



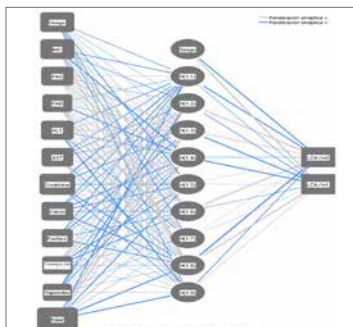
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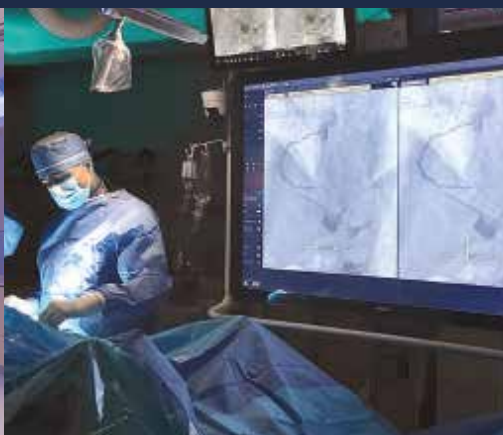
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Transthyretin amyloid cardiomyopathy: the importance of early intervention to improve prognosis.

Montserrat Carrillo Estrada, Axel H. Hernández Pineda

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ABSTRACT

The article "Transthyretin Amyloid Cardiomyopathy: clinical features and staging, indications for treatment and mortality" describes the clinical characteristics of 32 patients diagnosed non-invasively with transthyretin amyloid cardiomyopathy (ATTR-CM). Most patients had wild-type ATTR-CM and presented with New York Heart Association (NYHA) functional class II symptoms, preserved left ventricular ejection fraction, and typical cardiac magnetic resonance findings associated with the disease. Atrial fibrillation was present in 50% of the patients, while 25% had moderate or severe aortic stenosis. The NAC staging system was used in these patients to establish prognosis, with 75% of patients were classified as stage I. Notably, only 25% of patients received the transthyretin stabilizer tafamidis, and most of those who died had not received disease-modifying therapy.

Transthyretin amyloid cardiomyopathy (ATTR-CM) has become extremely important in recent years due to advancements in noninvasive diagnosis and treatment, as well as a higher awareness on the disease. This pathology is characterized by an anomalous folding of transthyretin, a protein synthesized mainly in the liver, leading to the formation of a material called amyloid, depositing in the cardiomyocytes interstitia. This may lead to restrictive cardiomyopathy, which has a somber prognosis if detected in late stages.¹

In the article "Transthyretin amyloid cardiomyopathy: clinical features and staging, indications for treatment and mortality", the authors present the results of a retrospective investigation describing the clinical characteristics, treatment and mortality in a cohort of patients with this diagnosis.² Most of the current information about ATTR-CM is drawn precisely from single-center and observational studies, and registries, allowing to learn about the contemporary behavior of this pathology.

The 32 patients included were diagnosed by a noninvasive modality, with a radioactive tracer bone scan with positive bone uptake (degrees 2 or 3 of Perugini), ruling out a monoclonal component with measurement of serum free light chains, as well as electrophoresis with serum and urine immunofixation. This highlights the current usefulness of bone scans with pyrophosphates for a noninvasive diagnosis of this disease, remembering that in some cases

with non-conclusive results, histological confirmation for cardiac amyloidosis will still be required.³

In this study, in patients in whom the genetic test to detect hereditary ATTR-CM cases was performed, the Val-30Met mutation was found in 6.2% of cases. Half of the patients included in this cohort were in functional class II of the New York Heart Association; and the most frequent extracardiac manifestations were digestive disorders, carpal tunnel syndrome and the presence of peripheral neuropathy. All patients presented abnormal surface ECG. As to the imaging tests, patients presented preserved left ventricular ejection fraction in most cases; with an E/e' median of 16.5 and a global longitudinal strain median of -9.5%, which translates a significant increase in left ventricular filling pressures, as well as deterioration of longitudinal strain in fibers. Cardiac MRI was conducted in 50% of cases, observing typical findings, suggesting a manifest state of the disease. Most patients with reduced ejection fraction died during follow-up.

A very relevant finding is that half of patients included had atrial fibrillation and a fourth presented moderate or severe aortic stenosis. Given the high thromboembolic risk accompanying ATTR-CM, anticoagulation in patients presenting atrial fibrillation is indicated in all patients, regardless of risk estimated by scores such as CHA2DS2-VA; pharmacological strategies for rhythm or rate control should be used cautiously, due to the low tolerance of nega-

tive chronotropic drugs in this population.⁴ Aortic stenosis that coexists with ATTR-CM is associated with a high rate of adverse cardiovascular events and mortality; in these cases, transcatheter valve implant has proven to be a feasible treatment option, added to disease-modifying therapy.⁵

There are different publications focused on risk stratification in patients with transthyretin amyloid CM; the different available scores include clinical and biochemical characteristics, such as renal function tests and myocardial injury biomarkers measurement (troponins and natriuretic peptides). In this research, the British score of the National Amyloidosis Centre was used, which includes 3 stages and takes NT-proBNP into account (with a cutoff point of 3000 ng/L) and glomerular filtration rate (cutoff point of 45 ml/min).⁶ It was found that three fourths of patients were in stage I. This probably translates the impact of new diagnostic methods enabling a detection of this disease in less advanced stages. Recently, risk estimation has also been proposed with the heart failure classification of the American College of Cardiology/American Heart Association, showing it has a good performance to predict mortality in patients with ATTR-CM.⁷

In the patients included, only a fourth had disease-modifying therapy with tafamidis, a transthyretin tetramer stabilizer, indicated in the treatment for ATTR-CM, both the wild-type and hereditary.³ Recently, the ATTRIBUTE-CM trial has proven the efficacy of acoramidis, another stabilizer with great transthyretin affinity, in terms of mortality, morbidity and functionality compared with placebo.⁸ Also, in the HELIOS-B trial, it was proven that use of vutrisiran, a therapeutic agent of RNA interference, reduced all-cause mortality and cardiovascular events in patients with wild-type and hereditary ATTR-CM, even in those with no treatment with tafamidis.⁹ This makes it a promising therapeutic alternative.

It is important to highlight that in this cohort, most patients that died had no treatment with tafamidis. Ideally, great advancements to achieve an early diagnosis of ATTR-CM should be followed by the onset of disease-modifying treatment. It is particularly important to identify the obstacles there may be in the environment for the administration of a drug that has proven to decrease mortality in patients with ATTR-CM.¹⁰ These real world studies make the gaps between the development of new therapies, scientific validation and their subsequent effective implementation in clinical practice visible.

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When distance is the enemy: barriers in the treatment of acute myocardial infarction

Claudio Tinoco Mesquita, Carlos Henrique Bonfim Osaka.

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ABSTRACT

Cardiovascular disease is the leading cause of death in Latin America, and ST-segment elevation myocardial infarction (STEMI) accounts for a large portion of this burden. The editorial comments on a study that examined how distance from the healthcare center affects reperfusion time and clinical outcomes in Santa Fe, Argentina. Results show that delays in care increase with distance, reducing the chances of reperfusion. A survey also identified major structural barriers, including lack of cardiologists and thrombolytics in first-contact centers. The editorial emphasizes the need for regional infarction networks, use of telemedicine to interpret ECGs, wider availability of thrombolytics, and clear referral protocols. These findings highlight how disparities in access to care adversely affect outcomes and provide actionable strategies to improve cardiovascular prognosis in Latin America. The study demonstrates that addressing geographic and structural barriers is essential to reduce inequities and improve survival in patients with acute myocardial infarction.

"They always say time changes things, but you actually have to change them yourself"

Andy Warhol

Acute Myocardial Infarction (AMI) is the leading cause of death from cardiovascular diseases (CVD). Latin America has one of the highest global rates of cardiovascular mortality, with myocardial infarction standing out, surpassing even the average mortality rates of developing regions in Asia and being four times higher than in high-income countries¹. In Argentina, cardiovascular diseases are responsible for approximately 30% of deaths in the country, highlighting a serious public health issue². A recent meta-analysis showed that the in-hospital mortality rate for ST-segment elevation myocardial infarction (STEMI) in Argentina ranged from 8.0% to 14.0%, with a pooled average of 9.6%—figures like those observed in Brazil but higher than those in high-income countries³. Among the possible causes of this higher in-hospital mortality are the lower use of reperfusion therapies, such as primary angioplasty and fibrinolysis, as well as delays in care and structural barriers within the health system³.

We must congratulate the authors on the publication of the study: 'Delay in the transfer of patients with infarction

in the central-north region of Santa Fe. It is time to work in networks.' The study draws attention to an important issue: the impact of the distance between a patient's residence and the healthcare center on the outcomes of acute myocardial infarction treatment. This is an observational, retrospective, single-center study conducted between 2016 and 2023, involving 415 patients with ST-segment elevation myocardial infarction (STEMI) admitted to a coronary unit in Santa Fe, Argentina. Patients were classified into four zones based on their distance from the center (Z1: Santa Fe; Z2: ≤100 km; Z3: 101–200 km; Z4: >200 km). Clinical data, time to reperfusion, in-hospital events, and reasons for no reperfusion were analyzed. In addition, a telephone survey was conducted with 73 referring centers to identify logistical barriers. The main finding was that the time from symptom onset to admission increased progressively with distance (Z1: 4h; Z4: 16h), which impacted the reperfusion rate — 70.1% — with the main reason for no reperfusion being arrival outside the therapeutic window (60.5%). The survey of the centers revealed a shortage of specialists, lack of thrombolytics, and logistical failures as recurring barriers⁴.

In addition to clinical analyses, the authors conducted a telephone survey with coronary care units. The results revealed significant deficiencies: 34.2% of the centers did not have cardiologists on staff, and 50.7% had limited tempo-

rary hospitalization capacity, highlighting the fragility of the healthcare network. The study's findings underscore the importance of an organized healthcare system with specialized support to improve patient prognosis.

WHAT ARE THE MAIN LEARNING POINTS FROM THE STUDY?

The main learning point is the confirmation that distance directly impacts the time to reperfusion and is an important predictor of delay in the treatment of acute myocardial infarction⁵. It was observed that patients transferred from more distant regions had higher mortality and more in-hospital complications (heart failure, cardiogenic shock, lower ejection fraction). Another important insight is that the lack of specialists, lower use of thrombolytics, and insufficient coordination between care centers are systematic barriers contributing to delays. Most of the non-reperfused cases occurred due to arrival outside the therapeutic window, highlighting failures in care logistics.

The study reports how the lack of specialized professionals in primary care centers represents a serious issue for confirming the diagnosis of myocardial infarction (MI). In the same direction, Diercks et al, highlighted how delays in ECG interpretation during STEMI affect therapeutic prognosis, even when the patient is within the therapeutic window⁶. The absence of cardiologists in primary care centers, as pointed out in the current study, is a significant barrier to the prompt confirmation of MI diagnosis through electrocardiogram (ECG). This delay in ECG interpretation and therapeutic decision-making contributes to postponing the implementation of the most appropriate reperfusion strategy, whether thrombolysis or transfer to a center with angioplasty capability. Both studies, therefore, converge on the idea that the shortage of qualified professionals leads to critical delays in the diagnosis and treatment of MI, which, in turn, is associated with worse clinical outcomes, including a higher risk of complications such as cardiogenic shock and increased mortality. This adverse scenario is not exclusive to Argentina—it is shared by many countries in Latin America and demonstrates the urgent need to reduce disparities in access to emergency cardiovascular care in Latin America to improve patient outcomes^{7,8}.

HOW CAN WE USE THIS INFORMATION TO PROPOSE IMPROVEMENTS THAT IMPACT POPULATION HEALTH OUTCOMES?

Some potentially useful actions to improve the chances of early reperfusion in STEMI (Figure 1):

- 1) Implement regional infarction networks with clear triage and referral protocols based on geography and the technical capacity of centers.
- 2) Expand access to digital tools that support electrocardiogram interpretation, such as telemedicine or artificial intelligence, especially in primary care centers, for early diagnosis (ECG interpretation) and shared decision-making on therapy.

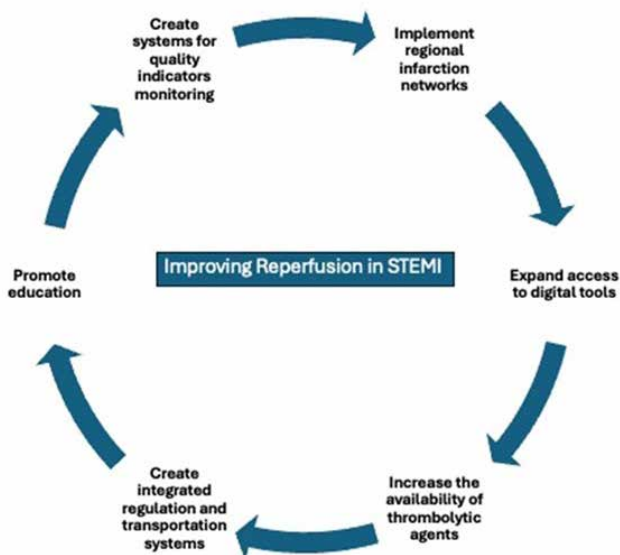


FIGURA 1.

Potentially useful actions to improve the chances of early reperfusion in STEMI.

STEMI: ST-segment elevation myocardial infarction

- 3) Increase the availability of thrombolytic agents in first-contact centers, with ongoing team training for their safe and effective use.
- 4) Create integrated regulation and transportation systems between lower- and higher-complexity centers, with clear clinical criteria not based on financial coverage.
- 5) Promote education for the population and healthcare professionals about early symptom recognition and the importance of timely care.
- 6) Finally, create systems that enable continuous monitoring of quality indicators in the care of myocardial infarction patients, such as door-to-balloon time, reperfusion rates, and adjusted mortality, to evaluate the impact of implemented interventions.

Studies like this one are fundamental, as they provide concrete data to highlight critical gaps in acute myocardial infarction care and point to opportunities for improvement. Improving outcomes requires a multifaceted approach that integrates educational actions, prevention strategies, early diagnosis, timely treatment, strengthened infrastructure, and continuous quality monitoring. Transforming the current scenario demands the implementation of well-structured networks, with clear protocols for the rapid recognition of infarction and prompt patient transfer. It is important to ensure greater access to cardiologists—either in person or via telemedicine—for appropriate support in decision-making⁷. Likewise, expanding the availability of thrombolytics in lower-complexity units is a strategic measure to increase access to reperfusion and reduce preventable mortality. As Andy Wharol said: Time won't change anything on its own; we need to take deliberate steps to reshape the present.

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Review Article

Vaccination in cardiovascular prevention: a tool not always adequately appreciated

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ABSTRACT

Chronic coronary artery disease and heart failure remain leading causes of morbidity and mortality in Western countries. Beyond conventional treatments, complementary strategies such as vaccination have shown significant cardiovascular benefits. This narrative review explores the relationship between several vaccines—particularly those for influenza, SARS-CoV-2, pneumococcus, and herpes zoster—and the prevention of cardiovascular and cerebrovascular events, both in primary and secondary prevention contexts. The pathophysiological mechanisms linking respiratory infections to acute events such as myocardial infarction and stroke are analyzed, as well as clinical evidence supporting vaccine use in patients with preexisting cardiovascular disease. Adverse effects, though rare, are also discussed, given their disproportionate media and scientific attention. Additionally, the article addresses vaccine hesitancy, examining its sociocultural determinants and emphasizing the crucial role of healthcare professionals in counteracting misinformation through education and strong patient-provider relationships. Overall, vaccination emerges not only as an essential tool for preventing infectious diseases, but also as an effective strategy to reduce the cardiovascular burden in high-risk populations.

INTRODUCTION

Chronic coronary artery disease (CAD) and heart failure are still the main mortality causes in Western countries. In spite of advancements in the standardized treatment of both conditions and a reduction in attributable mortality of up to 25% in the last decade, new supplementary strategies have emerged, not directly related with cardiovascular physiology, but proving to have a positive impact on the comprehensive management of these patients. Between these strategies, the administration of several vaccinations stand out. They not only protect vulnerable patients from the severe consequences of preventable infectious diseases, but as we will see, they are also associated to a reduction in the incidence of acute myocardial infarction (AMI).^{1,2} This narrative review is focused on the impact of vaccination on the development of CAD, as well as its role in the protection of individuals with cardiovascular disease.

RELATIONSHIP BETWEEN VACCINE-PREVENTABLE DISEASES AND CARDIOVASCULAR HEALTH

Since the end of the 1970s, there is experimental evidence linking certain viruses, particularly the herpes zoster

virus, with the development of atherosclerotic disease in animal models.³ Later, epidemiological observations, such as the seasonal increase in mortality by cardiovascular cause during the winter months in cold regions of Europe, as well as the identification of procoagulant factors associated to AMI, established the foundations to research the relationship between infectious diseases and the subsequent cardiovascular disease.^{4,5}

Already in the 21st century, the FLUVACS study showed that vaccination against influenza can reduce mortality in up to 75% in 6 months and close to 50% of the combination of mortality, reinfarction and readmission by ischemia in post-AMI patients or who have undergone elective angioplasty, in comparison with non-vaccinated individuals.⁶

Since year 2006, the American Heart Association supports and promotes the yearly vaccination against influenza in patients with preexisting cardiovascular disease, based on evidence from cohort studies and randomized clinical trials.⁷ This recommendation is aimed at reducing both cardiovascular morbidity and general mortality in this vulnerable population.

EFFICACY OF VACCINES IN THE PREVENTION OF CARDIOVASCULAR DISEASES

To understand the protective effects of certain vaccines on cardiovascular diseases, it is essential to analyze the pathophysiological relationship between vaccine-preventable infections and cardiovascular system compromise.

In general terms, severe respiratory infections are usually accompanied by fever, hypoxemia and exacerbated adrenergic response, particularly in the presence of septic syndrome. These factors may trigger myocardial ischemia by increase in oxygen demand, originating type 2 AMI. Furthermore, the systemic inflammatory response, mediated by proinflammatory cytokines and procoagulant factors, favoring endothelial dysfunction and thrombi formation. Interleukins such as IL-1b, IL-6 and tumor necrosis factor alpha (TNFa) have proatherogenic effects, promoting neutrophil and monocyte infiltration within atherosclerotic plaques, which accelerates its progression and may trigger type 1 AMI.

On the other hand, the direct viral replication in cardiomyocytes may trigger myocarditis, ventricular arrhythmias and contractile failure. Likewise, in patients with chronic CAD, the macrophages present in plaques may suppress helper T lymphocyte activity, weakening antiviral immune response.⁸

In the specific case of the vaccine against influenza, numerous observational studies and meta-analysis have shown a decrease in mortality in patients with heart failure with reduced ejection fraction (<40%). Although no randomized studies have been carried out in this subgroup, indeed there is sound evidence, both from controlled and randomized studies, backing its efficacy for primary prevention of AMI.⁸ In post-AMI patients, the administration of vaccination up to 72 hours after the event has shown to reduce all-cause mortality by 28%, as well as the incidence of new AMI and stent thrombosis up to a year after the event.⁸ Flu vaccines have also been associated to less incidence and severity of cerebrovascular diseases (CVD), as well as a reduction in risk of hospital admission.⁸

As to pneumococcus (*Streptococcus Pneumoniae*), the relationship with cardiovascular disease is bidirectional: the presence of cardiovascular disease worsens the evolution of pneumonia, and in turn, this is associated to a greater risk of acute coronary syndrome (OR 3.02), CVD (OR 2.88) and mortality (3.22) in patients with acute community-acquired pneumonia. Pneumococcal vaccination (whether by the sequential scheme of 13 and 23 serotypes, or with a conjugate vaccine of 20 serotypes) is indicated in people older than 65 years, as well as in patients with immunodeficiency, cerebrospinal fluid fistulae or cochlear implants.⁹ A prospective study that evaluated the combined vaccination against influenza and pneumococcus reported significant reductions in mortality (35%), CVD (33%), AMI (48%) and acute pneumonia (43%).⁸ Other studies also have shown relevant decreases in the rate of hospitalization due to heart failure and other causes between

patients vaccinated for pneumococcus.

Around 20% of admitted patients with infection by SARS-CoV-2 virus, the agent causing COVID-19, have shown biochemical evidence of myocardial compromise and increase in mortality. The heterogeneity of the presentation in several forms of the disease makes it difficult to obtain accurate data on the real incidence of cardiovascular compromise in COVID-19. However, it is known that, in cohorts in the United States, where vaccination predominates with vaccines mediated by messenger RNA, partial and full immunization are associated to an increasingly less incidence of major cardiovascular events.^{8,10}

Also, a growing interest has been observed on the respiratory syncytial virus (RSV) impact, including hospitalization and death, particularly in patients with preexisting cardiovascular conditions. Just as with influenza in past decades, yearly peaks of infection by RSV coincide with a greater number of cases of first AMI, recurrent AMI and CVD. However, the new vaccines against RSV, that reduce the incidence of pulmonary infection, have not yet proven a protective effect before cardiovascular complications.^{8,11}

Finally, a systematic review researched the efficacy of the vaccine against herpes zoster in prevention of infarction, heart failure, major cardiovascular and cerebrovascular events, having found only two studies were a reduction close to 12% was proven in the incidence of CVD, or of 50% in the report of new CVDs between vaccinated people older than 65 years.¹²

ADVERSE EFFECTS OF VACCINES USED IN PATIENTS WITH CARDIOVASCULAR DISEASES

Vaccines represent, after access to drinkable water, the most effective public health strategy to reduce morbidity and mortality associated to infectious diseases. Since mid-20th C, multiple vaccines have been developed and widely used: the vaccine against tetanus, diphtheria and whooping cough started to be used in 1940, with its acellular formulation (DTPa) being introduced in 2005; flu vaccines have been applied since the same decade; and the MMR vaccine (measles, mumps and rubella) has been available in its current version since 1971. More recently, vaccines against SARS-CoV-2 were authorized to be used between the end of 2020 and the beginning of 2021.

In spite of the overwhelming evidence on the efficacy of these vaccinations, the public and scientific focus have often focused on their adverse effects, some of which (although rare) have generated concern due to their severity or media impact. In the United States, the VAERS (Vaccine Adverse Event Reporting System) allows any person (health care professionals, patients, carers, educators or manufacturers) to report possible adverse events associated to vaccination (<https://vaers.hhs.gov>). From the existing documents in this database, or the systematic study of cases and cohorts, it is known now that the adverse cardiovascular effects of vaccines are scarce and essentially limited to cases of myocarditis and pericarditis.^{8,13}

We should highlight that establishing a causal relationship between a vaccine and a specific adverse effect is complex in epidemiological studies, due to the lack of mechanistic information that would allow confirming such connection. Instead, case reports and clinical series may contribute more clarity when there are criteria backing causality: a well-defined time association, pathophysiological evidence obtained from experimental models and, if possible, the reproducibility of the adverse effect after a new exposition to the vaccination agent.¹⁴

Within this framework, a recent systematic review gathered reports and series of patients who experienced cardiovascular events after vaccination, whose findings are summarized in [Table 1](#).¹³

On the other hand, a rare syndrome has been described, characterized by thrombocytopenia and thrombosis (frequently with dural venous sinuses compromise) in association with vaccines against SARS-CoV-2 that use adenoviral vectors, as those developed by AstraZeneca and Johnson & Johnson.⁸ Although these events are very rare, their early detection has enabled establishing specific protocols for diagnosis and treatment, minimizing their clinical impact.

RESISTANCE TO VACCINES AND HOW TO APPROACH IT

Beyond the specific disease they prevent, of their efficacy, safety profile and administration access, vaccines may be classified in a pragmatic way in two large groups: those that provide individual protection (such as vaccines against tetanus and rabies) and those that offer community protection (such as measles, influenza and COVID-19). In scenarios of outbreaks, epidemics or pandemics, a collective solidarity sense emerges, where individuals understand that their decision to get a vaccine can benefit the whole community.

