 86 pg/mL, 38.2% with values ≥125 pg/mL) and 8040 had measurements at 1 year (median of 82 pg/mL, 37.4% with values ≥125 pg/mL). A total of 62.6% had values <125 pg/mL at baseline; of these, 11% had an increase, 17.7% had a decrease, and 71.3% had no significant change. Among the 37.4% of patients with NT-proBNP ≥125 pg/mL, 16.7% had an increase, 12.9% had a decrease, and 70.3% had no significant change. Increased NT-proBNP was associated with older age, worse renal function and lower SPB. Glomerular filtration rate declined in all groups, with only small differences according to baseline and direction of NT-proBNP change; but SBP reduction was higher in those with decreased NT-proBNP (>20 mmHg) than in those with increased NT-proBNP (about 11 mmHg). In patients with decreased NT-proBNP, diuretic use increased over the year. In contrast to hsTnT, IT was associated with a significant 10% decrease in NT-proBNP values, even when adjusting for changes in glomerular filtration rate. When adjusting for changes in SBP, the effect difference between IT and ST on NT-proBNP disappeared.

Both increases in hsTnT and NT-proBNP were associated with higher incidence of all-cause death and incidence of HF. In formal mediation analyses, changes in NT-proBNP explained 15.4% of the treatment effect on HF incidence, and 10.4% of the effect on the composite endpoint. In contrast, changes in hsTnT did not contribute to explain the treatment effect.

The substudy we are considering provides very interesting conclusions. It confirms that in the follow-up of patients with arterial hypertension, treatment has certain effects on the two most frequently used biomarkers, but they are not always as expected. Initially, both appear to be strongly linked to prognosis. But we have noted that the IT, associated with better evolution in the study, has a counterintuitive effect on hsTnT: in more than 80% of the cases there is no significant variation (when improved prognosis would have been expected to be associated with a reduction in the values), and, in fact, when hsTnT is considered as a continuous variable, its values increase. It is true that the increase is small (overall 3%), and that it is diluted when considering the variations in glomerular filtration rate. It could also be thought of the effect of IT by reducing diastolic BP (DBP) and thus generating coronary hypoperfusion, as an alternative hypothesis for the increase in troponin. However, in the multivariate analysis, the changes in DBP do not explain the changes in hsTnT. The increase is then the result of the treatment effect on renal function. Finally, this goes along with the fact that it is not possible to verify an independent influence of the biomarker on the prognosis in hypertension treatment. Therefore, is hsTnT useful for monitoring the effect of antihypertensive treatment?

In contrast, the effect of the IT on NT-proBNP is remarkable (10% decrease), independent of changes in glomerular filtration rate, and clearly associated with the effect on BP. In this case, we found no differences between what has been expected and what has been found. This decrease generates a reduction in wall stress and filling pressures. Moreover, in the mediation analysis, changes in the biomarker influence on patients' life course.

This analysis, then, sheds light on an infrequent phenomenon, but one which have just seen: the lack of absolute correlation between the treatment effects on surrogate endpoints and the clinical phenomena that such treatment aims at, and generates. A wake-up call to avoid automatic thinking, which does not consider the nuances and interactions between the different factors that condition prognosis.

Congenital long QT syndrome: how to avoid overdiagnosis. A report from the Mayo Clinic

Bains S, Neves R, Bos JM, Giudicessi JR, MacIntyre C, Ackerman MJ. Phenotypes of Overdiagnosed Long QT Syndrome. **J Am Coll Cardiol 2023;81:477-86. https://doi.org/10.1016/j.jacc.2022.11.036.**