In the cardiovascular field, only vaccines against SARS-CoV-2 and influenza have proven to provide benefits both at individual and community levels.

In 2019, the World Health Organization identified the hesitation before vaccines as one of the ten main threats to global health.¹⁵ Since the publication (and subsequent recantation) of the infamous article in The Lancet in 1998, linking the MMR vaccine (measles, mumps and rubella) to autism, mistaken concepts on vaccination have spread, generating unfounded doubts in the population. In epidemiology, it is taught that the absence of evidence does not necessarily entail evidence of absence; however, multiple studies have refuted the most common beliefs against vaccines, such as saturating the immune system, inducing autoimmune diseases or negatively affecting the course of pregnancy.¹⁵

Although it is not completely clear if the attitude by parents before child vaccination predicts their behavior in regard to their own immunization, research in the United States, Canada and the United Kingdom has identi-

TABLE 1.
Case reports of cardiovascular compromise after vaccination

Type of vaccine	Number of studies	Number of cases	Manifestation
Influenza	11	34	Myocarditis (2) Pericarditis (27) Pericardial effusion (2) Takotsubo (2) Kounis syndrome (1)
COVID subtype J&J: 1 Pfizer: 35 Moderna: 26 Covishield: 4 CoronaVac: 1	18	67	Myocarditis (55) AMI (7) Kounis syndrome (1) MINOCA (1) Pericarditis (2)
Smallpox	20	232	Myocarditis (75)Pericarditis (7)Myopericarditis (121) Ischemia (26) Dilated cardiomyopathy (2) Trigeminy (1) Ventricular tachycardia (1)
Pneumococcus	2	2	Myocarditis (1) Pericardial effusion (1)
Tetanus	3	3	Myocarditis (2) Myopericarditis (1)
Cholera	1	1	AMI (1)

fied certain factors associated to further hesitation: young parents, lower educational level, strong religiousness and low trust in health care professionals.¹⁶ Different studies also have observed that people with no strong stance (either in favor or against) are susceptible to the influence of public figures, whether physicians, politicians or celebrities, which may lead them to modify their decisions on vaccination.^{17,18,19,20,21} In turn, excess of information in social networks, with no effective mechanisms for verification, not just feeds doubts, but may generate paralysis before decision-making.²²

These observations underscore the critical role that health care professionals play, whatever their specialties, at the time of advising their patients. Scientific evidence, persistence by physicians and the quality of doctor-patient relationships are fundamental elements to encourage vaccination, and thus, protecting both individuals and communities.

CONCLUSIONS

Vaccination against influenza, SARS-CoV-2 and pneumococcus is associated to cardiovascular protection by mechanisms independent from cardiovascular physiology. The vaccine against herpes zoster would have a protective role against cerebrovascular disease. Although other vaccines do not directly reduce cardiovascular or cerebrovascular risk, patients with these comorbidities are particularly vulnerable to severe forms of preventable infectious diseases. In this scenario, vaccination consolidates as an essential tool to protect this population from risk.

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Review Article

Subcutaneous implantable cardioverter defibrillator. Clinical evidence and recommendations

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Implantable cardioverter defibrillator, subcutaneous implantable cardioverter defibrillator, sudden cardiac death, defibrillator.

ABSTRACT

Currently, implantable automatic defibrillators (ICD) have demonstrated unobjectionable effectiveness in the primary and secondary prevention of sudden cardiac death (SCD) in the population of patients with high-risk heart diseases. However, its application is not free from complications, difficulties and inconveniences mainly related to intravascular catheters, which are more prevalent in a subgroup of selected patients, such as young active patients, patients with susceptibility to infections and with absent or difficult intravascular access. In response to this problem, the subcutaneous cardioverter defibrillator (S-ICD) emerged in 2009, a completely extracardiac and extrathoracic device, whose design has been optimized in recent years and which, despite its limitations, such as the absence of a pacemaker, has proven an efficacy not inferior to that of the conventional ICD, without the complications inherent to the procedure of handling it and the permanence of intravenous catheters. This makes the S-ICD a useful and effective option, being ideal for those patients who do not require anti-bradycardia or anti-tachycardia cardiac stimulation or cardiac resynchronization.

PREFACE

This review suggests a very special time for Argentine electrophysiology.

Currently, in 2024, 38 years have elapsed since the first implantable cardioverter defibrillator was implanted for the first time in Argentina and Latin America, thanks to the work by Drs. Ricardo Pesce, Elina Valero de Pesce, and Dr. Mariano Favalaro. Our greatest acknowledgement to all of them.

In year 1986, implants were surgical and therapies were administered in a blind manner. The procedure had a considerable rate of complications and perioperative mortality, which turned it into a strategy implemented exceptionally.

Nowadays, we see how medical knowledge and technological input have changed the history of patients with high risk of sudden cardiac death. Endocavitary cardioverter defibrillator implants have meant a qualitative advancement, becoming a safe and predictable alternative, with excellent results in terms of effectiveness, complications and survival. This has made it possible for the range of patients reached by this therapy to increase significantly. We have gone in this short period of time, from treating terminally ill patients to treating in primary prevention.

I celebrate the work by Drs. Rosmiro Javier Fernández and Daniel Víctor Ortigoza, member of the committee on Arrhythmias and Electrophysiology of FAC, who made this

magnificent review, showing the evolution of ventricular defibrillation that was started already 38 years ago in Argentina, by medicine eminent figures.

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INTRODUCTION

In the Western world, cardiovascular disease constitutes the main cause of death, with sudden cardiac death (SCD) being the culprit event in 60% of cases.¹ So much so, that in developed countries, mortality by cardiac arrest exceeds the summation of mortality by lung cancer, breast cancer, cervical cancer, colorectal cancer, diabetes, HIV / AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome), domestic fires, traffic accidents, prostate cancer, suicides and Alzheimer's disease.² In the West, the epidemiology of SCD is closely linked to CAD, which is responsible for up to 75-80% of cases of SCD.³ Implantable cardioverter defibrillators have consistently proven to be superior to the best pharmacological therapy available for the prevention of SCD in patients with previous cardiac arrest (secondary prevention) and for patients in high risk,

with depressed ventricular function or an arrhythmogenic condition (primary prevention). For this reason, implantable cardioverter defibrillators (ICD) are the gold standard of SCD prevention.²

Transvenous ICD (TV-ICD) has shown benefits; however, to this date there are numerous complications inherent to the system, mostly related to the intravascular catheters used, whose incidence has been reported to be between 1 and 14%, according to the different publications.⁴ To prevent these complications, among other reasons, in year 2008 the completely subcutaneous ICD (S-ICD) emerged. It was approved to be commercialized in the European Union in 2009 and in 2012 in the United States.⁵

COMPLICATIONS ASSOCIATED TO INTRAVASCULAR CATHETERS

Conventional ICDs are exposed to a wide variety of complications, with the most frequent and significant ones being those related to intravascular catheters.

We could start by mentioning acute complications, inherent to the implant technique for catheters, which go from the difficulty to reach venous access, which may significantly prolong the time of the procedure and the exposition to X-rays, and in some cases lead to failure, catheter shifting, exposing patients to surgical reinterventions and more severe complications, such as pneumothorax, hemothorax, cardiac perforation and tamponade. The incidence of complications is estimated in 1.5% of ICD implants.^{4,6}

As these are intravascular devices, catheters are susceptible to thrombogenicity and infection. Mainly *Staphylococcus* and *Streptococcus* are the bacterial species involved, which create a biofilm on the surface of the catheter and lead to infectious endocarditis, which cannot be eradicated by antibiotic treatment and requires extraction of the device. On the other hand, ICD pocket infection is one of the most frequent complications, whose incidence increases in up to 3% after repeated generator exchanges.⁵ It also requires extraction of the device to prevent infectious endocarditis. This is a risky procedure, mainly in old implants, which due to the phenomena of thrombosis, fibrosis and adherence of catheters, may make extraction difficult, with a risk of perforation, valve disruption and death, with a rate of major complications of between 1 and 4%, and mortality of 0.8% in the more experienced centers.^{2,7}

Furthermore, the presence of thrombi adhered to catheters has been observed using intracardiac ultrasound in 30% of cases, which contraindicates its use in patients with venous-systemic shunt, and increases the risk of thromboembolism thrice in patients with patent foramen ovale.¹

Another potential complication related to intracardiac leads is valve dysfunction caused by the catheter passing through the tricuspid annulus. A study showed a worsening in tricuspid regurgitation in 15% of implanted resynchronizers, which was correlated with worse clinical and echocardiographic response to cardiac resynchronization therapy (CRT).⁸

Finally, we should mention the catheter failures related to the long-term deterioration of its components. This wear and tear mainly affects insulating materials (polyurethane and silicone) and is due to the repetitive mechanical movement occurring beat to beat when going through the tricuspid annulus, and to friction when going through the costoclavicular ligament, when subclavian puncture is used as access (subclavian crush syndrome), and in the fixation point at the level of the pectoralis major.⁴ The incidence of this type of failures increases according to the time elapsed since the implant, which may reach 20% in 10 years according to some studies and it is more prevalent in young patients (younger than 50 years) with intense physical activity.^{4,8} These defects may cause an increase in impedances, oversensing and inappropriate shocks, requiring surgical review and electrode replacement.

The National Cardiovascular Data Registry of the US reported that women with TV-ICD have a greater risk of post-implant complications than men, with a higher rate of hospital readmissions within 6 months and a greater risk of acute complications such as pneumothorax and cardiac perforation.⁹ This same registry also showed a higher risk of infections related with TV-ICD in the population of patients in hemodialysis.¹⁰

TECHNICAL CONSIDERATIONS OF S-ICD

Unlike conventional transvenous ICDs (TV-ICD), whose system has intravascular/intracavitary leads, S-ICDs are entirely extracardiac and extrathoracic devices. They have 2 main components (*Figure 1*).

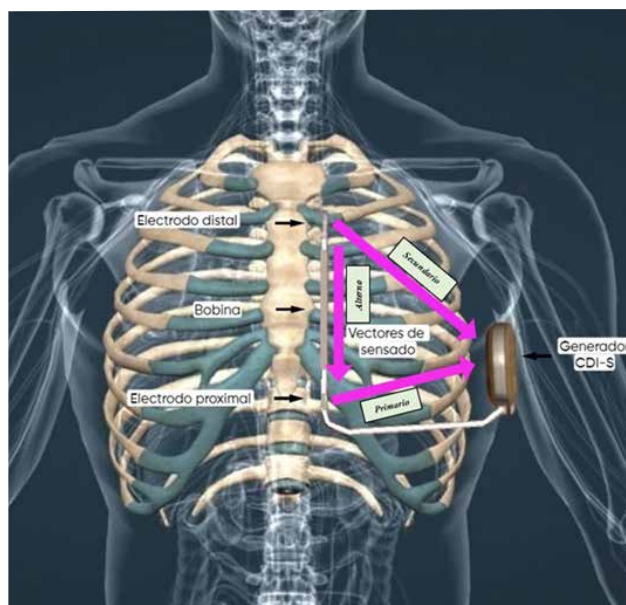


FIGURE 1.

Graphic representation of S-ICD and its components. Position of S-ICD (subcutaneous implantable cardioverter defibrillator) and graphic representation of the generator, the catheter and its leads (proximal, distal and the coil). The 3 sensing vectors available are represented: primary (inferior), secondary (superior) and alternate (medial). Purple arrows.

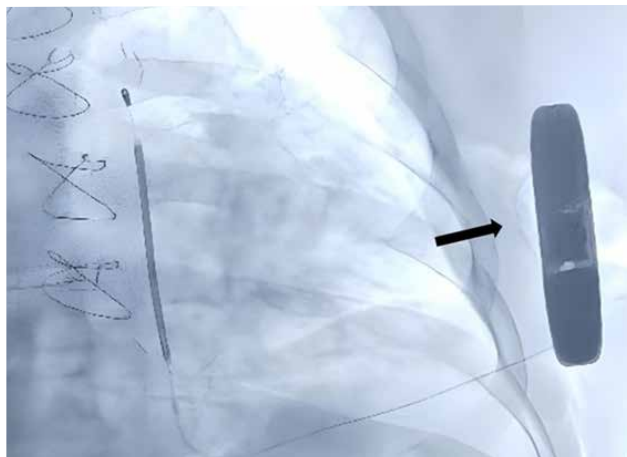


FIGURE 2. Radioscopy image of patient with S-ICD (subcutaneous implantable cardioverter defibrillator indicated by black arrow). Courtesy of Dr. Ignacio Mondragón. ICBA, Buenos Aires.

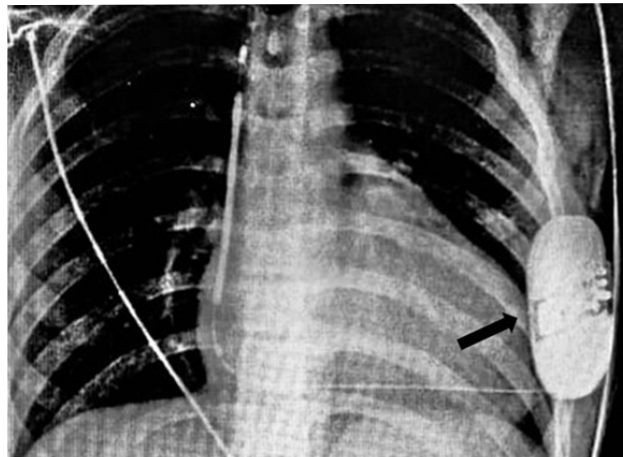


FIGURE 3. The S-ICD generator is in a submuscular plane (black arrow) and the catheter has a right parasternal trajectory. Courtesy of Dr. Mónica Benjamín, Hospital Argerich, Buenos Aires.

- A generator, whose weight and volume is greater than in TV-ICD, with a capacity of providing high-energy shocks, of up to 80 Joules, and pacemaker after shock, at 50 bpm for 30 seconds if asystole is detected for more than 3.5 seconds. The generator design was optimized from the original versions, that had 145 g of weight, 65 ml of volume and an estimated useful life of 5 years, to current versions (third generation), with 130 g of weight, 59.5 ml of volume, and an estimated useful life of 8.7 years.¹¹
- A single subcutaneous catheter of 3 millimeters of diameter (9 French) and 45 cm of length, which is channeled through the lateral chamber where the generator is placed medially, up to the xiphoid process, where it is fixed, and later it is tunneled in a cephalic direction (at 1 to 2 centimeters to the left or right, in a parallel line to the sternum), trying to place the distal end of the catheter close to the sternal manubrium. This subcutaneous catheter has 2 leads along its parallel trajectory to the sternum (a proximal one and a distal one) with sensing capacity. The defibrillation coil extends between the 2 sensing electrodes, which along with the generator close the defibrillation circuit (active case).²

There is a huge difference between the subcutaneous and transvenous ICDs implant techniques. In intravascular devices, the generator is generally located in the left infraclavicular region, and the placement of the lead(s) requires venous access toward the right ventricle, through the subclavian, axillary or cephalic veins. In contrast, the generator of the subcutaneous device is located laterally in the chest, at the level of the 5th or 6th left intercostal space, and the lead is tunneled subcutaneously from the pocket of the generator to the left parasternal edge in the conventional technique.²

The standard implant procedure of the generator and catheter entails 3 incisions: a lateral one for the generator, and two parasternal ones for the catheter.

The first incision is made laterally, parallel to the inframammary fold, at the level of the 5th or 6th intercostal space, between the mid and anterior axillary lines. The aim of this incision is the creation of the generator's pocket. The second incision of 1 to 1.5 cm is located medially, adjacent to the left edge of the xiphoid process. Subsequently, the lead is tunneled, from the lateral incision up to the xiphoid one, using the appropriate tools and is held with nonabsorbable sutures to maintain the fixation in the long term, and thus prevent lead migration. A third superior left parasternal incision is made at the level of the sternal manubrium, repeating the tunneling and fixation procedure of the lead at this level (Figure 2).²

There are alternatives to this technique: locating the generator submuscularly and the catheter in a right parasternal position, as shown in the radiographic image in Figure 3. On the other hand, the third incision is prone to causing discomfort in patients, and in turn, there are aesthetic consequences as it is more visible, and furthermore, it is more prone to infection. These issues led to the development of a technique with just 2 incisions, which means the lead tunneling and release in a cephalic direction through an 11 French peel-away introducer for the left parasternal edge, not requiring a third incision. The cost of obviating the third incision and lead distal fixation is a greater chance of electrode dislodging, although currently, the rate of dislodgement is very low with this technique.¹²

Another aspect to underscore is that more than 95% of the procedures can be done using only anatomical references, not requiring fluoroscopic guide, which means an additional advantage for operators, medical staff and patients.¹²

Currently, the technique that has shown best results, and therefore, the one most used, is the so-called intermuscular implant technique with 2 incisions, consisting of the combination of the lead fixation technique with 2 incisions already described, and positioning the generator at

an intermuscular plane, between the serratus anterior and the latissimus dorsi, instead of the classical subcutaneous pocket. This technique has displayed a decrease in the risk of pocket-related complications, such as erosion and infection, and in turn decreases the risk of device migration and achieves better cosmetic results for patients, being particularly useful in obese and very thin patients.¹³

PRE-IMPLANT SCREENING

Unlike conventional cardioverter defibrillators, a pre-implant screening using surface leads is a crucial requirement when applying S-ICD. This is because of S-ICD susceptibility to undersensing (due to the distance of the subcutaneous lead and the heart) and to double counting the cardiac signal by T-wave oversensing, generating a high risk of inappropriate shock. Patients failing the screening (check-up) should not be selected for S-ICD implant.

Several groups have evaluated the eligibility of patients based on standard screening, observing a rate of lack of selection between 7 and 10%. The least eligible patients are those with hypertrophic cardiomyopathy and congenital heart diseases. On the other hand, a screening methodology has been proposed both in rest and during exercise to decrease the rate of T-wave oversensing.²

Kooiman et al, made an elegant study, where they observed that 7 in every 8 inappropriate shocks by T-wave oversensing occurred during exercise and 1 during atrial fibrillation of high response, proposing exercise screening in patients in high risk of T-wave oversensing.¹⁴

PROGRAMMING

S-ICD was designed with a high level of automaticity. Unlike TV-ICD, which presents more than 100 programmable parameters, S-ICD has less than 10, among which the following can be mentioned: sensing vector, detection heart rate in each of the 2 zones, post-shock pacing (on/off), polarity of the following shock and delay time between each shock. The third generation devices also have the activation option of high-frequency filter: the Smart Pass filter.

In the first experiences, a single detection zone was programmed, with an HR above 200 bpm, with no rhythm discrimination, so the rate of inappropriate shocks was around 20% in 3 years. With the addition of a conditional second detection zone, a decrease was achieved in inappropriate shocks of up to 11.7% in 3 years.¹⁵ The analysis of the IDE study ratifies the importance of programming 2 zones, which reduces the rate of inappropriate shocks by supraventricular arrhythmia by 70%.¹⁵ Furthermore, it was proven that the addition of a second detection zone, with an active discrimination algorithm does not extend the detection time, nor increases the incidence of syncope.¹⁶

Several studies on TV-ICD showed the importance of programming of high heart rates of detection and a prolonged detection time to reduce the amount of shocks, as a direct relationship was observed between the number of shocks with an unfavorable evolution of patients. Because

of this, a conditional zone of 200 bpm and a non-conditional zone of between 220 and 230 bpm are suggested.²

The last generation of S-ICD has incorporated, between its sensing and arrhythmia discrimination tools, a high-frequency filter called Smart Pass. This filter activates when the sensed signal reaches a minimum width ≥ 0.5 mV and is capable of discriminating the signals corresponding to QRS (>10 Hz) from those of T wave (<9 Hz). A prospective study has shown that the Smart Pass filter availability in S-ICD leads to a significant decrease in inappropriate shocks, not affecting performance in terms of appropriate shocks.¹⁷

This filter has proven to be so effective, that its implementation turned supraventricular tachycardia into the main cause of inappropriate therapies, just as with TV-ICD.¹⁸

The interventions to prevent recurrent inappropriate shocks include: a proper implant technique, optimization of sensing vector, addition of a conditional zone if there is none, Smart Pass filter activation, modification of detection rate, obtaining a reference template during exercise test.

Other interventions available are the optimization of antiarrhythmic treatment and eventually, radiofrequency ablation, and in selected cases, surgical intervention could be necessary to reposition the catheter or the generator.²

DISADVANTAGES OF S-ICD

Many of the S-ICD design characteristics that make it superior to TV-ICD also entails limitations and disadvantages (Table 1).

As this is an entirely extracardiac device, it depends on far-field sensing algorithms for the detection and diagnosis of heart rhythm. This fact implies the need to perform a pre-implant screening in all patients, so as to guarantee a reliable sensing and to prevent oversensing and inappropriate shocks, which would mean a screening failure, and therefore, the exclusion of 7 to 8% of patients candidates to this therapy.¹

Another negative aspect is the size and weight of the generator of the S-ICD, presenting approximately twice the volume and weight in comparison to TV-ICD, as it requires high-energy shocks (80 J), and therefore, batteries with more capacity. This detail could be a problem, mainly in children and patients with low subcutaneous cellular tissue, which may favor skin erosion, decubitus lesions and pocket infection.⁶ However, the advancements in the design have achieved an acceptable generator weight and volume of 130 g and 59.5 ml in the most recent versions.²

The limited longevity of the battery is a consequence of the need to apply high-energy shocks (80 J) to achieve an effective therapy, and it is still a weak point in comparison with TV-ICD. With technological improvements, longevity could be significantly extended, from 5 years in the first models, to 8.7 years in third-generation ones, according to a remote follow-up study.¹⁹

The rate of inappropriate shocks represented a disadvantage in the first-generation S-ICDs, but, as mentioned abo-

TABLE 1.

Summary of the S-ICD and TV-ICD devices (single-chamber)

	S-ICD	TV-ICD
Pre-implant	Requires screening	Does not require screening
Generator implant	Subcutaneous or intermuscular	Subcutaneous or submuscular
Catheter implant	Subcutaneous, 2 vs 3 incisions technique	Transvenous, requires intravascular access
Battery longevity	7.3 – 8.7 years	11-12 and more than 13 years
Generator size	59.5 cm3, 130 g	30 cm3, 68.9 g
Energy discharge	Up to 80 J	Up to 42 J
Energy required to defibrillate	36.6 ± 19.8 J	11.1 ± 8.5 J
Capacitor charge time	Long (14.6 ± 2.9 sec)	Shorter (7.1 ± 1.8 sec)
Shock wave	Biphasic	Biphasic
Shock tilt	Fixed 50%	Fixed 50%
Permanent pacemaker capacity (ATP/antibradycardia/CRT)	Not available	Available
Risk of infection in 4 years	0.9%	1.9%
Catheter failures/ complications	1.4%	6.6%
MRI compatibility	Yes	Yes
Atrial arrhythmia monitoring	Yes (AFib-detection algorithm)	Yes (several programmable options)
Remote monitoring	Yes	Yes

Adaptado de Tan y cols²¹

ve, with technological and programming improvements, a significant reduction in it was achieved, being currently comparable with that of TV-ICD, although the mechanisms are different, with T-wave oversensing being predominant in S-ICD.¹

Another disadvantage is the chance of a greater discomfort produced by the high-voltage therapies required for an effective shock of the S-ICD and being more harmful than those of TV-ICD. However, it seems there is little correlation between shock voltage and the discomfort provoked, as this is a phenomenon that mainly depends on sensitivity and individual pain threshold in each patient.⁶ On the other hand, as to the myocardial damage caused, studies in animals showed that S-ICD shocks were less damaging for the myocardium than those generated by TV-ICD, with less troponin I elevation when comparing subcutaneous 80 J shocks with intracardiac 35 J in pigs.²⁰ Although this phenomenon still has to be tested in humans, which at first sight may appear as a disadvantage, it could rather be an advantage.

The charge and shock therapy time is significantly higher in S-ICD compared with TV-ICD. However, evidence has not shown negative clinical consequences in relation to

this phenomenon. In fact, the more prolonged detection times correlated with favorable clinical outcomes in patients with TV-ICD (SIMPLE trial). Both types of devices are the foundation for current programming.

Undoubtedly, the greater disadvantage and the Achilles heel of S-ICD currently still is the inability for permanent pacing and ventricular oversensing as anti-tachycardia pacing (ATP). This limitation restricts S-ICD indication to patients without current or future pacing indication, including cardiac resynchronization therapy and patients with no monomorphic VT that could benefit from ATP.¹ Nevertheless, there are data from the SCD-HeFT trial indicating that the yearly rate of reverted VT episodes thanks to ATP is very low: <2% per year, interestingly less than the risk of complications by transvenous catheters. Moreover, there is evidence showing more mortality associated to the acceleration of tachycardia treated by ATP from a study with remote ICD monitoring.² Finally, the emerging technology of leadless cardiac pacing and its combination with S-ICD is a promising solution for this limitation. This new concept proved to be reliable and effective, with an excellent performance in an 18-month follow-up, in a pre-clinical study in animals.²¹ Currently, there is an ongoing trial in humans, in its clinical phase, that will evaluate safety, performance and effectiveness of combined S-ICD and leadless pacemaker.¹⁹

CLINICAL EVIDENCE AND RECOMMENDATIONS

Since its approval in the European Union in 2009 to this date, use of S-ICD for sudden cardiac death prevention has grown exponentially, exceeding 100,000 around the world.² Numerous clinical and preclinical studies have proven its safety and efficacy in the treatment of ventricular arrhythmias.

The first clinical trials date back from 2008. Bardy et al. made the first pilot study in human phase with S-ICD and proved that the posterolateral position of the generator was capable of offering an optimal and safe defibrillation chronically, although with defibrillation thresholds significantly greater than those of TV-ICD.¹⁵

Since the moment when it was ready to be sold, plenty of studies have been published on different clinical conditions and populations of patients. Among the most relevant ones, we can mention:

In 2009, 2 large prospective trials, with similar design and endpoints studied the efficacy and safety of S-ICD: the IDE study enrolled 308 patients, and the EFFORTLESS trial, 568 patients. The population of patients included were mainly young patients, with higher ejection fraction in comparison with other studies with TV-ICD, and 70% had indication as primary prevention. Both trials were analyzed jointly and showed a high efficacy in spontaneous VT/VF cardioversion, with 90% efficacy in the first shock and total efficacy of 98%. In turn, the rate of complications was low. A point to highlight is that programming was evaluated in one and two zones (conditional zone) of detection, showing a rate of inappropriate shocks in 3 years of 20.5% with programming

TABLE 2.Recommendations for S-ICD implant – 2022 European Guidelines for Sudden Cardiac Death²⁵

Recommendations	Class (a)	Level (b)
Implanting a subcutaneous cardioverter defibrillator should be considered as an alternative to the transvenous implantable cardioverter defibrillator in patients with indication of ICD, when pacing for bradycardia, cardiac resynchronization therapy or antitachycardia pacing are not necessary.	IIa	B

(a) Recommendation class (b) Level of evidence

in one zone in comparison with 11.7% with programming in two zones. The main cause for inappropriate shocks was T wave oversensing.[15] In 2018, the Propensity Score was published, a study comparing the rate of complications, appropriate and inappropriate shocks between the population of patients with VT-ICD from the SIMPLE trial vs the population with S-ICD from the EFFORTLESS trial. There were no significant differences in the endpoints evaluated. In regard to the rate of complications related to catheters, as expected, it was significantly less in the S-ICD group (0.3% vs 2.3% in 3 years). A remarkable datum is that a higher rate of inappropriate shocks was observed with S-ICD, 11.9% vs 7.9% in the TV-ICD group, that did not have statistical significance. The main cause of inappropriate shocks was supraventricular arrhythmia in TV-ICD and oversensing in S-ICD.[23] We should highlight that the evaluated devices were mostly (60%) of the first generation, with no Smart Pass filter available to minimize inappropriate shocks due to oversensing.

Between 2011 and 2017, the PRAETORIAN trial was carried out, which was the first noninferiority randomized prospective trial, comparing S-ICD vs TV-ICD. There were 876 patients with ICD indication, but without cardiac pacing indication, randomized to S-ICD or TV-ICD. During a mean follow-up of 49 months, noninferiority was proven for the primary aim of complications related to the device and inappropriate discharges. The rate of inappropriate discharges was 9.7% in the S-ICD group and 7.3% in the TV-ICD group (HR 1.43; 95% CI 0.89-2.30). There were no differences observed either, in the secondary aim of death and appropriate discharges; but the trial did not have enough statistical power to show noninferiority for this second aim.⁶ We should point out that more than 80% of the patients included had class I and II of NYHA and were younger than in other previous trials with ICD. Currently, there is an ongoing extension of the PRAETORIAN XL trial follow-up (not published yet), with the aim of establishing the superiority of S-ICD over TV-ICD.

The UNTOUCHED trial was a prospective, multicenter, non-randomized trial, published in 2021, evaluating the incidence of inappropriate shocks by S-ICD of second and third generations in 1111 patients with indication as primary prevention for sudden cardiac death. This study

TABLE 3.Recommendations for S-ICD implant – 2017 AHA Guidelines on Sudden Cardiac Death²⁶

Recommendations	Class (a)	Level (b)
S-ICD implant is recommended in patients meeting ICD criteria, and that have inadequate vascular access or high risk of infection, and in whom cardiac pacing for bradycardia, antitachycardia pacing or resynchronization are not necessary or expected.	I	B
S-ICD implant is recommended in patients meeting ICD criteria, and in whom cardiac pacing for bradycardia, antitachycardia pacing or resynchronization are not necessary or expected.	IIa	B
S-ICD should not be implanted in patients with cardiac pacing indication due to bradycardia, indication for antitachycardia pacing or resynchronization.	III	B

(a) Recommendation class (b) Level of evidence

showed a high efficacy and safety with contemporary devices and the lowest rate reported of inappropriate shocks, 3.1% yearly, with programming in 2 zones of detection and the algorithms of morphology discrimination (Smart Pass filter).¹⁶

The ATLAS trial was prospective, randomized and controlled, published in 2022, which revealed a rate of catheter-related complications within 6 months that was 93% less in S-ICD in comparison with TV-ICD (0.4% vs 4.8%). On the other hand, there were no differences in performance in terms of failed shocks and rate of inappropriate shocks between both devices.²³

POSTAPPROVAL is the largest trial, made to this date and with a more prolonged follow-up. It was published in August 2023, and it is a multicenter trial directed by the FDA, and designed to evaluate the safety and efficacy of S-ICD in a population more adjusted to the real world. There were 86 centers from the US participating, which enrolled 1643 patients, with a 5-year follow-up, and proved that S-ICD is a safe and efficient device in a long-term follow-up, with a rate of complications of 7.3% per year and 13.5% in 5 years.²²

Nowadays, the weight of the evidence available supports using S-ICD for primary and secondary prevention of sudden cardiac death, as long as the need for cardiac pacing is not present or expected, whether due to bradycardia, antitachycardia pacing or resynchronization therapy. The last American and European guidelines gave S-ICD a class IIa indication, with level of evidence B. Also, the American Guidelines consider a class I indication in patients that also present inappropriate vascular access and high risk of infection (*Tables 2 and 3*).^{3,24,25} We have to highlight that the last Guidelines were written before the publication of the most recent trials, and therefore, the level of recommendation of S-ICD therapy should be increased in the next update.²¹

SELECTION OF PATIENTS FOR S-ICD

Most candidates to ICD in primary prevention are also eligible for S-ICD implant. The patients requiring cardiac pacing for an extended time should not be considered for S-ICD. However, evidence shows that, if pacing is not needed at the time of the implant, the future chance of needing it is low, and if it so happened, there is always the alternative of adding a transvenous or leadless pacemaker.²

The need for antitachycardia pacing (ATP) as indication to implant TV-ICD, although supported by guidelines, remains controversial. Although ATP is clinically effective in some patients to prevent unnecessary shocks, extending the detection time and/or programming high VT detection could be equally effective. On the other hand, predicting which patients will benefit from ATP is hard to define. If the data from the SCD-HeFT trial are observed, the tachycardias that were treated effectively by ATP were scarce, with an incidence of less than 2% per year, which is less than the rate of failures of transvenous catheters.²

There is a large population of patients, in whom the implant of transvenous devices is not possible or it is difficult. This would be the case of pediatric or adult patients with congenital heart diseases, many of which lack venous accesses. The risk of sudden cardiac death could be high in these patients, depending on the underlying heart disease and S-ICD emerges as a first-line option. On the other hand, by pre-implant venogram, a study has proven the presence of stenosis or obstruction in the central venous system in 7% of patients, particularly in those with previous permanent transvenous catheters; therefore, in patients with multiple damaged or dropped catheters, a change to S-ICD is a reasonable option.²⁶ Something similar occurs with patients in hemodialysis, in whom central venous access is usually a great hindrance.

Patients with high risk of infection represent another population to take into account for S-ICD implant. Those with endocarditis or infection in IV devices, in whom the risk of recurrent infection is high, are excellent candidates to S-ICD after extraction. Patients in hemodialysis, those who are diabetic, immunosuppressed and oncological also are included in this group of patients, and therefore, should be considered for S-ICD.¹

Another piece of information to take into account in the selection of patients for S-ICD is age. Young patients are a population that could benefit mainly with S-ICD, given the chance of complications associated to catheters over their life.

Young patients with hereditary arrhythmic syndromes also result in a population appealing for S-ICD, in whom the risk of developing bradycardia and need for permanent pacing is low. In this group, patients are included who present: long QT syndrome, short QT syndrome, early repolarization syndrome, and some patients with arrhythmogenic right ventricular cardiomyopathy. These patients are prone to developing polymorphic VT and VF rather than monomorphic VT.¹ This group also includes patients with Bruga-

da syndrome, in whom evidence has reported a high rate of failures in transvenous catheters of up to 2% per year, which is 4 times more than in the general population, and over the course of the life of these patients, the risk of complications related to transvenous devices may reach up to 9%.²⁶ For this reason, patients with Brugada syndrome are first-line candidates for S-ICD.

Patients with hypertrophic cardiomyopathy, who usually have high defibrillation thresholds with TV-ICD, also represent a group to take into account for S-ICD.²¹ Both patients with Brugada syndrome and those with hypertrophic cardiomyopathy have electrocardiographic characteristics that may potentially predispose to double counting of QRS and T wave respectively, with the subsequent risk of inappropriate shocks. Therefore, a careful pre-implant screening is necessary in this group of patients.¹

A study evaluated the experience of S-ICD in teenagers and young adults, demonstrating its safety and efficacy in this population. Although there was also evidence of a higher rate of inappropriate shocks in younger patients, this same trend is observed with VT-ICD.²⁷

Finally, for patients with indication of ICD implant temporarily, as those in a waiting list for heart transplant, S-ICD represents an advantageous alternative, preventing venous fibrosis, and it facilitates extraction during surgery.¹

Figure 4 summarizes the most important factors to take into account in the selection of patients candidates to S-ICD implant.

LIMITATIONS

The initial aim of this article was to make a short review about S-ICD, focused on recommendations and selection of patients. The bibliographical search process started revealing a large amount of material, which, given its richness

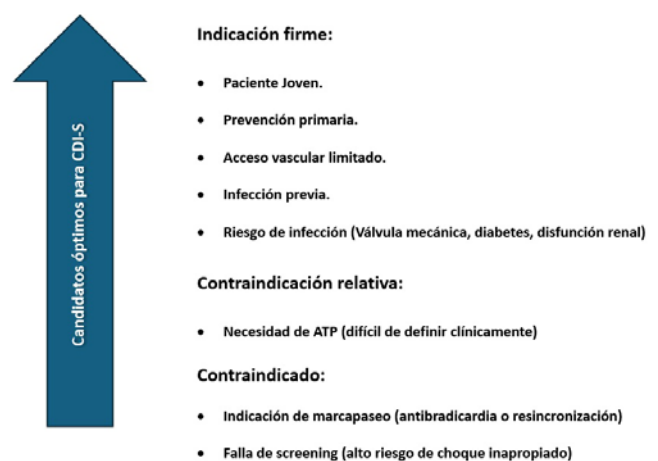


FIGURE 4.

Flowchart of S-ICD (subcutaneous implantable cardioverter defibrillator) indications, showing the direction of indications of the device for the patients that benefit the most.

Adapted from McLeod et al.¹²

and pertinence was difficult to leave aside, consequently producing a more extensive publication, and perhaps less concise and friendly for reading than intended.

CONCLUSION

Since its release in 2009 to this date, S-ICD has gone from being an emerging therapy, with limited indications, to a sound, safe and effective alternative to TV-ICD in primary and secondary prevention, in a wide population of patients, averting the multiple complications inherent to permanent intravascular catheter implants. However, this technology still presents limitations, such as the absence of pacing, restricting its use to patients not requiring antibradycardia or antitachycardia pacing. Ideal candidates are patients with limited vascular access and in whom life expectancy or their clinical conditions turns them more susceptible to intravascular catheter-related complications. In spite of this, a promising scenario is observed for a not-too-distant future, with technological advancements and the emergence of leadless pacing, which could be coupled with S-ICD, thus turning it into a comprehensive tool for the prevention of sudden cardiac death, antitachycardia pacing, and even cardiac resynchronization.

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Original Investigation Reports

Mitral annular plane systolic excursion in moderate-severe aortic stenosis, low flow and preserved systolic function

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ABSTRACT

Background: low flow (LF) (stroke volume index (SVi) <35 ml/m²) serves as a prognostic marker of aortic stenosis (AS). Longitudinal strain assessed by speckle tracking is a determinant of LF. However, this method requires an adequate ultrasound window. Mitral annular plane systolic excursion (MAPSE) functions as an alternative for longitudinal strain.

Objectives: to investigate the relationship between MAPSE and LF in patients with moderate AS (MAS) or severe AS (SAS).

Methods: patients with MAS (valve area <1.50 cm²) or SAS (valve area <1 cm²) and an ejection fraction ≥ 50% were evaluated. The average MAPSE was calculated utilizing the lateral and medial MAPSE. All parameters related to LF (not involved in its calculation) were analyzed, and a logistic regression model was performed.

Results: a total of 222 patients were evaluated, 59.5% presented with SAS. The prevalence of LF in the general population was 16.7%. The median MAPSE was 1.34 cm (1.2-1.46) in patients with normal flow and 0.99 cm (0.90-1.06) in those with LF (p<0.001). MAPSE demonstrated an area under the curve of 0.89 for the prediction of LF. Multivariate analysis was conducted with the significant variables from the univariate analysis, with age (p=0.011), body surface area (p=0.003), heart rate (p=0.03), and MAPSE (p<0.001) remaining significant.

Conclusion: patients with MAS, SAS, and LF had lower MAPSE than those with normal flow. MAPSE is an excellent predictor of LF, and it was the only echocardiographic parameter associated with LF in a multivariate analysis.

INTRODUCTION

Aortic valve stenosis is a growing health issue with a considerable financial impact. Currently, aortic valve replacement is indicated in patients with severe aortic stenosis (SAS) that develop symptoms. The management of asymptomatic patients with AS is still being debated. In recent years, class I indication for aortic valve replacement is only for patients who present ejection fraction (EF) drop below 50%.¹ Patients with EF ≥50% and low transvalvular flow (LF) (stroke volume index (SVi) <35 ml/m²), present a worse prognosis than patients with SVi >35 ml/m².^{2,3,4} LF is due, among multiple causes, to a greater peripheral vascular resistance, decrease of systemic arterial compliance, as well as a higher level of valvulo-arterial impedance (Zva).^{5,6,7} On the other hand, patients with LF present lower values of global longitudinal strain (GLS) than those with preserved flow, caused by early compromise of subendocardial fibers of the left ventricle, which may lead to a drop in SVi.^{3,8} The speckle technique is the one most used by GLS measurement, but it is not available in all echo-

cardiography laboratories, the presence of inappropriate ultrasound window may generate variability between results, and in spite of differences between brands having diminished, some still persist, both in methods used and in established cutoff points.^[9] Mitral annular plane systolic excursion (MAPSE) is an alternative to GLS. Regardless of the method used for measuring, left ventricular systolic longitudinal strain is the longitudinal shift in relation to its initial length in diastole, measured in apical views: (telediastolic length – telesystolic length) / telediastolic length. The difference between telediastolic length and telesystolic length is given by MAPSE, then: MAPSE / telediastolic length is an alternative for longitudinal function measurement. Stoylen et al. advise to not carry out MAPSE normalization by telediastolic length, as it increases dependence on body surface and gender in the parameter.¹⁰

The aim of this study, therefore, is to assess the LF-MAPSE relationship in patients with moderate aortic stenosis (MAS) and SAS, with EF ≥50% and the predictive capacity of LF that MAPSE may present.

MATERIALS AND METHODS

Patients with SAS (valve area <1 cm²) and MAS (valve area <1.50 cm²) were included prospectively, who had been referred to Doppler echocardiogram as outpatients, since August 2022 until September 2024. The following patients were excluded: with EF <50%; another left valve disease, from major to mild; severe mitral annulus calcification; and prosthesis in mitral position.

Complete transthoracic echocardiography was carried out in all patients. All echocardiographic measurements were made following the current recommendations.¹¹ Left ventricular stroke volume was estimated in the following manner: left ventricular outflow tract x velocity-time integral of the left ventricular outflow tract measured by pulsed-wave Doppler. Furthermore, multiple transducer

positions were applied to record the peak velocities of the aortic jet. The highest transaortic velocity was used for the continuity equation.

Systemic blood pressure was measured manually, with a sphygmomanometer cuff (in the arm), of the aneroid type, while Doppler measurement was carried out on the left ventricular outflow tract stroke volume. As a measure of the global load of the left ventricle, we estimated an $Z_{va} = (SBP \times TPG) / SV_i$, where SBP is systolic blood pressure and TPG is the net transvalvular pressure gradient. Therefore, Z_{va} represents the valvular and arterial factors opposing ventricular ejection when absorbing the mechanical energy developed by the LV. Patients presenting $Z_{va} \geq 4.5$ mmHg.ml-1.m² were considered to have a high Z_{va} .

MAPSE was obtained by M mode from the apical,

TABLE 1.
Clinical and echocardiographic variables.

VARIABLE	GENERAL	NORMAL FLOW	LOW FLOW	p
n	222	185	37	
AGE (mean (SD))	72,95 (10,67)	72,05 (10,90)	77,46 (8,17)	0,005
Male gender (%)	128 (57.7)	101 (54.6)	27 (73)	0.06
BS (m²)	1.89 (0.21)	1.87 (0.21)	1.97 (0.21)	0.009
DIABETES n (%)	68 (30.6)	54 (29.2)	14 (37.8)	0.397
HTN n (%)	173 (77.9)	144 (77.8)	29 (78.4)	1
DYSLIPIDEMIA n (%)	110 (49.5)	89 (48.1)	21 (56.8)	0.435
OBESITY n (%)	86 (38.7)	70 (37.8)	16 (43.2)	0.666
AMI n (%)	12 (5.4)	9 (4.9)	3 (8.1)	0.69
CAD n (%)	50 (22.5)	38 (20.5)	12 (32.4)	0.172
SBP (mmHg) – IQR	140 [121- 150]	140 [125 -150]	134 [120-150]	0.371
DBP (mmHg) – IQR	80 [70- 85]	80 [70- 85]	80 [70-90]	0.762
HR (bpm) – SD	71.1 (10.24)	70.2(9.67)	75.2 (12.02)	0.007
LVDD (mm) – SD	47.4 (4.71)	47.2 (4.58)	48.6 (5.23)	0.084
LVSD (mm) – SD	28.35 (4.25)	28.05 (4.24)	29.89 (3.98)	0.016
EFS (% average) - SD	40.27 (6.34)	40.63 (6.37)	38.47 (5.97)	0.06
LVEDDI (ml/m²) - SD	48.8 [38-58]	49 [38.6- 58.2]	45.4 [37.9- 55]	0.358
LVESDI (ml/m²) – IQR	16.7 [12.7- 21.5]	16.7 [12.9-21.2]	16.39 [11.7-21.9]	0.943
EF (% average - SD)	65.1(6.1)	65.4 (5.9,)	63.4 (6.8,)	0.08
RWT - IQR	0.41 [0.365-0.4]	0.40 [0.36-0.44]	0.42 [0.38- 0.52]	0.026
LVMI (g/m²) – IQR	126.9 [107.6-153.2]	124 [106.3-147.7]	150.1 [118.1-170.3]	<0.001
Ee – IQR	10.2 [7.6-14]	9.9 [7.5- 13]	12.16 [10.3- 18.7]	<0.001
TRV (m/sec) – IQR	2.60 [2.42, 2.91]	2.57 [2.42, 2.85]	2.78 [2.43, 3.01]	0.15
LAV (ml/m²) – IQR	44 [38-52]	44[38- 51]	49 [38- 56]	0.098
LVOTD (cm) – IQR	2.08 [2- 2.18]	2.08 [1.99-2.17]	2.10 [2- 2.20]	0.541
SVi (ml/m²) – SD	43.2 (8.31)	45.6 (6.74)	31.08 (3.16)	<0.001
APV (m/sec) – IQR	4.06 [3.3 –4.48]	4.06 [3.25-4.48]	4.12 [3.35-4.47]	0.779
MPG (mmHg) – IQR	38 [25- 48.7]	38 [24- 48]	40[27- 49]	0.856
AVA (cm²) – IQR	0.94 [0.76, 1.16]	0.98 [0.80, 1.19]	0.73 [0.60, 0.88]	<0.001
PVR (mmHg-min/l) - IQR	1170.6 [972.7-1505]	1109.5 [950.2- 1456.9]	1447 [1170- 1750.6]	<0.001
Zva (mmHg.ml-1.m²)-IQR	3.19 [2.72- 3.77]	3.01 [2.63-3.48]	4.24 [3.83-4.73]	<0.001
MAPSE (cm) – IQR	1.31 [1.09-1.44]	1.34 [1.20-1.46]	0.99 [0.90-1.09]	<0.001

HTN: hypertension; AMI: acute myocardial infarction; CAD: coronary artery disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; EFS: endocardial fractional shortening; LVEDDI: left ventricular end-diastolic diameter index; LVESDI: left ventricular end-systolic diameter index; EF: ejection fraction; RWT: relative wall thickness; LVMI: left ventricular mass index; Ee: mitral Ee ratio; TRV: tricuspid regurgitation velocity; LAV: left atrial volume; LVOTD: left ventricular outflow tract diameter; SVi: stroke volume index; APV: aortic peak velocity; MPG: mean pressure gradient; AVA: aortic valve area; PVR: peripheral vascular resistance; Zva: valvulo-arterial impedance; MAPSE: mitral annular plane systolic excursion; SD: standard deviation; IQR: interquartile range.

4-chamber view at the lateral and medial mitral annulus level. The M mode cursor was aligned parallel to the left ventricular walls. MAPSE was measured from the lowest point at the end of diastole to the peak point measured at the end of T wave in ECG. Two measurements were made on both sides, and they were averaged.

STATISTICAL ANALYSIS

Quantitative variables of normal distribution are presented as mean±standard deviation; those with nonparametric distribution are described by median and interquartile range; and qualitative variables are presented as percentages. A t test was conducted for the evaluation of normal distribution variables and Mann-Whitney test for those not presenting normal distribution. Chi-square test or Fisher's exact test were implemented (when necessary) to compare categorical variables. Sensitivity and specificity were estimated using standard definition; receiver operating characteristic curves were built and area under the curve was estimated to predict SVi <35 ml/m². P values <0.05 were considered statistically significant. The analysis was made by Rstudio, version 4.3.2.