Congenital long QT syndrome (LQTS) is characterized by a prolonged QT interval and ventricular arrhythmia primarily caused by adrenergic activation. Mean age of presentation is 14 years. The annual rate of sudden cardiac death (SCD) in untreated asymptomatic LQTS patients is less than 0.5%, a figure that rises to 5% in those with a history of syncope. There are 3 genes indisputably linked to LQTS, which cause the LQTS1, LQTS2 and LQTS3 forms: KCNQ1, KCNH2 and SCN5A, respectively, which are specifi-

cally activated by exercise (LQTS1), emotional stress (LQTS2) and sleep (LQTS3). The diagnosis rests on the ECG, where a QTc ≥480 msec fundamentally, and to a lesser extent also a QTc of 460 to 479 msec in the presence of arrhythmic syncope or cardiac arrest or torsade de pointes; and then a QTc of 450-459 msec in men, or alterations of the T wave, and even less bradycardia according to age are all elements to consider. Clinical (history of syncope with or without stress), familial (family members with a definite diagnosis of LQTS or a history of SCD in a first-degree relative <30 years), and genetic (verifiable pathogenic mutation) findings contribute to the diagnosis. All this information is condensed in the Schwartz score, and a score >3 (QTc ≥ 480 msec by itself already adds 3.5 points, the same as a pathogenic mutation; unexplained syncope, torsade de pointes or a QTc of 460-479 msec in the presence of syncope add up to 2 points) makes a diagnosis of LQTS. It is essential not to be mistaken in the diagnosis, because it implies, depending on the case and the type, the use of antiarrhythmic drugs, the implantation of a cardioverter defibrillator (ICD) or cardiac sympathetic denervation. That is why the publication we are commenting on is so interesting.

The authors, from the Mayo Clinic, explored the records of the arrhythmia clinic database from July 2000 to October 2021 and, of all patients admitted with a diagnosis of LQTS, identified those in whom finally that diagnosis was discarded. Among 1841 patients, this occurred in 290 (16%), 60% women with a mean age of 22±14 years. Twenty per cent of these patients had self-referred to the Clinic, the rest had been referred by a physician. The initial QTc was 504±39 ms. 80% were receiving beta-blockers, and 8% had received an ICD. In 67% of the cases LQTS had been diagnosed for a single reason, in the rest for more than one reason.

What were the reasons that led to an overdiagnosis of LQTS? The authors divided them according to the diagnostic criteria that we cited. Clinical causes were present in 38% of cases. As the sole cause or associated with others, vasovagal syncope was the most frequent. As striking data, mean QTc in the ECG after syncope was 487 msec; the one measured in the consultation at the Clinic was 422 msec. Another frequent clinical cause was a prolongation that was later interpreted as isolated or transient, for different reasons: panic attack, hypokalemia, hypoglycemia, drug action, etc. In 29% of the cases, the error was diagnostic, mainly due to including the U wave in the QT interval, or due to an erroneous measurement in cases of borderline intervals. There were also cases of QT prolongation overestimation in an epinephrine test, or in a tilt test (tests that are done in some cases to unmask occult LQTS). The diagnostic error was genetic in 17% of the cases. Among 290 patients, 196 had undergone a genetic test, which was initially positive in 68 (in two thirds of the cases for variants of uncertain significance, presumably linked to LQTS, and in the rest for "possibly pathogenic" variables). After the authors' analysis, the 68 cases were discarded, as they were deemed irrelevant, the relationship with LQTS was very doubtful, and occurred in the presence of an incompatible clinical condition. Finally, in 16% of the cases the error lay in a misinterpretation of the family history, for example SCD but in the context of an acute myocardial infarction, or a false diagnosis of LQTS in a close relative.

And how did rejecting the diagnosis affect the fate of the patients? Of those who were on beta-blockers, 84% stopped receiving them; of those with an ICD, 45% had it removed. A search of all patients and their vital records after passing through the Mayo Clinic revealed only 2 deaths from causes unrelated to LQTS.

The diagnosis of LQTS is of vital importance. This publication emphasizes the false positives of the diagnosis. Clinical and ECG diagnostic errors are frequent causes, and to a lesser extent a misinterpretation of family history or a misreading of genetic test results. Some keys to avoid misunderstandings are: a) adequately distinguish vasovagal syncope (generally preceded by characteristic prodromes) from arrhythmic syncope taking into account that in a vasovagal syncope there may be immediate QT prolongation, so subsequent ECG examination is fundamental; b) be sure not to include the U wave in the QT measurement; c) take into account electrolyte disturbances, drug use, clinical conditions, which may be associated with QT prolongation; d) interpret ECG changes in a clinical context; e) be very precise with the family history to avoid erroneous adjudications; f) it is fundamental to leave genetic diagnosis in the hands of experts who know how to deal with variants of uncertain significance and those associated with doubtful pathogenesis.