RESULTS

There were 222 patients evaluated, with mean age of 72.9 years (66-80), of whom 57.7% were males (*Table 1*). Patients presented SAS in 59.5%. Global prevalence of LF was 16.7%. In the group of patients with SAS, the prevalence of LF was 23.6% and in those with MAS it was 6.7% ($p < 0.001$).

The MAPSE median was 1.34 cm (1.20-1.46) in patients with NF and 0.99 cm (0.90-1.06) in those with LF ($p < 0.001$) (*Figure 1A*). No significant differences were found in EF or in endocardial fractional shortening (EFS) in the two

groups (*Table 1*). Patients with MAS and NF presented a MAPSE median of 1.37 cm (1.14-1.47); while those with LF 1.05 cm (0.94-1.09) ($p < 0.001$) (*Figure 1B*). In those with SAS and NF, MAPSE was 1.31 cm (1.14-1.46) and in those with LF 0.98 cm (0.89-1.06) ($p < 0.001$) (*Figure 1C*).

On the other hand, there were no significant differences in terms of EF or EFS in regard to stenosis severity; patients with SAS had a mean EF of 65% (± 5.83) and those with MAS 65.4% (± 6.44) ($p = 0.71$); EFS was 41% (± 6.22) and 40.3% (± 6.58) in patients with MAS and SAS respectively ($p = 0.39$); instead, there were significant differences in terms of MAPSE, with the MAPSE median in patients with MAS being 1.38 cm (1.21-1.46) and with SAS 1.26 cm (1.00-1.40) ($p < 0.001$) (*Figure 1D*). Patients with a high Zva presented less MAPSE than those with normal Zva, 1.02 cm (0.88-1.09) and 1.32 cm (1.11-1.45), respectively ($p < 0.001$).

The predictive capacity of MAPSE to determine the presence of LF presented an area under the ROC curve of 0.89; a cutoff point of 1.16 cm presented 91% sensitivity and 77% specificity (*Figure 2*).

The variables significantly associated with LF in univariate analysis, and that were not part of the stroke volume estimation, were evaluated in a logistic regression model, with age ($p = 0.011$), body surface ($p = 0.003$), heart rate ($p = 0.03$) and MAPSE ($p < 0.001$) (*Table 2*).

DISCUSSION

This study showed an association between the presence of LF and MAPSE. The patients with LF presented less MAPSE than those with NF. This association was observed both in patients with SAS and MAS, and it remained significant after multivariate analysis. This was not reflected in other parameters of systolic function evaluated, such as EF and EFS. MAPSE showed an excellent prediction for the

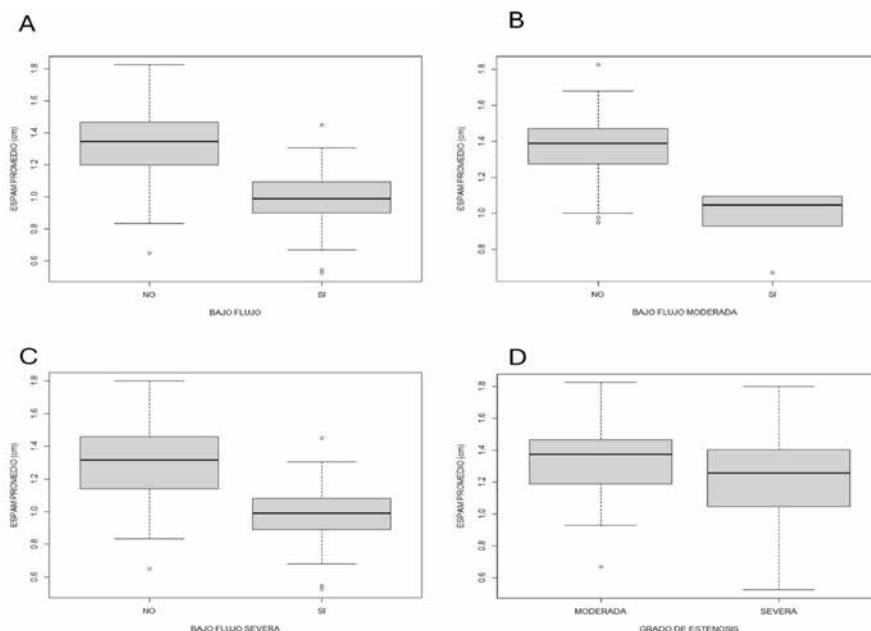


FIGURE 1.

MAPSE median according to the presence of LF in the general population (A). MAPSE according to the presence of low flow in patients with MAS (B) and SAS (C). MAPSE and AS severity relationship (D)

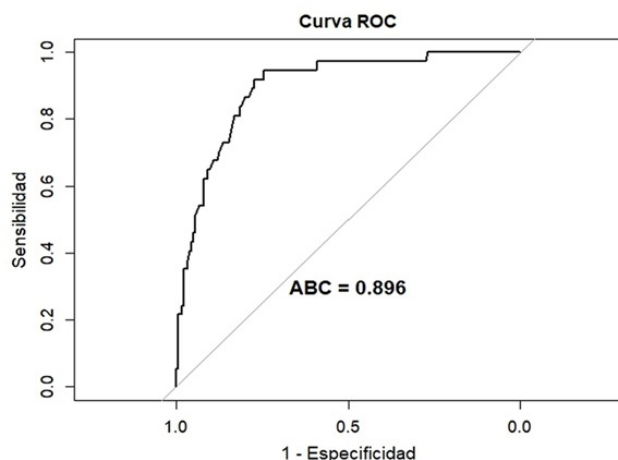


FIGURE 2. Curva ROC que muestra el área bajo la curva (ABC) del ESPAM promedio para la predicción de BF.

presence of LF, presenting an area under the curve of 0.89, with high sensitivity (91%) and proper specificity (71%).

LF is a condition presenting in up to 35% of patients with severe aortic stenosis, and the association of LF and low gradient (medium gradient < 40 mmHg) in patients with SAS presents in 10-25% of patients.^{4,12} In this study, we observed a global prevalence of 16.7% of LF, with patients with SAS being 23.6% and 6.7% in those with MAS. The latter, in previous studies, showed an LF prevalence of 7%, similar to that observed in our study.¹³

Patients with SAS, LF and EF $\geq 50\%$ present less survival after valve replacement; particularly those with low mean gradient (<40 mmHg).^{13,14,15} Beyond this, in patients with mid-to-high gradient (>40 mmHg) and EF $\geq 50\%$, those presenting LF, showed a worse prognosis in a mean follow-up of 48 months, thus reflecting the prognostic impact of LD per se, beyond the mean gradient.¹⁶

On the other hand, MAS is an entity that entails a risk of major events, and the presence of GLS deterioration, measured by speckle tracking, is a prognostic factor in the evolution of these patients, even in patients presenting EF deterioration.^{17,18,19,20} In this study, patients with MAS and low flow presented less MAPSE than those with NF (Figure 1C).

Parameters evaluating afterload beyond the one imposed by valve stenosis, such as PVR, SAC and Zva, affect cardiac mechanics and may have an impact on the evolution of patients after valve replacement.^{21,22} In this study, association between Zva and MAPSE association was observed, reflecting the sensitivity of the latter to the changes of the former.

Subendocardial fibers, responsible for longitudinal shortening, are affected early by different conditions, such as the overload imposed by AS. GLS, by speckle tracking, evaluates the function of said fibers. It was observed that patients with LF present less values than those with preserved transvalvular flow, so longitudinal function de-

TABLE 2.

Multivariate logistic regression analysis

Predictor	Estimator	EE	Z	p
Constant	-11.23588	6.23610	-1.802	0.072
AGE	0.08839	0.03480	2.540	0.011
MALE GENDER	0.46392	0.71429	0.649	0.516
BS	5.02726	1.68361	2.986	0.003
HR	0.05840	0.02697	2.166	0.030
LVSD	-0.02631	0.08441	-0.312	0.755
LVMI	-0.00428	0.00998	-0.429	0.668
RWT	2.27642	3.82240	0.596	0.551
Ee	-0.01334	0.05544	-0.241	0.810
MAPSE	-9.31400	1.80876	-5.149	<.001

BS: body surface; HR: heart rate; LVSD: left ventricular systolic diameter; LVMI: left ventricular mass index; RWT: relative wall thickness; Ee: mitral Ee ratio; MAPSE: mitral annular plane systolic excursion

terioration may lead, among other factors, to a drop in SVi.^{23,24} And beyond LF, the longitudinal function is an independent prognostic marker in patients with SAS, establishing as a marker of early compromise in the disease.^[25,26] However, the speckle tracking technique is not available in all laboratories, requiring a certain learning curve and a proper ultrasound window to minimize variability, and although they have been shortening, there are still differences observed between methods of analysis from different commercial brands.^[9,27,28]

The estimation of longitudinal function by MAPSE is a simple, generic measurement, with less interobserver variability, presenting a high correlation to the degree of myocardial fibrosis, measured with cardiac MRI in patients with AS.^[29,30] And that could be a marker of advanced damage, as LF has proven to be.

LIMITATIONS

The estimation of the area was made by continuity equation, with the probability of underestimating AVA. In spite of this, this estimation method was used in all these tests.

Larger studies are needed to establish values and cutoff points for MAPSE in its possible association with LF. In turn, follow-up studies are required to be able to establish the possible prognostic value of MAPSE.

CONCLUSION

MAPSE is decreased in patients with LF, both in MAS and SAS. MAPSE presented a high predictive capacity for LF and it persists, in a multivariate analysis, as the only independent echocardiography parameter associated to LF.

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Original Investigation Reports

Delay to reperfusion in patients with myocardial infarction in Santa Fe. It is time to develop a reperfusion network

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ABSTRACT

Introduction: Time to reperfusion in myocardial infarction is crucial and can be optimized. The use of reperfusion networks has shown to be useful in improving delays.

Objectives: to evaluate in-hospital outcomes in subjects with MI according to the distance of referral and to identify barriers associated with delays.

Methods: all consecutive MI admitted between 2016 and 2023 were analyzed. The sample was divided into groups according to the referral distance: Zone 1 (Z1) Santa Fe, Zone 2 (Z2) ≤ 100 km, Zone 3 (Z3) >100 and ≤ 200 km and Zone 4 (Z4) >200 km. In-hospital outcomes were analyzed. All referral sites were contacted to identify challenges and causes of delays.

Results: a sample of 408 STEMI was selected: 54.6% were from Z1, 27.9% from Z2, 13.7% from Z3 and 3.6% from Z4. It was observed that there was a significant difference between the referral zones and the time until admission (Z1 4 h, Z2 6 h, Z3 9 h y Z4 16 h ($p < 0.004$). Reperfusion was performed at 70.1% and the most common cause of the lack of reperfusion was the delay (60.5%). Cardiogenic shock and mortality were higher according to the distance of the transfer ($p = 0.02$ y $p = 0.01$, respectively). Referral sites were contacted, and common causes of delay were identified.

Conclusions: In-hospital outcomes are related to the delay to transfer. The implementation of networking might be useful to minimize this problem.

INTRODUCTION

Acute myocardial infarction (AMI) constitutes the most important cause of mortality in Argentina. National reports reflect that approximately 30% of deaths in the country are due to cardiovascular cause.^{1,2,3}

The time elapsed between the patient contacting the system (patient's delay) and reperfusion (system's delay) constitutes an aspect modifiable by health policies. Once the diagnosis of ST elevation myocardial infarction (STEMI) has been established by the emergency service, the immediate activation of the hemodynamics service reduces delay to reperfusion, and thus, mortality.^{4,5,6,7} These times can be optimized in a simpler manner in centers having a hemodynamic service, where organization at institutional level becomes the foundation for success. It is more difficult in centers with no capacity for angioplasty (TCA), where a referral should be made to the nearest center. In such case, the system's delay considers the confirmation of the patient being received by the TCA center and the transfer logistics.

National registries report that between 15 and 30% of patients with reperfusion criteria do not receive a proper treatment, and that in less than 45% of cases reperfusion is

reached within the recommended times due to a lack of an adequately organized access to the health care system.^{8,9,10,11} The implementation of referral networks for reperfusion in AMI has proven to be an essential tool to decrease these delays. This tool allows patients to be treated in appropriate times and places, as their operation is based on two crucial foundations: making a correct pre-hospital diagnosis and carrying out a coordinated work between centers with different complexities to optimize reperfusion.^{12,13}

OBJECTIVES

The objective of our study was to evaluate the in-hospital outcomes in patients admitted due to STEMI to an institution according to their origin location, and to identify the current obstacles making their referral difficult.

MATERIALS AND METHODS

All patients admitted to the Coronary Unit of the Sanatorio Diagnóstico, since July 2016 until December 2023, due to AMI, were analyzed. Patients with NSTEMI were excluded.

Acute myocardial infarction was defined as patients with clinical symptoms of ACS and cardiac biomarkers elevated, associated to the presence of some of the following

criteria: a) ST segment elevation ≥ 1 mm; b) motion or perfusion alteration in imaging study; c) evidence of intracoronary thrombus. Only type I AMIs, according to the fourth universal definition, were excluded.¹⁴

The sample was divided into zones according to distance in kilometers (km) until the institution in: Zone 1 (Z1) limited to the city of Santa Fe; Zone 2 (Z2) up to 100 km of distance; Zone 3 (Z3) between 100 and 200 km of distance; and Zone 4 (Z4) more than 200 km of distance. The estimation of distance was made by Google Maps, considering the fastest trajectory between the places where patients were assisted and the institution, going by land.

The variables of presentation were analyzed in patients at the time of hospital admission, as well as the treatment established and the following in-hospital events:

- **Heart failure:** presence of signs and/or symptoms of congestion upon admission and/or as they coursed.
- **Ventricular arrhythmias:** presence of tachycardia or sustained ventricular fibrillation or requirement for electrical cardioversion.
- **Kidney failure:** baseline value of serum creatinine > 2 mg/dl or its increase by 1.5 times the baseline value.
- **Cardiogenic shock:** defined as sustained systolic blood pressure of less than 90 mmHg, with no response to proper expansion and/or requiring vasopressor agents. It was considered both upon admission or during the patient's in-hospital course.
- **Mortality:** considered as all-cause death.
- **Composite events:** the addition of the abovementioned events.

Phone contact was made with all the locations included in the analysis, which corresponded to the center-north corridor of the province of Santa Fe. Locations in the south of the province were not included as referral is centralized in the city of Rosario. Data corresponding to the type of institution, availability of admission to ward or therapy, specialists, location of referral, hemodynamics and thrombolytic agents were surveyed.

For data analysis, the IBM SPSS Statistics 27 software was used. Quantitative variables are expressed as median and interquartile range; while qualitative variables are expressed as percentages and/or numbers. Chi-square test was applied to compare qualitative variables and Student's t-test for quantitative variables. In the cases of categorical variables, the ANOVA test and the chi-square test for trend were used, as it corresponded. A $p < 0.05$ value was considered significant.

RESULTS

During the analyzed period, a total of 693 patients were admitted to the Coronary Unit of the Sanatorio Diagnóstico due to AMI. From the total, those with NSTEMI ($n=278$) were excluded, constituting a final sample of 415 STEMI. From them, 53.9% ($n=227$) corresponded to Z1, 28.5% ($n=116$) to Z2, 13.9% ($n=57$) to Z3 and 3.7% ($n=15$) to Z4. The distance median of Z2 was 69.5 km (7 to 98 km), of Z3 119 km (101 to 186 km) and of Z4 248 km (213 to 366 km).

The referral locations for each zone were:

- **Zone 2:** Colastiné, Monte Vera, San José del Rincón, Santo Tomé, Arroyo Leyes, Empalme San Carlos, Recreo, Sauce Viejo, Franck, Laguna Paiva, Esperanza, Desvío Arjón, Nelson, San Jerónimo Norte, San Carlos Centro, Coronda, Humboldt, Llambi Campbell, Arocena, Gessler, Sa Pereira, San Fabián, Emilia, Pilar, Santo Domingo, Cayastá, Progreso, Barrancas, Videla, Gálvez, Nuevo Torino, Helvecia, Lopez, Bernardo de Irigoyen and Monje.

- **Zone 3:** Irigoyen, Felicia, San Justo, Maciel, Puerto Gaboto, Rafaela, María Juana, Colonia Macias, Marcelino Escalada, San Genaro, Sastre, Sunchales, Cañada Rosquín, Centeno, Soledad, San Javier, Gobernador Crespo, Colonia Dolores, La Lucila, La Criolla, San Cristóbal, Vera y Pintado, La Brava, El Trébol, Colonia Teresa and Pedro Gomez Cello.

- **Zone 4:** Calchaqui, Alejandra, Margarita, San Guillermo, La Gallareta, Vera, Malabrigo, Tostado, Reconquista, Avellaneda, Golondrina and Las Toscas.

The age median of the sample was 69 years (range from 30 to 95 years). The male gender was the most prevalent (64.4%) and the most frequent risk factor was hypertension (67.7%); 31.8% were diabetic and 17.1% presented history of ischemic heart disease (angina, AMI or previous PTCA). The rest of the basal characteristics of the population and the comparison between the different groups can be observed in [Table 1](#).

In regard to the time elapsed between the onset of symptoms and arrival to the institution, a statistically significant difference was evident between the different zones (median in h): Z1 4 h, Z2 6 h, Z3 9 h and Z4 16 h ($p < 0.005$). Also, it was observed that the presence of angina at the time of admission was less as the distance increased: Z1 85.5%, Z2 85.3%, Z3 77.2% and Z4 40% ($p < 0.005$). Likewise, at the time of admission, 64.9% did not present signs of heart failure (HF), 22.4% were in Killip Kimball II/III and 8.2% in cardiogenic shock ([Table 2](#)).

Reperfusion was carried out in 70.1% of cases by primary TCA. Between non-reperused individuals ($n=124$), the most frequent cause was being outside the therapeutic window (60.5%), followed by the presence of inappropriate anatomy (21.8%). A difference was observed in the reason not to reperfuse according to the different areas where the patients came from, with an increase being significant in late arrival to the reperfusion center according to the different areas of origin, as reflected in [Table 3](#).

An estimation was made of left ventricular ejection fraction (LVEF) in 95% of cases by echocardiogram, with a 50% median. It was observed that it was reduced as distance increased: Z1 50%, Z2 50%, Z3 46% and Z4 34% ($p < 0.005$).

In regard to in-hospital course, the most frequent complication was HF (34.6%), cardiogenic shock (16.3%), kidney failure (14.5%) and the presence of ventricular arrhythmias (VT/VF) (9.1%). Total mortality was 13%. A trend of increase was observed in the incidence of complications as referral distance increased: HF (Z1 36.6%, Z2 35.5%, Z3 45.6% and Z4 46.7%; $p=0.4$), kidney failure (Z1 12.3%, Z2 14.7%,

TABLE 1.
Basal characteristics of the population

	Total	Zone 1	Zone 2	Zone 3	Zone 4	P
Age (years)	69 ± 12	69 ± 12	69 ± 12	68 ± 11	67 ± 11	0,9
Male gender	64,6%	64,8%	67,2%	59,6%	60%	0,7
Risk factors						
Hypertension	67,7%	67,8%	65,5%	70,2%	100%	0,4
Diabetes Mellitus	31,8%	31,7%	29,3%	35,2%	40%	0,7
CV history						
Infarction	11,1%	12,8%	7,8%	8,8%	20%	0,3
Angioplasty	12,3%	12,8%	12,9%	8,8%	13,3%	0,8
Ischemic heart disease	17,1%	16,7%	17,2%	17,5%	20%	0,9
Vascular disease	10,6%	10,1%	12,1%	8,8%	13,3%	0,8
Heart failure	5,8%	6,2%	6%	3,5%	6,7%	0,8
Stroke	7%	7%	5,2%	10,5%	6,7%	0,6

TABLE 2.
Presentation variables upon admission to the center

	Total	Zone 1	Zone 2	Zone 3	Zone 4	P
Angina upon admission	82,7%	85,5%	85,3%	77,2%	40%	0,006
Onset of symptoms (h)	5 ± 8	4 ± 6	6 ± 8	9 ± 9	16 ± 9	0,004
Killip Kimball						
I	64,9%	70,9%	70,7%	59,6%	53%	0,09
II	18,8%	18,1%	18,1%	24,6%	26,6%	0,2
III	3,6%	3,1%	5,2%	3,5%	6,6%	0,3
IV	8,2%	7,9%	6%	12,3%	13,3%	0,01

TABLE 3.
Variables associated to a lack of reperfusion

	Total	Zone 1	Zone 2	Zone 3	Zone 4	P
Non-reperfused cases	29,9% (124)	26,9% (61)	28,4% (33)	36,8% (21)	60% (9)	0,03
Outside therapeutic window	60,5% (75)	52,5% (32)	69,7% (23)	71,4% (15)	77,8% (7)	0,04
Inappropriate anatomy	21,8% (27)	27,8% (17)	18,8% (6)	14,3% (3)	11,1% (1)	0,06
MINOCA	40,8% (11)	47% (8)	33,3% (2)	33,3% (1)	0% (0)	0,07
Failed primary TCA	22,2% (6)	17,6% (3)	11,1% (1)	33,3% (1)	100% (1)	0,22
Small vessel disease	18,5% (5)	23,6% (4)	11,1% (1)	0% (0)	0% (0)	0,32
LMCA and/or 3-vessel lesion	18,5% (5)	11,8% (2)	33,3% (2)	33,3% (1)	0% (0)	0,4
Hemodynamic instability	10,5% (13)	11,5% (7)	12,1% (4)	9,5% (2)	0% (0)	0,08
Without clinical and/or ECG criteria	7,2% (9)	8,2% (5)	6% (2)	4,8% (1)	11,1% (1)	0,41

Z3 22.8% and Z4 13.3%; $p=0.2$), ventricular arrhythmias (Z1 10.1%, Z2 15.5%, Z3 10.5% and Z4 26.7%; $p=0.1$); ACS (Z1 15.4%, Z2 21.6%, Z3 22.8% and Z4 33.3%; $p=0.02$) and death (Z1 11%, Z2 21.6%, Z3 22.8% and Z4 26.7%; $p=0.01$) (*Figure 1*).

Finally, a survey contact was made by phone about most institutions that make up the center-north corridor of the province. In it, we asked about the type of institution, availability of admission in ward or therapy, specialists, location of referral, hemodynamics and thrombolytic agents. From all surveyed centers ($n=73$), the following was observed:

- 34.2% were primary care centers and had no specialists available (cardiologists).
- 50.7% were medical care centers with scarce capacity for transient admission (in the general ward). From them, 30.1% had a specialist available for consultation.
- Only 15.1% of the centers included in the analysis had polyvalent units.
- 9.6% reported having thrombolytic agents available. From them, nearly half (42.8%) belong to centers with hemodynamic laboratory available and just a third (28.6%) reported having used them in the last 3 years.
- There are 14 centers with availability of hemodynamic laboratory (24/7). There is an additional center that only performs procedures in a scheduled manner (Mondays through Fridays at a specific time). From them, we should highlight:
 - 3 centers located in the north of the province (department General Obligado) have a distance to each other of less than 10 km. From them, 2 are in the same location (Reconquista).
 - 2 institutions located in the center of the province (department Castellanos) have a distance to each other of approximately 60 km. In turn, these are located at 121 km and 41 km respectively from the city of Santa Fe.
 - 1 center is located in a location close to Santa Fe (department La Capital), at 14 km of distance.
 - The city of Santa Fe has 8 institutions (7 private and 1 public) with hemodynamic laboratory available.
- 24.6% ($n=18$) of the locations refer to a center with higher complexity, which do not have thrombolytic agents or hemodynamic laboratory available either.
- 38.3% ($n=28$) of the locations included in the analysis referred patients to this institution, having closer centers with hemodynamic laboratory.

DISCUSSION

In this study, we observed there is a clear association between adverse in-hospital events and the area of referral of patients, which is due to delay to reperfusion and its complications (pump failure, less LVEF, ventricular arrhythmias, etc.)

The current recommendation by guidelines suggest, if possible, PTCA in cases of STEMI as long as it can be carried out within the first 120 minutes.¹⁵ Anyway, the real situation at world level is far from said recommendation, as between 20-60% of patients referred to centers with hemo-

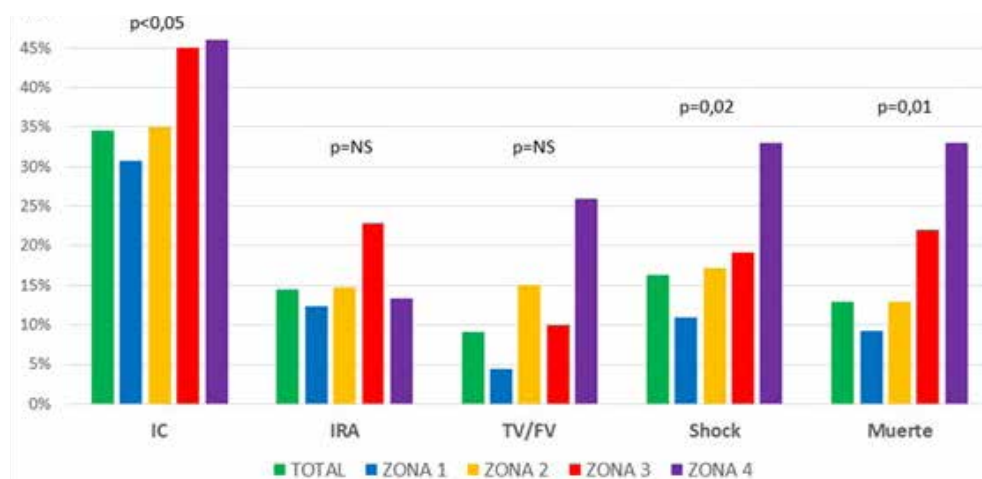


FIGURE 1.
In-hospital events

dynamic laboratory available arrive outside this time window.¹⁶ Thus, as these times extend, the benefits of mechanical reperfusion decrease, with a negative effect on mortality in the short and long terms.^{17,18,19}

National data from the third report on the ARGEN-IAM-ST registry point out to delayed presentation as the main cause for no reperfusion, being in most cases due to delay by the patient to consult (61%), followed by delays in transfer (35%).²⁰ This study plainly shows the real life obstacles for STEMI patients referral in the region. Clearly, a delay in diagnosis and referral of patients to a more complex center has a significant impact on in-hospital prognosis, reflecting on the rate of cardiovascular events.

It is important to highlight that, although this analysis is not based on timing, but on distance, it is possible to observe there is a directly proportional relationship between referral zones and the time between the onset of symptoms and arrival to a more complex center (ours). Previous publications based on distance also showed results similar to ours, with less reperfusion rate and increase in composite in-hospital events (recurrent ischemia, stroke and death).²¹

It has been proven that this delay in the system has a negative impact on clinical presentation and course: lower rate of reperfusion, larger AMI extension, less LVEF, higher incidence of HF upon admission, higher rate of complications during in-hospital course, with the subsequent cost that this represents for the health care system.

We should highlight that, as with national registries, the most frequent reason for a lack of reperfusion was being outside the time window, which significantly increased as the referral distance increased.

In regard to the survey of the centers from the different zones in the interior of the province, it was observed that in many small locations that only have primary care centers and with no specialists available, referral of patients (occasionally already with diagnosis of STEMI) is made to a nearby location, which does not have the necessary resour-

ces for reperfusion (with no thrombolytics or hemodynamic laboratory available). Once patients are received in these centers, diagnosis is made or confirmed, and then they are referred to a center of more complexity for reperfusion. It was also observed that many patients are referred to more distant locations solely due to medical insurance issues, as there are no agreements with closer centers. The same situation happens between the public and private sectors. These situations entail a delay related with the system (admission of patient, evaluation by specialist and transfer logistics, among others), which increases the total time of ischemia, with the subsequent adverse result in morbimortality.

In *Figure 2*, we show the geographical distribution of all the locations from where patients were received in this registry and the centers with hemodynamic laboratory available currently. Patients were received from the locations indicated by blue dots, showing an evident lack of logistics, as in many cases there were closer centers, capable of providing a proper reperfusion.

The implementation of an infarction network could improve this situation, providing support in locations receiving patients by telemedicine, for a proper analysis of ECGs and a joint decision on the most appropriate reperfusion therapy for each case. Data published by Silberstein et al. in regard to the AMI network of the El Cruce Hospital, proved to reduce the no-reperfusion rate from 39.3% to 20% with the implementation of telemedicine, shortening referral times and increasing reperfusion by fibrinolytics in a guided manner.²²

Recently, the infarction code of the Argentine Federation of Cardiology published in 2023 by Zapata makes evident the need to regionalize AMI treatment by the implementation of networks.²³ The mortality rate in Argentina is stable in spite of the effort to increase reperfusion strategies.²⁴ This reflects the need to implement measures to achieve patients having access to appropriate reperfusion therapies, in adequate times.

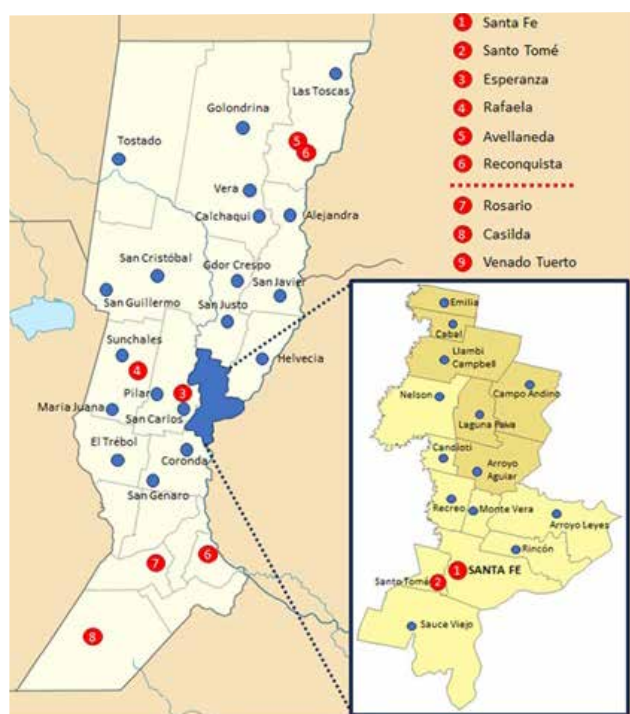


FIGURE 1.

Distribution of locations of referral and centers with hemodynamic laboratory.

Blue dots: referral locations. **Red dots:** locations with hemodynamic centers available (24/7 capacity).

LIMITATIONS

The small size of the sample and the descriptive character of the study are a limitation for the interpretation of results. On the other hand, the single-center design makes generalization difficult, as it corresponds to a private institution, where patients with medical insurance and/or pre-established agreements are admitted, which probably results in a more optimistic view of reality, not considering patients with difficulties for access to care.

We should highlight that, although in the survey multiple locations were included, always contemplating the most important ones in each department, we should consider a bias as we could not have all of them.

CONCLUSIONS

The delay in referral of patients with AMI has a clear negative impact on in-hospital evolution, representing a higher rate of complications and mortality.

Multiple obstacles were identified in the region, which may generate delays at the time of applying the most appropriate strategy for each patient, such as no availability of a specialist to confirm the diagnosis, the scarcity of thrombolytic agents, and a lack of logistics at the time of referral to more complex centers.

The implementation of networks for the reperfusion of AMI according to the geographical needs of each region may constitute a potential solution for a proper use of re-

sources. To fulfil such goals, it is crucial to have an adequate infrastructure with an efficient organization and governmental support. Public health policies are essential, integrating both the public and private health care areas.

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Original Investigation Reports

Transthyretin amyloid cardiomyopathy: clinical features and staging, indications for treatment and mortality

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Cardiomyopathy,
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ABSTRACT

Transthyretin amyloid cardiomyopathy is still an underdiagnosed disease, but it is progressive and fatal without treatment.

Methods: retrospective observational study to describe clinical characteristics, indications for disease-modifying treatment and mortality.

Results: between SEP-2019 and AUG-2024, 32 patients were diagnosed, 24 (75%) men, median age 81.5 years. Eighteen were wild type (56.2%) confirmed by genetic test and 2 of them (11.1%) had the Val30Met variant; in 12/32 (37.5%) the test was not performed. Seven patients (21.8%) were in NYHA class I, 16 (50%) in class II and 9 (28.1%) in class III; there were no patients in class IV. According to the National Amyloidosis Centre of the United Kingdom (NAC) 21 patients (75%) were in stage I, 4 (14%) in II and only 3 (10.7%) in III; 4 cases were not staged. Atrial fibrillation was observed at 16 (50%) and moderate or severe aortic stenosis in 8 (25%). Disease-modifying treatment (tafamidis) was indicated in 17 cases (53.1%) and was effectively received by 8 patients (25%). Nine patients died (28.1%), 7 due to cardiac causes without disease-modifying treatment and 2 due to non-cardiac causes with disease-modifying treatment.

Conclusions: most patients were in NYHA class I and II and NAC stage I and II, and atrial fibrillation and aortic stenosis were very frequent. Disease-modifying treatment was indicated in more than 50% of the cases, but only 25% received it; of the 9 patients who died, 7 were without disease-modifying treatment.

INTRODUCTION

Transthyretin amyloid cardiomyopathy (ATTR-CM), considered up to a few years a rare disease, is currently an increasingly diagnosed pathology due to more knowledge and diagnostic methods, mostly noninvasive, which allow its detection. However, still in many cases it is diagnosed in advanced stages, in which the specific treatment is less efficient.^{1,2} Transthyretin (TTR) is a tetrameric protein synthesized by the liver, which transports thyroxine and the retinol binding protein; in pathological conditions, the tetramer breaks down into folded dimers and monomers, and these become unstable forming poorly folded amyloidogenic monomers, which form accumulations of small oligomers, later amorphous aggregates and finally insoluble hydrophobic amyloid fibrils of 8-10 Angstroms of diameter, which progressively deposit in the tissues (osteoarticular system, heart, gastrointestinal tract, peripheral and/or autonomic nervous system, skin, subcutaneous tissue, sa-

linary glands, etc.).³ There are two clinical forms in ATTR-CM: one called wild type, which is the most frequent one, and whose cause is not well known to this date, although in most cases it is related to an advanced age; and another one, less frequent, which is hereditary, also called variant or mutant, caused by a genetic alteration where an amino acid is replaced by another, and this makes the TTR molecule unstable. ATTR-CM consists of amyloid deposition in the myocardial interstitium, causing a toxic restrictive infiltrative cardiomyopathy, with preserved left ventricular ejection fraction (PEF) in most cases. The disease is progressive and deadly depending on the time of diagnosis, but in most cases death occurs in 3.5 to 4 years with no specific treatment.^{4,5} The cardiac manifestations could be preceded several years before by extracardiac alterations: tendinous, digestive, neuropathic, urologic, etc., so ATTR-CM should be taken into account in the presence of interventricular septal (IVS) thickness ≥ 12 mm, accompanied by at least

one of the so-called red flags.⁶ On the other hand, before the suspicion of ATTR-CM, a very aggressive form should always be ruled out, light-chain (AL) amyloidosis, which is lethal in almost 50% of cases within the first 6 months, and whose treatment is completely different.⁵ Up to now there are at least 42 precursor proteins of pathological amyloid fibrils known, but 95-98% of cases are by TTR or AL, which in general simplifies diagnosis; but the other, rarer forms should not be forgotten, whose prognosis and treatment are different.^{7,8}

The goal of this work is to describe a series of cases of ATTR-CM, diagnosed in a referral center, its clinical characteristics at the time of diagnosis, and indications of disease-modifying treatment and mortality.

MATERIALS AND METHODS

This is an observational retrospective study, where the registry of patients of the institution, with diagnosis of amyloidosis, was investigated from September 18, 2019, to August 2, 2024. During 2020, there were very few studies due to the limitations of the COVID-19 pandemic. For the diagnosis of ATTR-CM, patients were included with symptoms or signs of heart disease, with an interventricular septum thickness ≥12 mm associated to ≥1 of the criteria called red flags, with bone scintigraphy with pyrophosphate labelled with technetium-99m (PYP-Tc99m) or with hydroxymethylene-diphosphonate (HMDP) labelled with technetium-99m (Table 1). Myocardial uptake of the radiotracer was evaluated in planar images with the Perugini grading scale: grade 0 normal bone uptake and absence of cardiac

uptake; grade 1 mild cardiac uptake and inferior to bone uptake; grade 2 moderate cardiac uptake accompanied by attenuated bone uptake; grade 3 strong cardiac uptake with mild or absent bone uptake.⁹ The images were taken 1 hour and 3 hours after the radiotracer injection. In all cases, it was completed with myocardial SPECT to rule out false positives by blood uptake, and also, other false positives were ruled out (recent myocardial infarction, chest trauma, cardiotoxicity by hydroxychloroquine, etc.); only patients with grades 2 and 3 were included, and lab tests were carried out to rule out monoclonal protein pathology (free light chains in serum, protein immunofixation electrophoresis in serum and 24 h urine). The staging of the disease was made according to the National Amyloidosis Centre (NAC) system.¹⁰ The measurement of glomerular filtration was made with serum creatinine using the 2021 CKD EPI equation. In all patients who gave their consent and in those in whom it was possible for logistical and financial reasons, testing was carried out to identify genetic variants. It was considered that patients were with disease-modifying treatment when they had continuous therapy with tafamidis 61 mg/day. Data are presented as summation (percentage), mean (standard deviation) or median (quartiles) when it corresponds. The study was approved by the Institutional Committee of Ethics for Health Research (CIEIS) of the institution.

RESULTS

There were 66 patients identified in the Amyloidosis registry, of whom 30 were negative in the evaluation, 2 had a teleconsultation with confirmed diagnosis of familial amyloid polyneuropathy by TTR with the Val30Met variant, 2 presented AL and 32 had ATTR-CM confirmed; there were 24 men (75%) and the median of age was 81.5 years (Figure 1). In 18 patients (56.2%), genetic testing was carried out, and in 2 (6.2%) the p.Val50Met c.148G>A was detected, also known as Val30Met; in 12 patients (37.5%), testing was

TABLE 1.
Search criteria for cardiac amyloidosis

Main criterion	Red flags
LV wall thickness >12 mm + >1 of the following:	. Heart failure in > 65 years . Aortic stenosis in > 65 years . Hypotension or normal BP if previously hypertensive . Sensitive compromise, autonomic dysfunction . peripheral polyneuropathy . Proteinuria . Skin bruising . Bilateral carpal tunnel syndrome . Biceps tendon tear . Cardiac MRI with subendocardial/transmural late gadolinium enhancement or increased extracellular volume . Reduced LV global longitudinal strain with apical preservation . Decreased QRS voltage in relation to LV mass . Pseudo Q waves in ECG . AV conduction disorders . Possible family history

(Based on: García-Pavía P et al. Eur Heart J 2021;42:1554–1568.)
AV: atrioventricular; ECG: electrocardiogram; LV: left ventricle.

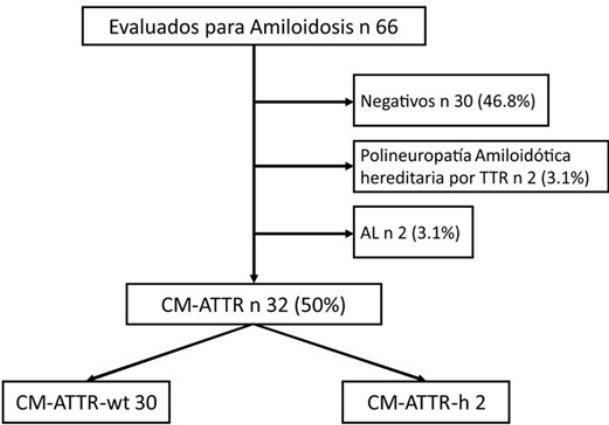


FIGURE 1.
Flowchart of patients with transthyretin amyloidosis
AL: light-chain amyloidosis; ATTR-CM: transthyretin amyloid cardiomyopathy; h: hereditary; wt: wild type; TTR: transthyretin.

TABLE 2.

Characteristics of 32 patients with ATTR-CM

ATTR-CM: transthyretin amyloid cardiomyopathy; **h:** hereditary; **wt:** wild type; **ICD:** implantable cardioverter defibrillator; **LVEF:** left ventricular ejection fraction; **PEF:** preserved LVEF; **mrEF:** mildly reduced LVEF; **rEF:** reduced LVEF; **hs-cTnT:** high-sensitivity cardiac troponin T; **PPM:** permanent pacemaker; **NAC UK:** National Amyloidosis Centre United Kingdom; **NT-proBNP:** N-terminal pro-B-type natriuretic peptide; **NYHA:** New York Heart Association; **GLS:** global longitudinal strain; **VT:** ventricular tachycardia; * also known as Val30Met; ** in some cases there was more than one manifestation in the same patient.

not made due to the family doctor decision, costs, logistics or due to the patient's decision. In *Table 2*, the main findings at the time of diagnosis are described. Approximately one every five patients were in class I of NYHA, half in class II and less than a third in class III; there were no patients in class IV. The most frequent extracardiac manifestations were digestive ones, in 1 in every 3 (particularly constipation that alternated with diarrhea episodes, not justified by any other pathology), followed by peripheral neuropathy (28.1%), carpal tunnel syndrome in 1 in every 4. Other pathologies with less prevalence were spinal stenosis, orthostatic hypotension, supraspinatus tendon tear, and less frequently bilateral biceps brachii tendon tear and Dupuytren contracture (*Table 2*). Among the cardiac manifestations, the most frequent were heart failure (78% in class II and III of NYHA), followed by atrial fibrillation (AF, 50%) and complete heart block (CHB) with permanent pacemaker (PPM) implant. In two patients, sustained ventricular tachycardia (SVT) was detected at the time of the diagnosis, so implantable cardioverter defibrillator (ICD) was implanted; one of them was in NYHA class I and it was his first manifestation of ATTR-CM. In all patients (100%), surface ECG was abnormal. For all the group, the median of LV ejection fraction (LVEF) was 56% (50.5-60), with PEF in 25 (75%) patients, but almost one in five (6 patients, 18.7%) had reduced LVEF (<40%) and 2 (6.2%) had mildly reduced LVEF (40% to 49%). From the 6 patients with reduced LVEF, four died within the period of the study. The median of diastolic function showed E/e' ratio of 16.5 (15.7-28.7) and global longitudinal strain (GLS) a median of -9.5 (7.5-14); that is to say, severe left ventricular contractile function impairment in spite of preserved LVEF (*Table 2*). Biatrial dilatation and mitral and aortic valve sclerosis were very frequent (>80% of cases), and moderate or severe aortic stenosis was detected in 1 in every 4 patients (in a 58-year-old patient with bicuspid aortic valve and one with double aortic and mitral valve lesion by rheumatic fever in his youth). Eight patients (25%) had severe CAD associated. Five patients presented pericardial effusion (15.6%) and one of them had cardiac tamponade. Cardiac scintigraphy showed score grade 3 in 84% of cases, and the rest were grade 2. In 16/32 patients (50%), cardiac MRI was conducted with gadolinium, and in all cases the typical findings described for this pathology were found; in the rest of the cases it was not made as patients refused

Variables	
Male gender n (%)	24 (75)
Age	mean 79.8 + 7.9 – median 81.5 (74-86)
wt ATTR-CM (confirmed by negative genetic test) n (%)	18/32 (56.2)
ATTR-CM (without genetic test) n (%)	12/32 (37.5)
h ATTR-CM (p.Val50Met c.148G>A)* n (%)	2/18 (11.1)
Perugini score 3 n (%)	27 (84.3)
Perugini score 2 n (%)	5 (15.6)
NYHA class n (%)	
I	7 (21.8)
II	16 (50)
III	9 (28.1)
IV	0
Other extracardiac manifestations** n (%)	
Gastrointestinal disorders	11 (34.3)
Carpal tunnel syndrome	8 (25)
Peripheral neuropathy	9 (28.1)
Spinal stenosis	5 (15.6)
Orthostatic hypotension	4 (12.5)
Supraspinatus tendon tear	3 (9.3)
Biceps brachii tendon tear	1 (3.1)
Dupuytren contracture	1 (3.1)
Abnormal ECG n (%)	32 (100)
Atrial fibrillation n (%)	16 (50)
Sustained VT n (%)	2 (6.2)
PPM n (%)	5 (15.6)
ICD n (%)	2 (6.2)
LVEF %	mean 53.8 + 9.4 – median 56.5 (50.5-60)
PEF n (%)	24 (75)
mrEF n (%)	2 (6.2)
rEF n (%)	6 (18.7)
E/e' n=22	mean 19.3 + 8.6 – median 16.5 (15.7-28.7)
GLS n=24 (%)	mean -11.2 + 3.9 – median -9.5 (7.5-14)
Biatrial dilatation n (%)	26 (81.2)
Pericardial effusion n (%)	5 (15.6)
Cardiac tamponade	1 (3.1)
Aortic and mitral sclerosis n (%)	27 (84)
Moderate/severe aortic stenosis n (%)	8 (25)
Severe aortic stenosis n (%)	6 (18.7)
Moderate aortic stenosis n (%)	2 (6.2)
6 min walk test n (%)	15 (46.8)
Cardiac MRI n (%)	16 (50)
NT-proBNP n=26 (pg/mL)	mean 2695 + 2933 – median 1995.5 (749.5-3500.2)
hs-cTnT n=26 (ng/L)	mean 51.5 + 41.6 – median 42.5 (19.2-85.2)
Glomerular filtration (mL/min/1.73 m2)	mean 55.0 + 8.0 – median 53.5 (48.2-63.2)
NAC UK stage n=28	
I n (%)	21 (75)
II n (%)	4 (14.2)
III n (%)	3 (10.7)
Living	23 (71.8)
Deceased	9 (28.1)
Cardiac cause	7
Non-cardiac cause	2

due to claustrophobia, or due to metal devices not compatible with the study (PPM, mechanical heart valves, ICD), or due to the decision of the family doctor. NT-proBNP and hs-cTnT were measured in 26 patients and both biomarkers showed significant elevations, although with a very wide range for NT-proBNP (172 pg/mL to 14,400 pg/mL); the median of glomerular filtration showed mild to moderate deterioration of renal function (stage 3a). In 28/32 patients, staging of the disease was made according to the NAC; in those that this was not made it was because of absence of NT-proBNP measurement. Twenty-one patients (75%) were in stage I, 4 (14%) in stage II and just 3 (10.7%) in stage III. The baseline walk test was made in 15/32 patients (46.8%) and all walked more than 100 m; in the rest, it was not obtained for different reasons: refusal by patients, difficulty to walk due to arthrosis, not coming to the appointment, etc.

During the period studied, 9 patients died (28%), 7 due to cardiac cause and 2 by non-cardiac causes; from those who died, seven had no disease-modifying treatment (tafamidis) and the two remaining ones had it, and both died due to non-cardiac causes: one due to persistent hyponatremia with neurological deterioration (with no brain structural disease in two consecutive CTs), and another one due to sepsis secondary to traumatic skin lesion (Table 2).