The authors emphasize that overdiagnosis generated in their population no less than 500 years of unnecessary drug treatment, and at least (corroborated by subsequent evolution) half of pointless ICD implantations. And it is clear that all this is true. Of course, we must also bear in mind that here we are talking about false positives. Unfortunately, there are no reports of false negatives, those LQTS carriers who never reached the diagnosis. And that error is as burdensome as the one analyzed here. In conclusion, remembering the existence of the syndrome, being alert to the possibility of finding it, and at the same time, ready to avoid misdiagnosis, seems to be the best advice.

Low QRS voltages: a finding with its own weight in the context of cardiac amyloidosis

Cipriani A, De Michieli L, Porcari A, Licchelli L, Sinigiani G, Tini G et al. Low QRS Voltages in Cardiac Amyloidosis: Clinical Correlates and Prognostic Value. **JACC CardioOncol 2022;4:458-70. https://doi.org/10.1016/j.jaccao.2022.08.007.**

The diagnosis of cardiac amyloidosis (CA) relies essentially on imaging methods and laboratory measure-

ments, which allow confirming or ruling out the presence of light chain (AL) amyloidosis or transthyretin (ATTR) amyloidosis based on their results. However, the ECG is still a gateway to diagnosis, and can provide useful information. A series of "red flags" have been indicated in the ECG that should make us suspect the pathology: atrial fibrillation, atrioventricular conduction disorders, P wave alterations, but fundamentally the patent of pseudoinfarction, and the presence of low QRS voltages (LQRSV) coexisting with increased wall thickness in the echocardiogram. And it is true that when, in a patient with heart failure and increased thicknesses on the echocardiogram, the ECG indicates the presence of LQRSV, the presumptive diagnosis of CA immediately arises. Now, what is the prevalence of this finding in patients with CA? What is its significance beyond guiding us in the diagnosis? A recent publication brings the answer to these questions.

This is a retrospective study carried out in 6 Italian referral centers for patients with CA, which included 411 patients (120 with AL, 291 with ATTR) diagnosed between the beginning of 2017 and the end of 2020. ECG, echocardiogram, laboratory tests that included the measurement of natriuretic peptides, and nuclear medicine studies. LQRSV was defined as QRS complexes with an amplitude ≤5 mm in all peripheral leads, including the positive and negative component in each complex. A QRS score was also considered by adding the amplitude of the Q, R and S components, in the limb and precordial leads.

Seventy-four percent of the patients were in sinus rhythm. Most were in FC I-II (65% in AL amyloidosis and 78% in ATTR); 169 patients (41%) presented LQRSV (55% with AL, 35% with ATTR, $p < 0.001$). The voltage-to-mass ratio was somewhat lower in the ATTR than in the AL CA, but without significant difference. The prevalence of LQRSV was higher in younger patients, in FC III, with higher values of natriuretic peptides, lower ventricular volume, and more pericardial effusion. In patients with AL CA, LQRSV were also associated with a pseudoinfarction pattern and greater wall thickness on echocardiography. In patients with ATTR CA, LQRSV were less common in stage I of the UK National Amyloidosis Center (NAC) classification, which is defined as NT-proBNP ≤3000 pg./mL and glomerular filtration rate ≥45 mL/min (the stage III corresponds to NT-proBNP > 3000 pg./mL and glomerular filtration rate < 45 mL/min, and stage II to intermediate values). In multivariate analysis, LQRSV were independently associated with younger age, more advanced FC, and higher natriuretic peptides in AL CA, and with pericardial effusion and less tricuspid annular plane systolic excursion (TAPSE) in ATTR CA.

The median follow-up was 33 months. In AL CA, the probability of survival at 40 months was 90% in the group without LQRSV, and 60% in the group with the finding ($p=0.003$). In multivariate analysis, LQRSV were independent predictors of cardiovascular death (HR 1.76; 95% CI 2.41-10.18; $p= 0.031$). In the ATTR CA, the probability of survival at 40 months was 95% in the group without LQRSV, and 80% in the group with the finding ($p=0.009$). In multivariate analysis, LQRSV were independent predictors of cardiovascular death (HR 2.64; 95% CI 1.82-20.17; $p= 0.005$). In this type of CA, the finding of LQRSV added prognostic value to the NAC classification only in stage II, not in I or III.

The refinement of diagnostic methods and the appearance of treatments that can modify the evolution of CA (an entity that until a few years ago had always an ominous prognosis), has led to greater awareness of its presence. There is undoubtedly more CA than we suspect; many cases of hematological disease, aortic stenosis, hypertrophic cardiomyopathy, HF with preserved left ventricular ejection fraction, present with amyloidosis. And, in this context, as we said, the ECG does not confirm or rule out CA, but it can act as an "alarm clock" that leads us to follow a diagnostic path. The publication we are commenting remarks the finding of LQRSV, by demonstrating its prognostic capacity. It is true that LQRSV are not a specific finding of CA: we can find them in chronic obstructive pulmonary disease, marked obesity, large pericardial effusion, and arrhythmogenic cardiomyopathy. For this reason, it is essential to interpret its presence in the clinical context and in light of other complementary studies.

LQRSV are more prevalent in AC AL than in ATTR. Different explanations can be put forward. The mechanisms involved in the gestation of LQRSVs may have to do with a decrease in the myocytes mass (due to necrosis because of a direct toxic effect of the myofibrils, or due to the action of circulating immunoglobulins) or to an infiltration phenomenon that reduces the electrical signal. In AL CA there is more myocardial edema and inflammation in earlier stages, and this may explain the high prevalence of LQRSV. ATTR CA occurs in older patients, with a higher prevalence of age-associated left ventricular hypertrophy, the presence of arterial hypertension or valvular disease, all plausible reasons to justify a lower presence of low QRS voltages. Undoubtedly, systematic cardiac magnetic resonance imaging would have contributed to explain the differences between the two entities. What is clear is that, present in half of the patients with A CAL, and in a third of those with ATTR CA, in both cases the LQRSV indicate sicker patients and have independent prognostic value. So, they should be considered, beyond the anecdotal, as an indicator of greater severity and therefore the need for more advanced therapy.

2023 Academic Ceremony Speech

Discurso del acto académico 2023

Authorities of: National Academy of Medicine, Argentine Society of Cardiology, Argentine Foundation of Cardiology, Argentine Journal of Cardiology, Colleagues, family, and friends.

Today, I assume the presidency of the Argentine Society of Cardiology (SAC), a high responsibility that I hope to carry out satisfactorily.

I thank all those who supported me in this difficult but honorable task for giving me this opportunity; I will not disappoint them.

I will tell you a brief story about my origins, which will help you understand the honor and joy I feel as I assume this position.

My roots are very humble. My grandfather, a Syrian immigrant, began to earn his living selling combs and hair combs using a Syrian accent and ended up burning garbage in the furnace of the Municipality of the City of Buenos Aires. Maybe that is why my grandfather, even with his bad pronunciation, sang "la marchita".

My parents, Zulema and Enrique, had no choice but to live with my grandparents in the chorizo house in the neighborhood of Boedo. My sister Victoria and I were born there; each family had only one room.

My years at school were characterized by a terrible behavior, with absolutely no dedication to study. With my dear friends of those days, Tito, Rubén and twenty others, we just wanted to play football, and since we lived only five blocks away from San Lorenzo Club, we were eager to play the role of parking attendants when "El Ciclón" was playing.

Nowadays, I admire the great effort and the categorical arguments that my Dad used to make me change my attitude.

My father sorted letters at the Central Post Office, and later worked as a collector for a cosmetics company. He used to insist me to go to San Lorenzo club to practice different and more productive activities than the ones I was doing at that time. Finally, I listened to him and chose judo, a practice that had the advantage of learning how to fight, something I was looking forward to at the time, especially beating the big guys.