In regard to disease-modifying treatment, 8 patients (25%) received tafamidis 61 mg continuously, in 5 cases (15.6%), the medication was indicated but there were obstacles to provide them, and in 2 patients (6.4%) the treatment was indicated but they refused it for personal reasons. At the time of this publication, 2 patients (6.4%) are doing the paperwork to obtain the medication from the medical insurance; in other words, in 17/32 cases (53.1%) the indication was considered appropriate. In 5 patients (16%), it was not indicated by cognitive deterioration observed when evaluated by neurologists or the family doctors, or due to an advanced age with frailty, in whom no significant improvement was expected in the next 18 months. Four patients (12.5%) presented severe comorbidities like cancer (Merkel cell carcinoma, stomach cancer) or severe anemia due to chronic non-amyloid gastrointestinal disease (2 patients: one due to upper gastrointestinal bleeding and another due to lower gastrointestinal bleeding); in 3 cases (9.6%), it was not indicated due to the family doctor's decision making the referral to the center, and in an equal number to the Group of Amyloidosis of the institution considering that there would be no benefit from the indication (Table 3).

DISCUSSION

The main findings in this study were: 1) nearly two thirds of the patients (72%) were in class I and II of NYHA and 79% in stages I and II of NAC; 2) in nearly all cases, there was at least one extracardiac manifestation that preceded the diagnosis of ATTR-CM; 3) in most, LVEF was preserved, but in 1 in every 5, LVEF was mildly reduced or reduced, and in the latter, 4 out of 6 died; 4) AFib was the most frequent arrhythmia, detected in 50% of cases; 5) moderate

TABLE 3.
Reasons for disease-modifying treatment indication

Characteristics	n (%)
In treatment n (%)	8 (25)
Barriers for the administration of the treatment n (%)	5 (15.6)
Indicated but the patient refuses the treatment n (%)	2 (6.4)
Medication requested and paperwork is advancing with the medical insurance n (%)	2 (6.2)
Not indicated due to cognitive deterioration/ advanced age n (%)	5 (16.1)
Not indicated due to severe comorbidity n (%)	3 (9.3)
Not indicated by family doctor n (%)	3 (9.6)
Not indicated by Amyloidosis Group n (%)	3 (9.6)

or severe aortic valve stenosis was diagnosed in 1 in every 4 patients; 6) in more than half of cases, disease-modifying treatment was considered appropriate; 7) from the 9 deceased patients, 7 were without disease-modifying treatment and died due to cardiac causes.

Currently, the incidence and prevalence of ATTR-CM is unknown, but we can state that it is no longer a rare disease; however, it is still underdiagnosed, in part because LVEF is preserved and it is mistakenly diagnosed as other etiologies (HTN, hypertrophic cardiomyopathy, hypertrophy caused by aortic stenosis, etc.).^{11,12,13,14} Due to TTR deposition being systemic, extracardiac manifestations are frequent and may precede the heart disease by 5-15 years; particularly gastrointestinal disorders of uncertain origin, non-diabetic peripheral neuropathy with fine fibers compromise, bilateral carpal tunnel syndrome or tendon tears; this is important for timely diagnosis and for the specific treatment to be more efficient.^{15,16} Heart failure was the main manifestation in this series; García-Paiva et al. showed that prevalence in patients with heart failure and preserved LVEF was 16.8% and 95% of cases were in class II and III of NYHA (48.4% and 46.8%, respectively).¹⁷ In this series, 78% were in this condition. It is remarkable that from the nine deceased patients, four had reduced LVEF, which would be an indicator of severity and progress of the disease. The ATTR-ACT study (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial) showed that in patients in class I through III of NYHA, treated with tafamidis for 30 months, mortality was reduced by 30% and hospital admissions due to cardiovascular causes by 32% in comparison with placebo, although the highest benefit was observed in classes I and II.¹⁸ Patients in class III had more hospital admissions in comparison with those in class II; but in a post-hoc analysis, a significant improvement was observed in quality of life in patients in class III.¹⁹ Furthermore, in the long-term extension trial of the ATTR-ACT (58.5 months of follow-up), where since 30 months all patients received tafamidis, including those who had initially received placebo, mortality reduced by

44% in those in classes I and II of NYHA (0.56 [0.38-0.82]; $P=0.003$), and in 35% for class III (0.65 [0.41-1.01]; $P=0.06$). The survival curve tended to change from a descending direction to a more horizontal one in patients who had initially received placebo and later started with the active drug, similarly to the curve of those receiving the drug from the onset of the study.²⁰ Anyway, the higher benefit in mortality reduction, hospital admissions, quality of life and 6-minute walk tests was observed in those receiving the drug from the onset of the study, indicating that the earliest and longest the treatment, the greater the benefit.²⁰ In a study in the real world by Nies et al. on 366 patients, 55% were in class I and II of NYHA, while in this small series it was 72%; this clinical condition is important because it would indicate an early stage of the disease, with more potential benefit with the treatment.²¹

Equally, 75% of patients were in stage I of NAC, which also matches a not so advanced age of the disease, a greater survival and greater potential of response to the treatment.¹¹ Another indicator of ATTR-CM evolution is renal function; the UK National Amyloidosis Centre group showed a >20% reduction in glomerular filtration in one year significantly increases mortality both in the wild type of ATTR-CM and in the hereditary one, and for any of the NAC staging groups.²²

Typically, ATTR-CM is described as restrictive and with preserved LVEF, although in reality there is contractility impairment that could be detected with GLS measurement, reflecting longitudinal deformity or myocyte contractile function, which was found deteriorated in all patients in whom it was measured, in spite of an apparently normal LVEF.^{5,12,16} In ATTR-CM there is also a group of patients that present LVEF <50%. In this series, 25% of cases had reduced or mildly reduced LVEF, so with this condition, the presence of ATTR-CM cannot be ruled out. In this subgroup, probably a low LVEF is due to prolonged evolution of the disease by two mechanisms: 1) a continuous deposition of amyloid fibers in the myocardial interstitium; 2) poorly folded oligomers and monomers of a smaller size (<100 kDa), containing hydrophobic amino acids, bind with the cell membrane causing direct damage to cardiomyocytes and/or nerve fibers, and this is more pronounced in the hereditary forms than in wild-type ones.^{23,24} Another factor is that ATTR-CM can coexist with other cardiac pathologies which, in the long run, also affect the LV structure and function, as hypertension, CAD or congenital or rheumatic valve disease, as observed in two cases.

Pericardial effusion was mild in most patients, but there was a severe one with cardiac tamponade, a finding similar to other series.²⁵ All patients had abnormal ECG, and although they are not described in detail, the whole range of ATTR-CM findings was observed (QRS microvoltage, pseudoinfarctions, discrepancy between LV thickness in echocardiogram or MRI and QRS voltage, AV blocks with PPM implant, branch blocks, etc.). The most frequent arrhythmia was AF, worsening ATTR-CM prognosis; Bandera

et al. showed in a histological test on explanted atria, that they present extensive amyloid infiltration with loss of normal architecture, amyloid infiltration in atrial arteries and veins, capillary disruption and subendocardial fibrosis; furthermore, in echocardiogram with speckle tracking on 906 patients with ATTR-CM, they detected increase in atrial rigidity, significant deterioration of the three functional phases of the atria: reservoir, conduit and booster-pump, all of which was related to a poor prognosis. Also, they found that in 22% of patients in sinus rhythm, mechanical contraction of the atria was absent, and this "atrial electromechanical dissociation", as they called it, had a prognosis similar to those with AF.²⁶ In this center, we have started to measure atrial strain in these patients, as they may require oral anticoagulation even being in sinus rhythm. Ventricular arrhythmias are frequent and non-sustained ventricular tachycardia (NSVT) has been described in up to 74% of patients and SVT or ventricular fibrillation (VF) in 19%; in this series, it was remarkable that a patient debuted with SVT as first manifestation, and another presented NSVT during the diagnostic evaluation.²⁷ In both, ICD was implanted, and later received appropriate discharges during follow-up. Currently, it is considered that there is not enough evidence for ICD implant as primary prevention in ATTR-CM or AL outside the indications recommended by the Guidelines or Consensuses, and the decision to do it should be individualized.⁵ The prevalence of aortic stenosis in ATTR-CM is variable due to the different populations studied (Asian or European), and evaluation methods (imaging and endomyocardial biopsy (EMB)), but there is an agreement that it would be around 6% in patients receiving surgical valve replacement and 16% in transcatheter aortic valve implantation (TAVI); it has been proven by EMB that amyloid deposition may occur in the myocardium and the valve, but also in isolation in the valve with no septal myocardium compromise.^{28,29} In this series, the prevalence of moderate or severe aortic stenosis was 25%. Although aortic stenosis and wild-type ATTR-CM is more prevalent since age 65, in a 58-year-old patient, before surgical valve replacement by bicuspid valve in another center, there were signs highly suggestive of amyloidosis in cardiac MRI with gadolinium, which was confirmed 5 years later with PYP-Tc99m. Therefore, in patients with moderate to severe aortic stenosis, if there are red flags or suggestive signs, they should be evaluated for amyloidosis because their prognosis worsens with this association; also in severe stenosis, patients should be evaluated by a Heart Team and TAVI should be considered, as reports have shown better results with pharmacological treatment rather than surgery, because amyloidosis significantly increases morbidity and mortality and surgical risk.³⁰

In this institution, the cases of amyloidosis by TTR or AL are discussed in a multidisciplinary group (Amyloidosis Group), where the following intervene: clinical cardiologists, internists, intensivists, imaging specialists, hematologists, neurologists, nephrologists, pulmonologists,

hemodynamics specialists, cardiovascular surgeons and other specialists when it corresponds (ophthalmologists, gastroenterologists, etc.). In the indication of disease-modifying medication, the recommendation of the Group is taken into account, as well as patients' wishes, and the opinion by the family doctor. In this series, 53% of cases had an indication of disease-modifying medication, although just 25% received it effectively; in those that had it indicated and did not receive it, it was due to the decision by the patient or the family doctor, and in 15.6% it was not provided due to access issues. In the remaining 47%, there were different medical reasons to not indicate it, as advanced age or biological conditions in which no benefit is expected in the next 18 months (a period over which, a reduction in mortality was observed with tafamidis in the ATTR-ACT trial), progressive cognitive deterioration, current cancer or another severe condition that may influence poor outcomes in spite of the specific treatment for amyloidosis. In this series, 25% of patients received disease-modifying treatment, similar to the Ioannou et al. study, where 23% of 2001 patients received this treatment, in contrast with 77% of 293 patients that received tafamidis in the real world study by Nies et al., so every case should be carefully evaluated individually and by a team, considering the likely benefits, safety and costs.^{5,21,22}

LIMITATIONS

As this is a retrospective, single-center study, some variables were not complete for the 32 patients. The hereditary ATTR-CM research was limited by the decision of the patients or due to logistical reasons, and although we tried to investigate all of them, this was not possible in 37.5% of them, so in spite of the prevalence of the variant form in this group being relatively low, it could be considered unknown. The 6-minute walk test, a marker of the disease progress, was only carried out in nearly 50% of cases. However, the description of clinical, management and mortality variables represent a cohort from the real world.

CONCLUSIONS

In this series of patients with ATTR-CM, 11% of patients with genetic test had the variant or hereditary form, nearly 3 in every 4 patients were in functional class I-II of NYHA and 9 in every 10 in stages I and II of NAC, suggesting that they were diagnosed in relatively early stages of the disease. Fifty percent presented AF and one in every four patients had moderate or severe aortic stenosis. Nine patients (28%) died during the period of study, and from them, seven who had no disease-modifying treatment, did it due to cardiovascular cause; the two remaining ones who had modifying treatment died by non-cardiac causes. In 53% of cases, the disease-modifying treatment was considered indicated, but only 25% received it effectively; in the rest, there were medical reasons to not consider the indication appropriate. The management of patients with ATTR-CM is challenging due to the complexity proper of the pathology

and due to the coexisting diseases, so a multidisciplinary team is required for diagnosis, follow-up, treatment indication and rational use of resources and costs.

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Original Investigation Reports

Multicenter catheter ablation registry in Argentina

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ABSTRACT

Introduction: electrophysiology has had constant growth in recent years, both in diagnostic and therapeutic methods. This leads to the need for registries that can provide representative data of the therapeutic procedures performed in a large number of medical centers in Argentina. The objective of the registry is to provide updated information on the current status of catheter ablation in the different centers in Argentina. In this new edition, as in the previous one, the 3 scientific societies, FAC, SAC and SADEC are present in the preparation of the registry.

Methods: retrospective registry of catheter ablation procedures performed between January 1 and December 31, 2023 in centers in Argentina. The data were obtained through a standardized Google form that was sent via email and telephone to the participating centers.

Results: 894 ablation procedures performed in 19 centers in 8 regions of Argentina were analyzed. Unlike the previous registry and similar to current registries in Latin America, the most frequent substrate was atrial fibrillation ablation. The overall success rate was 96% and 97.65% of the procedures were free from complications.

Conclusions: an adequate and immediate global success rate of 96% was observed, which was 94.71% in the previous registry. The overall success rate, as well as in the different substrates, is similar to international multicenter reports. An increase in the number of procedures in all substrates was observed in 2023 compared to 2020, with Atrial Fibrillation being the substrate that grew the most. A systematic continuation of carrying out future registries is essential to evaluate the results and direction of electrophysiology in the centers of Argentina.

ABREVIATURAS:

INRT: intranodal reentry tachycardia
AVN: atrioventricular node
AVNRT: atrioventricular nodal reentry tachycardia
FAT: focal atrial tachycardia
AFL: atrial flutter
AFib: atrial fibrillation
VA: ventricular arrhythmias.

INTRODUCTION

Electrophysiology has constantly grown in recent years, both in diagnostic and therapeutic methods. This leads to requiring registries that can provide representative data on catheter ablation, a therapeutic procedure that is performed in plenty of medical centers in Argentina.^{1,2,3,4}

The multicenter registry on catheter ablation of Argentina has the goal of providing updated information on the

current state of catheter ablation in the different centers of Argentina. In this new edition, just as with the previous one, doctors from the three scientific societies, FAC, SAC and SADEC are present to construct the registry.

MATERIALS AND METHODS

This new edition of the multicenter registry of catheter ablation, just as with the previous one, was carried out retrospectively. All electrophysiologists of Argentina were invited to participate willingly, through a standardized Google form, which was sent by e-mail and phone, facilitating data upload in comparison with the previous one. They were invited to enter data to the form, about the ablation procedures made from January 1 to December 31, 2023. The participating centers were not required to express their written or oral commitment in regard to the increase in the total of procedures performed in their center. Registry data were processed anonymously by its authors.

Just as with the 2019-2020 registry, the different cardiac rhythm alterations were classified into 7 categories, facilitating data gathering and the subsequent analysis: intranodal reentry tachycardia (INRT), atrioventricular node (AVN), atrioventricular nodal reentry tachycardia (AVNRT), focal atrial tachycardia (FAT), atrial flutter (AFL), atrial fibrillation (AFib) and ventricular arrhythmias (VA).

Procedures were considered successful when the substrate was removed and/or post-ablation arrhythmia could not be induced; and for atrial fibrillation, when pulmonary veins were isolated.

Complications included conduction disorders (branch block, 2nd degree AV block, types I, II, 2:1 or high degree and complete heart block), vascular disorders related to access (hematoma, fistula, pseudoaneurysm), pericardial effusion, cardiac tamponade, pericarditis, myocardial infarction, transient ischemic attack and stroke, pulmonary vein stenosis, bleeding, atrioesophageal fistula, esophageal injury, gastrointestinal motility alteration, phrenic nerve paralysis, mediastinitis, death and other complications.

The technique used, the approach, type of energy used, echocardiographic assistance during ablation, acute success (at the end of the procedure), type of ablation catheter used, and number and type of complications, including peri-procedure death, were the most common variables analyzed. Specific variables in certain substrates like the type, location or underlying heart diseases were the specific variables. The use of fixed or mobile electroanatomic mapping systems was evaluated, and if procedures were carried out without fluoroscopy.

Data were expressed as percentage for categorical variables and as mean or median for continuous variables.

RESULTS

Characteristics of participating centers

In this edition of the registry, 19 centers participated, from 8 Argentinian regions (Buenos Aires, CABA, Córdoba, Corrientes, Mendoza, Neuquén, Santa Fe and Misiones)

(*Figure 1*). From all 19 participating centers, 73.6% (14/19) belong to the private sector, 15.7% (3/19) to the public sector and 10.5% (2/19) belonged to both health care sectors (*Table 1*); 47.3% (9/19) of these centers train electrophysiologists (6 private centers, 2 public ones, and 1 that belongs to both sectors); 94.7% (18/19) of participating centers reported cardiovascular surgery availability during the analyzed period. Anesthesia was available in all centers. Most centers (68%, 13/19) included in the registry do not have an electrophysiology laboratory exclusively; but from all centers, 7 had more than 1 interventional radiology suite available, and 2 centers even had 3 suites available. From all the participating centers, 3 presented more than 1 fluoroscopy device, and one even had 3 devices available. The fluoroscopy devices available were: fixed C-arm 31.5% (6/23), portable C-arm 15.7% (3/23), rotational angiography 73.6% (14/23). Just 2 (10.5%) centers did not have non-fluoroscopic navigation systems, 8 (32.1%) had fixed C-arm and 9 (47.3%) had a mobile C-arm. Five centers had more than 1 navigational system available, and one had 3 systems. Intracardiac echocardiography was available in 31.5% (6/19), and cryoablation in 47.36% (9/19). Ablation by ultrasound was not available in any center.

From the participating centers, 89.4% (17/19) had floor nurses available, 84.2% (16/19) had floor technicians, and just 21% (4/19) had floor engineers.

GENERAL RESULTS

In this new edition, the number of participating centers was maintained in comparison to the previous one, although from the total, the participating centers were not the same, a situation observed in other registries where the fluctuation of ablations and participating centers becomes evident.^{1,3} The total of ablations performed was 894, an increase from the data obtained in 2020 (623 ablations), not reaching the number of ablations from 2019 (1044), the stage previous to the Covid-19 pandemic (*Figures 2 through 4*). The most frequent substrate, unlike previous registries, with a noticeable increase, was AFib, representing 27% (242/894), and the second most frequent substrate was AFL. All ablated substrates, except for FAT, have increased in regard to the previous registry. The energy used most frequently is still RF, with 86%, with cryoablation representing the remaining 14%; 89.4% (17/19) have non-fluoroscopic navigation systems, whether fixed or mobile; cryoablation system was present in 9 centers, and intracardiac echocardiography in 6. Global and immediate success in the electrophysiology laboratory was 96%. In *Figure 5*, success of ablation per substrate and year are included. There was 97.65% of procedures with no complications, as observed in *Figure 6*.

Results, substrates and arrhythmogenic circuits

Tachycardia by intranodal reentry

INRT ablation is the third most frequent substrate, representing 20% (177/894) of procedures. This substrate was present in all centers and in 69% of cases, just as in

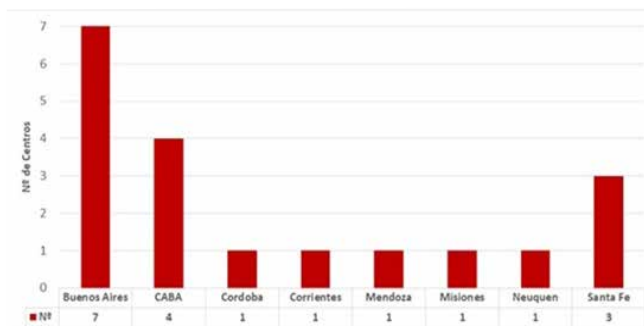


FIGURE 1.

Number of centers per regions participating in the 2023 ablation registry

the previous registries where the female gender prevailed. From the 177 ablations, 171 were the first, and just 6 were reablations; 97% (172/177) was made with conventional technique and just 3% (5/177) was made with non-fluoroscopic mapping systems. The only vascular access used was IV. The energy used most frequently was radiofrequency (RF) (163/177), and second, cryoablation (14/177) unlike the previous registry, where just RF was used for this substrate. Non-irrigated ablation catheter was used in 90% (159/177) and irrigated in 2% (4/177); the remaining cases (14/177) represent cryoablation catheters. From the total procedures, only in 8 cases echocardiogram was used to guide the procedure; in 4 cases peripheral venous contrast echocardiography was used, and in 4 cases, intracardiac echocardiography. The global success of the procedure was 99.4%, maintaining the efficacy of the registry from 2020. A complication arose, a pseudoaneurysm, representing 0.6%. After the ablation of this substrate, in 4% (8/177) of cases, additional substrates were ablated: 6 atrial tachycardias and 2 atrial flutters.

Atrioventricular node ablation

Eighteen AVN ablations were carried out during the registry. IV access and conventional technique with RF were carried out in all procedures. No non-fluoroscopic mapping systems were used, and the most used catheters were non-irrigated (13/18). No contact force-sensing catheters were used. Success was 100%, just as in the previous registry. Complications were present in 11.1% (2/18): 1 hematoma and 1 pseudoaneurysm. A procedure was accompanied by cardioverter defibrillator implant, with cardiac resynchronization system, and transesophageal echocardiogram (TEE) was used to guide the procedure. No additional substrate ablations were made.

Atrial tachycardia

FAT, just as in the previous registry, was the sixth ablated substrate during 2023, representing 4% (38/894) of all cases. This substrate is still more frequent in the female gender, with 61% of cases. The most frequent location was in the right atrium, with 78.9% (30/38) (10 crista terminalis, 10

TABLE 1

General characteristics of centers

General characteristics (n 19)	
Financing	
Public n (%)	3 (15,78)
Private n (%)	14 (73,68)
Both n (%)	2 (10,52)
Availability of heart surgery n (%)	18 (94,73)
Availability of anesthesia n (%)	19 (100)
Center with training for electrophysiologists n (%)	9 (47,36)
Laboratory staff	
N° of physicians (electrophysiologists)	3
N° nurses	2
N° technicians	2
N° engineers	0-1
Belonging to a group of electrophysiologists?	
Yes n (%)	16 (84,21)
Technical resources	
Room availability	
Exclusive n (%)	6 (31,57)
N° of rooms available	1,47
Fluoroscopy device	
Fixed arm n (%)	6 (31,57)
Portable arm n (%)	3 (15,78)
Rotational angiography n (%)	14 (73,68)
Non-fluoroscopic navigation systems available	
No n (%)	2 (10,52)
Mobile n (%)	9 (47,36)
Fixed n (%)	8 (42,10)
Non-fluoroscopic navigation systems	
Carto n (%)	5 (21,73)
Ensite n (%)	14 (60,86)
Columbus n (%)	4 (17,39)
Additional equipment	
Intracardiac echocardiography n (%)	6 (40)
Cryoablation n (%)	9 (47,36)
Ablation by ultrasound n (%)	0 (0)
No n (%)	9 (47,36)

coronary sinus, 3 right atrial appendage, 3 right atrial base, 3 right free wall and 1 vena cava) and in the left atrium 21.1% (8/38) (5 left atrial base, left free wall and 1 left atrial appendage). In all patients IV access was used. All patients with substrates located in the left atrium were approached by transseptal access. Just as with the previous registry, RF was the energy used most frequently; just 1 case was made with cryoablation (right free wall). The non-fluoroscopic mapping system was used in 53% (20/38) of cases. Non-

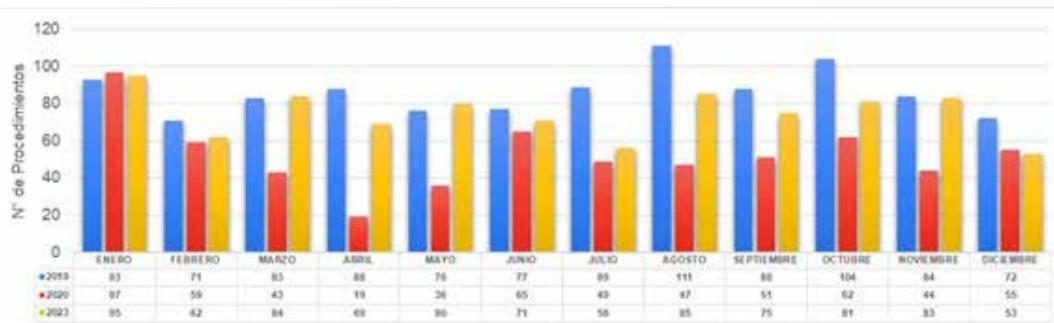


FIGURE 2.