At that time, besides practicing judo, I met other friends -Napia, Ovich, Rafa, Beto, el Fasu, Caru- and then I magically began to study, and was in the honor roll in high school. I entered the School of Medicine and after graduating, I became resident and chief resident in an institution that was just around the corner of this building, indeed, it depended on the National Academy of Medicine: the beloved Pombo Foundation.

My tribute to my parents for having completed my career and to this country that gives the emerging classes the possibility of training.

I started in the SAC a long time ago with the biannual cardiology course, and believe me, I was astonished when I saw this structure. In 2000, I began participating in the Council on Hypertension (CAHTA), which at that time was characterized for being very selective, and this was not fair for many people. With Alejandro Delucchi, Olga Páez, Pablo Rodríguez, Marquitos Marín, Laura Brandani and Diego Fernández, we sought to change it into an inclusive board. While I was director of CAHTA, Dr. Tajer commissioned me to organize an international course for the Pan American Health Organization (PAHO) on the management of hypertension in primary healthcare teams. With this task we learned a lot about timing and quality of presentation in virtual courses, and how to achieve international links.

Later, I recall, and I am grateful to Guillermo Fábregues for his generosity in offering me the position of Pro-Treasurer on the Board of Directors. Those were economically critical times for our society, but during those two years we worked in team to recover it.

Sometime later, Miguel González and Ricardo Migliore asked me to coordinate the Districts Area and to implement a reform. We carried out a "regionalization" with Fabiana and Rodrigo, represented by rotating conferences in each district so that each region would create its own program and be self-supporting. This plan was successful, and nowadays we count with 10 regional conferences.

I was immediately appointed Coordinator of Areas for one year, and before finishing this position, my friend Héctor Deschle offered me the position of General Coordinator of the 2020 Congress, an enormous challenge.

We started off well, and when COVID-19 emerged, no one believed in that "little flu", so we continued with the congress program. The program was ready by June, but we had to fully redo it, as it had to be transformed into a virtual event.

Then, the last twelve former presidents of the institution trusted in me and elected me first vice president.

The previous story serves as introduction of what I wish to communicate: the SAC does not put limits on anyone, each person -this was my experience- can meet people, change structures, learn and have fun at the same time. One person has his or her own limits. SAC belongs to its members.

The main intention of our team is to continue and promote the University Institute as the backbone of medical education, and to strengthen the councils, backbone of our structure, and districts, which are 35 nowadays; Santa Fe district was the last one to be created this year. A few years ago, the participation of the districts in the annual Congress was 9% and is 30% now. The Congress technical secretariat has been conducted by members of the districts over the last three years, and the director of the flagship course, PROSAC, is from La Rioja.

The concept and motto that characterizes us is an inclusive and open-door SAC.

We are creating a funding to support our own research.

Our obsession is to increase the participation of young professionals; we are projecting a future SAC for the next 10 years.

We are also aware of the back-and-forth interaction with international and national societies, so the proposal is to strengthen these relationships while paying attention to reciprocity.

Another pending goal is to improve our working conditions by interacting with the College of Cardiologists and opening up to health policies.

In addition, we must improve the administrative area, making it more efficient and professional.

I would like to make a special mention to my five children Yamila, Federico, Emiliano, Sebastián and Julián for representing the miracle of life. When I saw them for the first time my heart knew no bounds, thank you for supporting me in this profession. Also, for meeting Olga, who insisted on not letting me down, for her shrewdness, her unconditional support and for walking by my side along this path that led me to the presidency.

Finally, I want to say thank you very much, I hope we have a spectacular year, say goodbye to the committee that is leaving, I will miss you all, especially Héctor who worked with me on the Board of Directors in 2016, 2021 and 2022 and from whom I learned many things, just as I learned from Alejandro Hershon one year ago.

I also bid farewell to Verónica Wolberg and Héctor Santa María who had an excellent participation in our project.

I am grateful to the staff of the Society for their work, and particularly to Marina for her efficiency and dedication.

Thank you, and I hope we win on Sunday.

Dr. Claudio Majul
President of the Argentine Society of Cardiology

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