Number of procedures per month and year carried out during the 2019/2020 and the 2023 registries

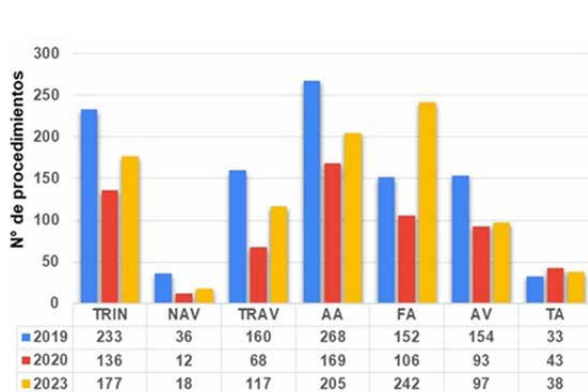


FIGURE 3.

Number of procedures per year according to the substrate made during the 2019/2020 and the 2023 ablation registries

INRT: intranodal reentry tachycardia; AVN: atrioventricular node; AVNRT: atrioventricular nodal reentry tachycardia; FAT: focal atrial tachycardia; AFL: atrial flutter; AFib: atrial fibrillation; VA: ventricular arrhythmias.

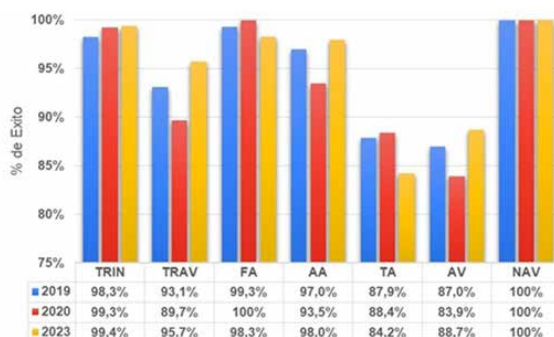


FIGURE 5.

Success of catheter ablation according to the substrate treated per year made, during the 2019/2020 and the 2023 ablation registries.

INRT: intranodal reentry tachycardia; AVN: atrioventricular node; AVNRT: atrioventricular nodal reentry tachycardia; FAT: focal atrial tachycardia; AFL: atrial flutter; AFib: atrial fibrillation; VA: ventricular arrhythmias.

irrigated catheters were used in 50% (19/38) of cases; irrigated no-contact-force sensing catheter in 21.05% (8/38), and with contact-force sensing in 26% (10/38). In 34% (13/38) of cases, echocardiography was used to guide the procedure (8 intracardiac echocardiography and 5 peripheral venous

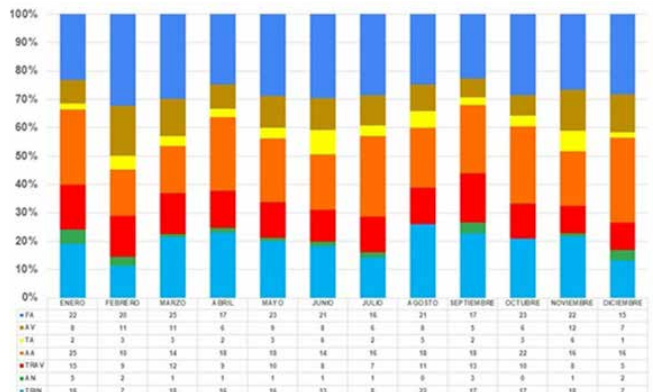


FIGURE 4.

Relative frequency of the different substrates treated during the ablation registry per month during 2023

INRT: intranodal reentry tachycardia; AVN: atrioventricular node; AVNRT: atrioventricular nodal reentry tachycardia; FAT: focal atrial tachycardia; AFL: atrial flutter; AFib: atrial fibrillation; VA: ventricular arrhythmias.

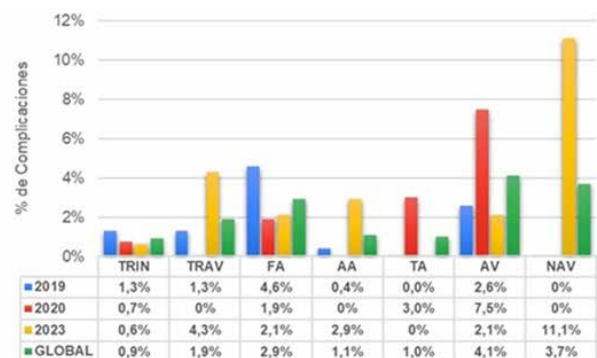


FIGURE 6.

Percentage of complications of catheter ablation according to the substrate treated per year made during the 2019/2020 and 2023 ablation registries.

INRT: intranodal reentry tachycardia; AVN: atrioventricular node; AVNRT: atrioventricular nodal reentry tachycardia; FAT: focal atrial tachycardia; AFL: atrial flutter; AFib: atrial fibrillation; VA: ventricular arrhythmias.

contrast echocardiography). The global success of this substrate is 82.4%. No complications related to this procedure were recorded. In 3 patients, additional substrate ablation was carried out (1 INRT, 1 AFL and 1 AVN).

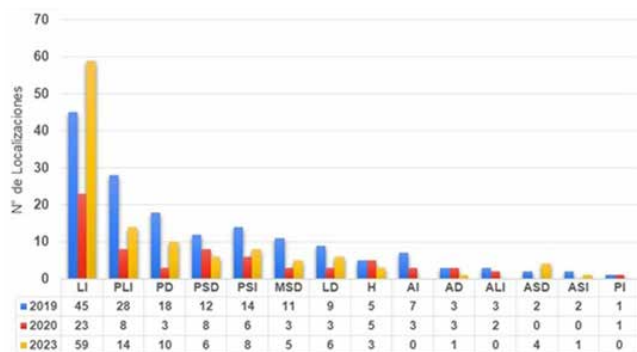


FIGURE 7.

Distribution of accessory pathways per year made during the 2019/2020 and the 2023 ablation registries

LL: left lateral; LPL: left posterolateral; RP: right posterior; RPS: right posteroseptal; LPS: left posteroseptal; RMS: right mid-septal; RL: right lateral; H: His bundle; LA: left anterior; RA: right anterior; LAL: left anterolateral; RAS: right anterosseptal; LAS: left anterosseptal; LP: left posterior.

Atrioventricular nodal reentry tachycardia

AVNRT represents the fourth most frequent substrate, with 13% (117/894) of all procedures, with its number increasing in regard to the 2020 registry, but not reaching the 2019 number of procedures. This substrate was more frequent in the male gender (63%). From all patients ablated due to AVNRT, 92% (108/117) were first procedure and the remaining 8% (9/117) were reablations; 63.25% (74/117) presented delta wave in ECG, 79% (92/117) presented orthodromic tachycardias, 2% (2/117) antidromic tachycardias, 4% (5/117) both, and 15% (18/117) did not present arrhythmias.

Just as with the previous registry, the left pathways were the most frequent ones with 70.08% (82/117). The locations per frequency were: left lateral 50.4% (59/117), left posterolateral 12% (14/117), right posterior 8.5% (10/117), left posteroseptal 6.8% (8/117), right posteroseptal 5.1% (6/117), right lateral 5.1% (6/117), right mid-septal 4.3% (5/117), right anterospetal 3.4% (4/117), His bundle 2.6% (3/117), right anterior 0.9% (1/117), left anterosseptal 0.9% (1/117), left anterior 0% (0/117), left anterolateral 0% (0/117) and left posterior 0% (0/117) (Figure 7).

RF was the most used energy, with 94% (110/117), the remaining 6% (7/117) corresponded to cryoablation. The most frequently used ablation technique was the conventional one in 85% (100/117) of cases. Non-fluoroscopic mapping systems were used in the remaining 15%. Access to left chambers was done by retrograde aortic access in 62.19% (51/82) of cases, and transseptally in 36.58% (30/82). One patient required epicardial access (1/82).

Non-irrigated catheters were used most frequently (96/117); only in 3% (4/117) of patients contact force-sensing catheters were used. In 9.4% (11/117) of the cases, peripheral venous contrast echocardiogram was used, and in 2.6% (3/117), intracardiac echocardiography.

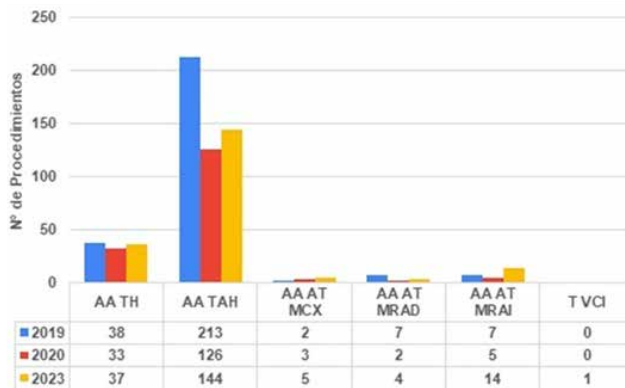


FIGURE 8.

Frequency of atrial flutters per year

CW T-AFL: clockwise typical atrial flutter; CCW T-AFL: counterclockwise typical atrial flutter; MR A-AFL Sx: macroreentrant atypical atrial flutter by surgery; RA MR A-AFL: right atrium macroreentrant atypical atrial flutter with no atriotomy; LA MR A-AFL: left atrium macroreentrant atypical atrial flutter.

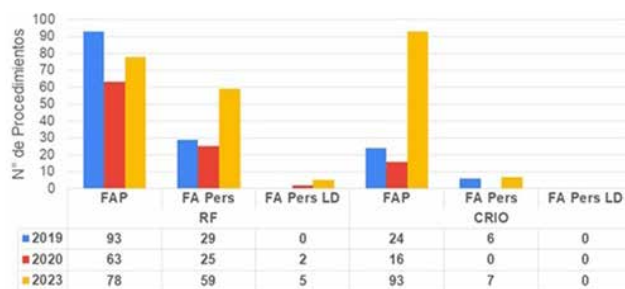


FIGURE 9.

Número de procedimientos por año, presentación clínica y energía utilizada para la ablación.

AFib: atrial fibrillation; PAF: paroxysmal atrial fibrillation; PsAF: persistent atrial fibrillation; LSPAF: long-standing persistent atrial fibrillation; RF: radiofrequency; CRYO: cryoablation.

The global success of AVNRT ablation was 94.9% (93.1% in 2019 and 89.7% in 2020). Complications appeared in 4.3% of cases (3 hematomas, 1 pseudoaneurysm and 1 conduction disorder [right bundle branch block]). In just 1 patient, 1 additional substrate ablation (INRT) was conducted.

Atrial flutter

Typical AFL (T-AFL) and atypical AFL (A-AFL) was the second most ablated substrate during 2023, after AFib ablation. In total, there were 205 procedures made, 23% of the total. Isthmus-dependent T-AFL with counterclockwise conduction (CCW T-AFL) was the most frequent variant, with 70% (144/205), and next typical AFL with clockwise rotation (CW T-AFL) 18% (37/207) (Figure 8). RF was the most used energy in 100% of cases; 95% of ablations were the first procedure. The conventional ablation technique was used in 77% (158/205), in the remaining 23% non-fluo-

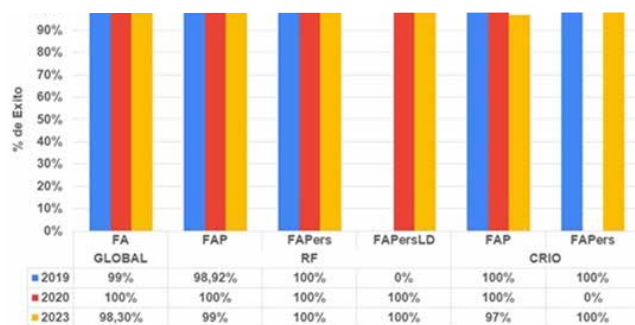


FIGURE 10

Percentages of success of procedures per type of atrial fibrillation, technique and year

AFib: atrial fibrillation; **PAF:** paroxysmal atrial fibrillation; **PsAF:** persistent atrial fibrillation; **LSPAF:** long-standing persistent atrial fibrillation; **RF:** radiofrequency; **CRYO:** cryoablation.

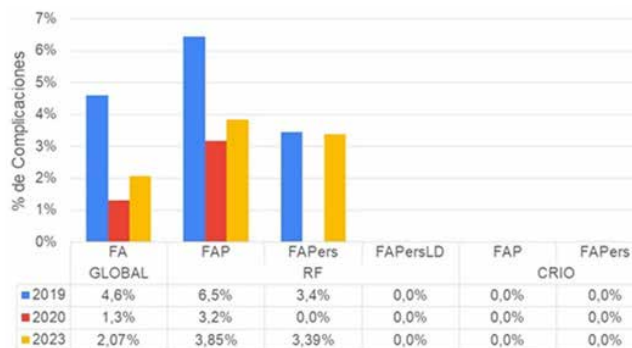


FIGURE 11

Percentages of complications of procedures per type of atrial fibrillation, technique and year

AFib: atrial fibrillation; **PAF:** paroxysmal atrial fibrillation; **PsAF:** persistent atrial fibrillation; **LSPAF:** long-standing persistent atrial fibrillation; **RF:** radiofrequency; **CRYO:** cryoablation.

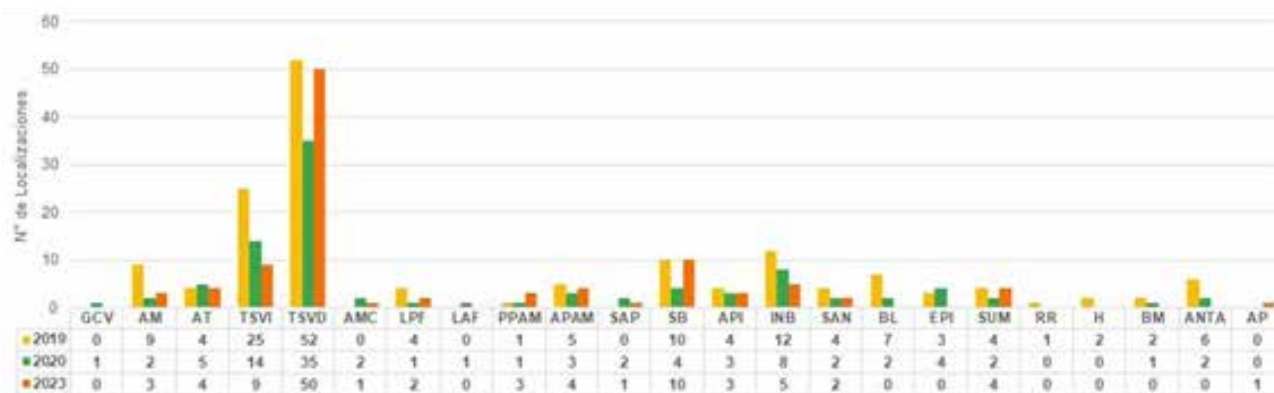


FIGURE 12

Distribution of ventricular substrates treated during the 2019/2020 and the 2020 registries

GCV: great cardiac vein; **MA:** mitral annulus; **TA:** tricuspid annulus; **LVOT:** left ventricular outflow tract; **RVOT:** right ventricular outflow tract; **AMC:** aortomitral continuity; **LPF:** left posterior fascicle; **LAF:** left anterior fascicle; **PMPM:** postero-medial papillary muscle; **ALPM:** anterolateral papillary muscle; **SAP:** septoapical; **BS:** basal septal; **ANS:** anterior septal; **API:** apical; **INB:** inferobasal; **ANTA:** anteroapical; **EPI:** epicardial; **SUM:** summit; **B-B:** branch-to-branch; **MB:** moderator band; **H:** His bundle; **PA:** pulmonary artery.

roscopic mapping systems (23 CCW T-AFL and 24 T-AFL). Access to left chambers (macro-reentrant atypical atrial flutter in left atrium) was made through transseptal access in 100% (14/14) of cases.

The most used catheters were non-irrigated with 70.73% (145/205). Contact force-sensing was only used in 8% (16/205) of procedures.

In 26 ablations, echocardiography was used as guide (5 peripheral venous contrast, 14 intracardiac and 7 TEE).

The global success of this procedure was 98% (97% in 2019 and 93.5% in 2020). The rate of complications was 2.9% (2.7% in 2019-2020) and corresponded to 2 hematomas, 2 pseudoaneurysms and 2 conduction disorders. In 11 patients, ablation of additional substrates (4 INRT, 5 AFib, 1 AVN and 1 FAT) was conducted.

Atrial fibrillation

AFib ablation was the most frequent procedure during

2023, with a total of 242 procedures, representing 27% of ablations; 52.63% (10/19) of centers carried out ablation of this substrate. The clinical presentation was paroxysmal (PAF) in 71% (171/242) of cases, persistent (PsAF) in 27% (66/242) and long-standing persistent (LSPAF) in the remaining 2% (5/242) (Figure 9). The most used energy was RF with 59% (142/242), and second, cryoablation with 41% (100/242). Cryoablation was applied in 93 patients with PAF and in 7 with PsAF. In 100% of the procedures made with RF, non-fluoroscopic mapping systems and irrigated catheters were used, with 65% being with sensing and 35% with no contact force-sensing. Access to the left chambers was transseptal in all cases. Peripheral vascular echocardiogram was used in 22% (53/242), intracardiac echocardiography in 43% (104/242) and TEE in 7% (17/242); 94% (228/242) were first procedure, only 14 reablations were recorded. Pulmonary vein isolation was carried out in 96.69% (234/242) of cases. In 16% (38/242), additional applications

were conducted (16 posterior box, 2 roofline, 9 fractionated potentials, 6 superior vena cava 2 vein of Marshall).

The global success of AFib ablation was 98.3%; in *Figure 10* the percentage of success of the procedure is shown, according to technique, type of AFib and year. The global rate of complications in AFib ablation was 2.7%; an improvement in regard to the previous registry. In *Figure 11*, the percentage of complications of the procedure is shown according to technique, type of AFib and year. In 30 patients, additional ablations were made of AFL, 1 FAT, 1 INRT and 1 AV.

Ventricular arrhythmias

The VA ablation procedures during 2023 represented 11% (97/894) of cases; 52.63% (10/19) of centers conducted ablation of this substrate. VA were subdivided into 4 groups to facilitate analysis: premature ventricular contractions (PVC), non-sustained ventricular tachycardia (NSVT), sustained ventricular tachycardia (SVT) and arrhythmic storm (AS); 70% (68/97) of procedures corresponded to PVC, and second, SVT with 24% (23/97). Four patients presented AS; 72.2% (70/98) of patients did not present structural disease, 19.6% (19/98) ischemic heart disease, 4.1% (4/98) Chagas cardiomyopathy, 2.1% (2/98) congenital heart disease and 2.1% (2/98) arrhythmogenic cardiomyopathy.

The ablated locations were: great cardiac vein 0% (0/102), mitral annulus 2.9% (3/102), tricuspid annulus 3.9 (5/102), LV outflow tract 8.8% (9/102), RV outflow tract 49% (49/102), aortomitral continuity 1% (1/102), left posterior fascicle 2% (2/102), left anterior fascicle 0% (0/102), postero-medial PAM 2.9% (3/102), antero-lateral PAM 3.9% (4/102), septoapical 1% (1/102), septobasal 9.8% (10/102), anterior septal 2% (2/97), apical 2.9% (3/102), inferobasal (4.9%) (5/102), anteroapical 0% (0/102), lateral basal 0% (0/102), pulmonary artery 1% (1/102), epicardial 0% (0/102), summit 3.9% (4/102), His bundle 0% (0/102), moderator band 0% (0/102), branch-to-branch 0% (0/102) (*Figure 12*). Four centers made applications in 2 foci (3 patients with ischemic heart disease and 1 without heart disease), and 1 center in 3 foci (patients with congenital heart disease).

In just 2 patients with RVOT PVC and no structural heart disease, conventional ablation was carried out. In the remaining 97.9% of patients, ablation guided by non-fluoroscopic mapping was made. The total of ablations was made with RF. IV access was used in 100% of patients, and access to the left chambers was made by transseptal access in 14.4% (14/97) and retrograde aortic access in 27.8% (27/98). Just one patient required epicardial access.

The most widely used catheters were irrigated ones, in 88% (85/97), 59% (57/97) had contact force-sensing. In 37 patients, intracardiac echocardiography was used to guide the procedure, and TEE and peripheral venous contrast echocardiography were used just in 1.

The global success of the AV ablation procedures was 88.65% (86/97); an improvement in regard to the previous registry. The success of the RVOT procedure was 91.83% and of LVOT 88.88% (*Figure 13*). Complications (cardiac

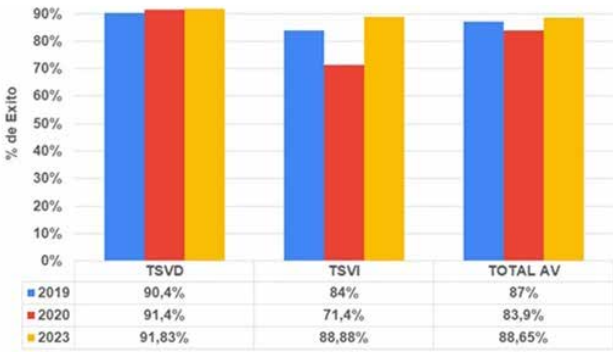


FIGURE 13
Percentages of success of the procedures of the total of ventricular arrhythmias and of RVOT and LVOT
RVOT: right ventricular outflow tract; LVOT: left ventricular outflow tract; VA: ventricular arrhythmias.

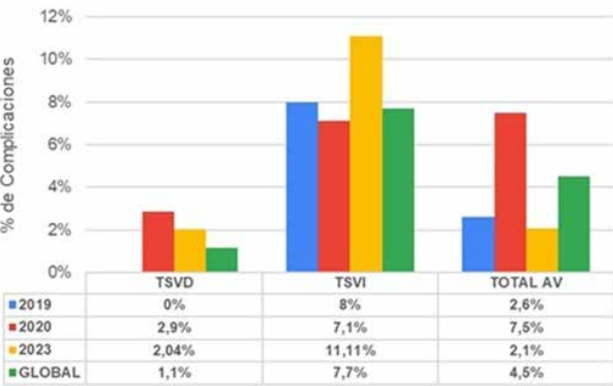


FIGURE 14
Percentages of complications of the procedures of the total of ventricular arrhythmias and of the RVOT and LVOT
RVOT: right ventricular outflow tract; LVOT: left ventricular outflow tract; VA: ventricular arrhythmias.

tamponade/perforation) were present in 2.1% (2/97) of patients, 1 in RVOT ablation and another in LVOT ablation (*Figure 14*). No additional substrate ablations were made.

DISCUSSION

In spite of having facilitated the load of cases by an on-line form with any device, leaving behind the so criticized previous system, there is still low involvement. This year, just as with the previous one, no written or verbal commitment was required for data upload. In recent times, communication through the different academic meetings between electrophysiologists belonging to the three societies has brought us closer. This support between colleagues allowed us to determine the significance and need to have our own data, reflecting the reality of Argentina. Despite what was mentioned above, the absence of many centers and groups is noticeable in these registries. This leads to redouble our efforts, so that national registries may have increasingly more participants and to be more representative.

ANNEX 1

List of participating centers

CITY	CENTER	PERSON IN CHARGE OF DATABASE	CHIEF OF SERVICE
La Plata	Hospital Interzonal General de Agudos San Martín	Monjes Enrique	Camerini Daniel
La Plata	Instituto Medico Platense	Monjes Enrique	Zabala Federico
Gran Buenos Aires	Hospital Interzonal General de Agudos Presidente Perón	Jurado Juan Carlos	Delgado Lorena
La Plata	Instituto del Diagnostico S.A	Monjes Enrique	Medesani Luis
CABA	Clinica Adventista Belgrano	Jurado Juan Carlos	Lopez Cabanillas Nestor
Gran Buenos Aires	Sanatorio Bernal	Jurado Juan Carlos	Delgado Lorena
Posadas	Instituto de Cardiología y Cirugía Cardiovascular	Moreno Gerardo	Moreno Gerardo
Corrientes	Instituto de Cardiología de Corrientes	Reyes Gabriela	Pozzer Domingo Luis
CABA	Clínica Santa Isabel	Jurado Juan Carlos	Elencwajg Benjamín
CABA	Hospital Británico de Buenos Aires	Iván Tello Santacruz	César Cáceres Monié
CABA	Hospital Churruca-Visca	Guzmán Juan Pablo	Díaz Uberti Pedro
Rosario	Instituto Cardiovascular de Rosario	Bravino Maria Florencia	Silvano Diangelo
Rosario	Hospital Privado de Rosario	Velasco Diego	Velasco Diego
Rosario	Hospital Centenario	Nannini Sebastian	Pellizzón Oscar
San Nicolas de los Arroyos	Fundación Nuestra Señora del Rosario	Trotta Omar	Telechea Trentin Juan
San Rafael	Hospital Español del Sur Mendocino - Incorsa	Cozzari Jennifer	Cozzari Jennifer
Córdoba	Instituto Oulton	Arabia Luis	Arabia Luis
General Roca	Sanatorio Juan XXII	Taquichiri Acuña Noemi	Raña Ramón

In this new edition of the catheter ablation registry, it was possible to observe that just as in others, participation by centers fluctuates.³ The presence of new centers was observed and the absence of others that had participated previously. There were centers that registered to it but did not upload cases. These centers were not included in the final report.

The relationship between centers financing, public or private, remained in favor of the latter, as in the previous registry. In this edition, there was a higher number of centers with 3D navigators; the rate of centers without this technology decreased from 22.2% to 10.5% in comparison to the previous registry. On the other hand, cryoablation availability increased in centers from 12.5% to 47.36%.

It is remarkable that a lower number of centers declares

having intracardiac echocardiography available (61.11% vs 31.5% in the current report).

From 83.33% of centers that had support cardiovascular surgery available, now 94.7% have it.

Month by month, except for January 2020, a greater number of procedures were carried out in 2023 in comparison to that year. However, 2023 had a lower number of procedures in comparison with 2019, showing the impact of the pandemic and the national context that are still influencing this practice.

In AVNRT ablation, it is possible to observe a partial return to the classically used technique. The approach, although depending on the access location, the experience of the operator, the availability of the necessary extra material, among other variables, experienced an increase in re-

trograde aortic access from 9.64% reported in the previous registry (2019-2020) to 62.19% in 2023.

In AFL, an increase was observed in the ablation of atypical flutters, that went from 6.17% to 18%; just as with the rate of use of navigators, that increased from 17.55% to 23%. Although low, an increase was observed in the use of contact force-sensing catheters, from 2.97% to 8%.

AFib ablation deserves special attention, as it reaches 3.6% of ablations in the 2007-2009 registry, and 15.51% in the previous registry (2019-2020), to becoming the most intervened substrate in 2023, with 27% of ablations, replacing AFL in the first place.^{1,2} In 2023, there were 242 procedures made of AFib ablation, exceeding both 2020 (106) and 2019 (152). Cryoablation is being more used in this substrate, going from 18.2% in the previous registry to 38.42%. Also, a mild decrease was observed in the rate of success, being 99.3% in 2019, 100% in 2020, and 98.3% in 2023. An increase in AFib ablation procedures was observed in all its presentations; however, a predominance was observed in the PsAF and LSPAF forms. An increase was verified in AFib ablation by radiofrequency of 1.23 times in its paroxysmal presentation, 2.36 times in PsAF and 2.5 times in LSPAF. In cryoablation, there was a 5.81 increase in PAF; while only 7 procedures for PsAF were carried out in 2023 in comparison with none in 2020.

Ventricular arrhythmias are perhaps one of the substrates where we are farthest from reaching the number of cases reported before the pandemic. There were 93 procedures made (11% of the total) in the current registry, the same number as in 2020, in comparison with 154 in 2019 (14.44%). Navigator use went from being used in 70.85% to 97.9%. A small improvement was observed in global success, with 88.65% in the current registry vs 85.8% (2019-2020).

From the complications observed in this registry, although a few, a greater number was reported in 2019 and 2020. The presence of pseudoaneurysms in procedures with exclusive venous access requires proposing strategies that would make vascular access safer, such as using peripheral venous contrast echocardiogram. This technique was used in 9.6% of AVNRT ablation procedures and in 2.43% of AFL.

CONCLUSIONS

An adequate and growing rate of global and immediate success was observed. It was 94.71% in the previous registry and 96% in 2023. Both the rate of global success and the rates in the different substrates are similar to international multicenter reports. Except for atrial tachycardia, an increase was observed in the number of procedures in all substrates in 2023 in comparison with 2020. The substrate that increased the most was atrial fibrillation, which grew 2.28 times in regard to the number of procedures in 2020, with a higher addition in the persistent and long-standing persistent forms.

This registry made in 19 centers in Argentina about catheter ablation displays significant information, whose usefulness is not just in the figures of procedures and substrates, but also in the dynamic changes occurring with the addition of techniques and technologies, but not exempt from receiving the influence of the social and financial problems of the country. About this, for 2023, we can infer that we were on our way to reaching the number of procedures previous to the pandemic. The systematic continuity of carrying out this survey with future registries is essential to assess the results and the direction of work in catheter ablation of arrhythmias.

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Original Investigation Reports

Predicting arterial stiffness with multilayer perceptron; a clinical data-driven approach

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ARTICLE INFORMATION

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neural networks, computer.

ABSTRACT

Introduction: arterial stiffness is a decrease in the elasticity of the arteries, mainly those of large caliber.
Objective: to predict the presence or absence of arterial stiffness through primary care examinations using multilayer perceptron.

Materials and methods: analytical and cross-sectional study of a secondary database made up of 801 patients undergoing estimation of cardio-ankle vascular index (CAVI) using an atherosclerosis detector. The dependent variables were left CAVI (LCAVI), right CAVI (RCAVI). The independent variables were 11 tests obtained through clinical history. Multilayer perceptron-type neural networks were used, from which the classification table, predictive capacity, and diagnostic tests were evaluated.

Results: for LCAVI, the model had an area under the curve (AUC) of 0.878. For RCAVI, the AUC was 0.869. The model test had a percentage of correct predictions for CAVI ≥ 9 of 70.70% and 67.10% for LCAVI and RCAVI, respectively. For CAVI < 9 it was 91.60% for LCAVI and 94.60% for RCAVI. The correlation between the presence and absence of arterial stiffness of the CAVI test of the atherosclerosis detector, and the CAVI obtained by multilayer perceptron was moderate for LCAVI ($K = 0.579$) and RCAVI ($K = 0.587$). Specificity values were 92% and 93% for LCAVI and RCAVI, respectively. The negative predictive value was 88% for LCAVI and 89% for RCAVI.

Conclusions: the multilayer perceptron-type neural network, based on primary care examinations, had a high predictive value for LCAVI and RCAVI to exclude the presence of arterial stiffness.

INTRODUCTION

Arterial stiffness is a natural process associated to biological ageing, accelerated by inflammation produced in a scenario of arteriosclerosis, caused by common mechanisms that include a reduced elastin/collagen ratio, due to cross linking of elastin, inflammation induced by reactive oxygen species, calcification, cell rigidity of the vascular smooth muscle and endothelial dysfunction.^{1,2} Ageing causes degenerative changes coursing with contractile impairment of the elastin located in the tunica media due to repetitive cycles of mechanical stress and increase and transformations of arterial collagen proteins generated to compensate elastin loss, as well as collagen reticulation due to the final products of advanced glycation.³ The increase in arterial stiffness is associated to a higher risk in cardiovascular disease (hypertension, myocardial infarction, heart failure, stroke), which are the first cause of death at world level, with more than 20 million yearly deaths.⁴

The determination of arterial stiffness can be made with cardio-ankle vascular index (CAVI), which measures arterial stiffness directly, is not invasive and has a high value to predict cardiovascular morbimortality, mainly in adults older than 60 years.⁵ It derives from the Bramwell-Hill equation and introduces the stiffness parameter β , representing arterial dilatability, which correlates with artery diameter changes during systole and diastole.⁶ CAVI can be obtained with electronic devices called "arteriosclerosis detectors", measuring blood pressure in arms and ankles, performing an ECG, phonocardiograms and determining pulse waves.

CAVI measurement is generally kept for patients with high risk factors of cardiovascular and cerebrovascular morbimortality.⁷ The measurement device of arterial stiffness is not used as an instrument of regular measurement in the general population going to the primary care and cardiology medical offices; however, this population may benefit from a preventive and monitoring point of view if they knew they have arterial stiffness or not, which may present a risk of circulatory disease.

In this regard, data stated in the clinical history, and laboratory and hemodynamic results performed as a routine, could be directly or indirectly related to CAVI and could work as an indirect instrument for the estimation of arterial stiffness reaching a greater number of patients. For this reason, the aim of this investigation may predict the presence or absence of arterial stiffness through primary care tests by multilayer perceptron.

MATERIALS AND METHODS

Study population and design

Analytical, cross-sectional study from data secondary to the Harvard Dataverse repository (*see Ethical Considerations*), consisting of adults who underwent chest CT scan without contrast and a measurement of arterial stiffness between March 2018 and October 2019.

The database was made up by a total of 801 adults from 18 years of age, who underwent chest CT scan, from whom 791 underwent LCAVI and 786 RCAVI. The authors of the original database reported that it is made up by people who lack significant arterial anomalies or diseases that may severely affect the structure of the arteries, with those being the following: history of aortic revascularization; stent implant or replacement; genetic syndromes identified or suspected, associated to aneurysms and chest aortic dissections (Marfan syndrome, Turner syndrome); congenital variation in a complete or significant branch of the aorta in adults (abnormal right subclavian artery, coarctation of the aorta); inflammatory diseases associated to the disease in thoracic aorta disease; acute arterial syndrome (including aortic dissection and intramural hematoma); aortic aneurysms; severe hypovolemia and unstable hemodynamics; severe heart failure with low ejection fraction; patients in hemodialysis. The total population of the database was used; hence, there was no sampling or randomization technique. The characteristics of the population are in [Table 1](#).

Measurements and variables

The dependent variable was the cardio-ankle vascular index (CAVI), whether right (RCAVI) or left (LCAVI); which is a test measuring the degree of arterial stiffness, and it was a qualitative dichotomous variable divided in ≥ 9 , corresponding to values of arterial stiffness, and < 9 corresponding to values of absence of arterial stiffness and pre-stiffness. According to the authors of the database, CAVI was obtained by an arteriosclerosis detector VS-1000. Before performing the measurement, the patient rested for 15 minutes, and then CAVI was measured in supine position. The device also recorded blood pressure, ECG, phonocardiogram and pulse waves, automatically estimating CAVI in the left and right sides.

The independent variables were 11 laboratory tests made as part of the patients' evaluation. Continuous variables were age (in years), body mass index (BMI), creatinine (in mg/dL), alanine aminotransferase (ALT, in U/mL), aspartate aminotransferase (AST, in U/mL), systolic and diastolic blood pressure (in mmHg), cholesterol (in mg/dL), triglycerides (in mg/dL), calcium (in mg/dL) and phosphorus (in mg/dL). These results were obtained from the clinical history.

STATISTICAL ANALYSIS

Tables were used for descriptive statistics, obtaining absolute and relative frequencies, and standard deviation. Neural networks were used of the multilayer perceptron

TABLE 1.

Characteristics of the database population

Variable	Value	n	Percentage	
LCAVI	≥ 9	204	25,50	
	< 9	587	73,30	
RCAVI	≥ 9	209	26,10	
	< 9	577	72	
Age group	18-48	196	24,50	
	49-54	177	22,10	
	55-66	216	27	
	> 66	212	26,50	
Smoker	No	536	66,90	
	Yes	265	33,10	
Currently drinking alcohol	No	574	71,70	
	Yes	227	28,30	
HTN	Yes	513	64	
	No	288	36	
T2DM	Yes	177	22,10	
	No	624	77,90	
Coronary artery disease	No	646	80,60	
	Yes	155	19,40	
Chronic pulmonary disease*	No	772	96,40	
	Yes	29	3,60	
	Minimum	Maximum	Mean	SD
BMI	15.30	40.20	24.55	3.30
SBP (mmHg)	91	2230	148.48	20.45
DBP (mmHg)	52	118	79.30	10.27
LCAVI	3.19	14.86	8.150	1.41
RCAVI	3.24	16.95	8.22	1.46
ALT (U/mL)	10	599	27.60	30.5
AST (U/mL)	11	444	24.57	21.01
Creatinine (mg/dL)	0.05	6.25	0.85	0.31
Calcium (mg/dL)	7.21	234.47	9.22	7.98
Phosphorus (mg/dL)	1.30	7.16	3.19	0.56
Total cholesterol (mg/dL)	72.97	375.29	171.92	43.22
Triglycerides (mg/dL)	36.28	1908.85	166.26	168.73

LCAVI: left cardio-ankle vascular index; RCAVI: right cardio-ankle vascular index; HTN: hypertension (systolic blood pressure ≥ 140 mmHg); T2DM: type 2 diabetes mellitus; chronic pulmonary disease included asthma, cystic fibrosis, chronic bronchitis, bullous emphysema, atelectasis, chronic obstructive pulmonary disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SD: standard deviation.

TABLE 2.

Summary of the neural network model of the multilayer perceptron type to predict the presence or absence of arterial stiffness according to LCAVI and RCAVI

		LCAVI	RCAVI
	Training	564 (71,60%)	547 (69,90%)
	Testing	224 (28,40%)	236 (30,10%)
Training	Percentage of incorrect prognoses	15.80%	15.90%
	Stopping rule used	1 consecutive step without error decrease	1 consecutive step without error decrease
	Time of training	00:00.1	00:00.1
Testing	Percentage of incorrect prognoses	13.80%	13.60%
	Area under the curve	0,878	0,869

type. The multilayer perceptron is an artificial neural network made up by several layers of interconnected units and neurons, analogous to biological neurons. Every neuron of the hidden and output layers has a nonlinear activation function, allowing the perceptron to model complex relationships.⁸ It can execute classification, prediction and regression tasks, and by backpropagation, it learns from labeled data, adjusting connection weights during training.⁹ The neural network was used to predict the presence or absence of arterial stiffness (CAVI ≥ 9), by evaluations included in the clinical history (age, BMI, creatinine, ALT, AST, SBP, DBP, cholesterol, triglycerides, calcium and phosphorus), which was made at the right (RCAVI) and the left (LCAVI). The way to develop the neural network was (in the SPSS statistics 25 software) the following: analysis $\rightarrow$ neural networks $\rightarrow$ multilayer perceptron, where the dependent variable (CAVI) and the co-variables corresponding to the independent variables were introduced. Hyperparameters were automatically selected by the software.

The results of the perceptron included the area under the curve (AUC), which evaluated the predictive efficacy of the neural network model, and which considers values between 0.6 and 0.7 as a poor model, 0.7 to 0.8 as an acceptable model, 0.8 to 0.9 as a good model, and more than 0.9 as an outstanding model.¹⁰ Also, a classification table was included for correct prognosis, where it was possible to determine the percentage of accurately predicted cases for CAVI values ≥ 9 and < 9 . Also, diagnostic tests were carried out for sensitivity, specificity, positive and negative predictive values between the total CAVI values predicted by the multilayer perceptron and CAVI values obtained from the arteriosclerosis detector.

Data processing and analysis, including the neural network modeling, was carried out with the SPSS statistics 25TM software.

Ethical considerations

The database was taken from the open data repository of the Harvard Dataverse, with open access under Creative Commons Zero (CC0) license, so no authorizations for use

or ethical committees were required as the research was conducted based on a secondary source, as well as because of the confidential aspect of the personal information of the analysis unit (surveyed individuals). The principles of the Declaration of Helsinki were followed.

The database is available at the following link: <https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/C0YY9I>

The database specifications can be found in the following link: <https://doi.org/10.3389%2Ffcom.2021.737161>

RESULTS

For LCAVI prediction, training was made with 564 patients, and testing with 224. For RCAVI, training was with 547 and the test with 236. For LCAVI, the percentages of incorrect prognoses were 15.80% and 13.80% in training and testing, respectively. For RCAVI, the percentage of incorrect prognoses was 15.90% in training and 13.60% in testing (Table 2).

The neural network for the prediction of presence or absence of left arterial stiffness (LCAVI) was made up of 3 layers, with an input layer with 11 units, a hidden layer with 9 units, and an output layer with 2 units, with hidden layer activation function of the hyperbolic tangent type and output layer activation function of the identity type. The area under the curve was 0.878, indicating a good predictive capacity for the model (Figure 1).

The neural network for the prediction of presence or absence of right arterial stiffness (RCAVI) was made up by 3 layers, with one input layer with 11 units, one hidden layer with 7 units, and one output layer with 2 units, with hidden layer activation function of the hyperbolic tangent type and output layer activation function of the identity type. The area under the curve was 0.869, indicating a good predictive capacity for the model (Figure 2).

The percentage of correct prognosis for CAVI < 9 was high in the training and testing of the neural network. The testing had a percentage of correct prognosis for CAVI ≥ 9 of 70.70% and 67.10% for LCAVI and RCAVI, respectively. For CAVI < 9 it was 91.60% for LCAVI and 94.60% for RCAVI (Table 3).

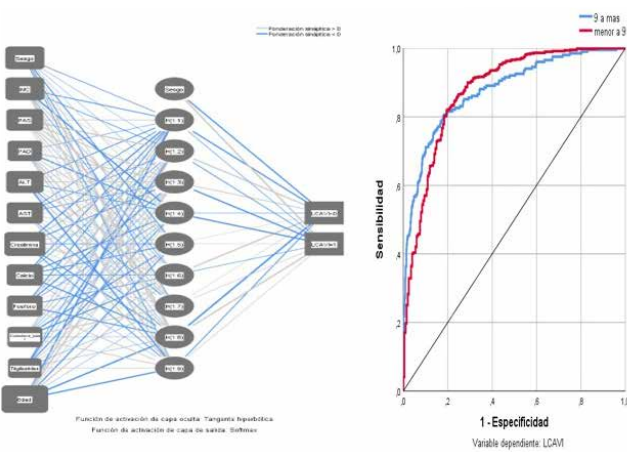


FIGURE 1
Neural network structure of the multilayer perceptron type and area under the curve for primary care tests predictors of presence or absence of arterial stiffness in the left side.

The correspondence between the presence and absence of arterial stiffness of the CAVI testing of the arteriosclerosis detector and the CAVI obtained by multilayer perceptron was moderated for LCAVI ($K=0.579$) and RCAVI ($K=0.587$). There were high specificity values, of 92% and 93% for LCAVI and RCAVI, respectively, and high negative predictive values of 88% for LCAVI and 89% for RCAVI (Table 4).

DISCUSSION

The variables introduced in the multilayer perceptron to predict arterial stiffness by the CAVI index, besides presenting a high correlation with the Cohen's Kappa test, had a high percentage of correct prognoses to detect cases where the CAVI index was less than 9, as well as high levels of specificity and negative predictive value, indicating that this neural network was very reliable to rule out the presence of arterial stiffness. Furthermore, the area under the curve was 0.878 and 0.869 for LCAVI and RCAVI, re-

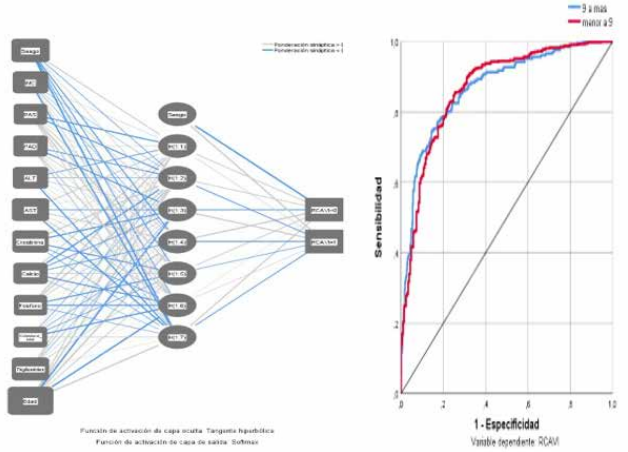


FIGURE 2
Neural network structure of the multilayer perceptron type and area under the curve for primary care tests predictors of the presence or absence of arterial stiffness of the right side.

spectively, showing a good performance of the classification model. These results allow to infer that it is feasible to create analytical models based on historical clinical data, which improve the performance of the multilayer perceptron by training the neural network for the qualitative estimation of arterial stiffness, with abilities similar to the arteriosclerosis detector test in terms of the ability to rule out arterial stiffness.

Recent studies have explored the chance of estimating arterial stiffness. Park and Shin. developed an artificial neural network to predict vascular ageing, using decomposition data of the waveform of photoplethysmogram as variables.¹¹ Li et al. developed a neural network to determine pulse waves based on history of cardiovascular disease and physiological parameters.¹² Hsiu et al. used the multilayer perceptron to predict arterial ageing using signals.¹³ Although previous studies have used information neural networks, this is probably the first study evaluating data cross-

TABLE 3.
Classification table of correct prognoses for the presence or absence of arterial stiffness (CAVI) through primary care tests by multilayer perceptron

		LCAVI			RCAVI		
		Predicted			Predicted		
Single		≥9	<9	Correct percentage	≥9	<9	Correct percentage
Training	≥9	85	58	59.40%	83	53	61.00%
	<9	31	390	92.60%	34	377	91.70%
	Global percentage	20.60%	79.40%	84.20%	21.40%	78.60%	84.10%
Pruebas	≥9	41	17	70.70%	47	23	67.10%
	<9	14	152	91.60%	9	157	94.60%
	Global percentage	24.60%	75.40%	86.20%	23.70%	76.30%	86.40%

TABLE 4.

Sensitivity, specificity, positive and negative predictive value and correspondence between presence or absence of arterial stiffness according to CAVI obtained through primary care by multilayer perceptron

	LCAVI		RCAVI	
	Value	95% CI	Value	95% CI
Se	0,63	0,56-0,69	0,64	0,57-0,70
Sp	0,92	0,90-0,94	0,93	0,90-0,95
PPV	0,74	0,67-0,80	0,75	0,69-0,82
NPV	0,88	0,85-0,90	0,89	0,85-0,90
K	0,579		0,587	

SE: sensitivity; **SP:** specificity; **PPV:** positive predictive value; **NPV:** negative predictive value; **K:** Cohen's Kappa coefficient.

referencing from clinical histories to evaluate the presence or absence of arterial stiffness. The results obtained based on predictor variables are based on the relation they have with arterial stiffness from a pathophysiological view.

Age influences on arterial stiffness due to arterial wall hardening, as they lose elasticity. Constant pulsing, over time, lead to fatigue and fracture of elastin fibers, increasing vascular calcification and endothelial dysfunction.¹⁴ BMI has been related to arterial stiffness as the increase in adipose tissue leads to dysfunction in vascular, endothelial and immune adipocytes with neurohormonal interactions that include insulin, the renin-angiotensin-aldosterone system, the sympathetic system, among others.¹⁵ Creatinine, coming from muscle catabolism, whose serum elevation is related to inappropriate kidney function, and consequently hypertension, has been associated to a higher risk of cerebrovascular disease after 10 years of follow-up in a study.¹⁶

Aminotransferases, which are inflammatory markers, have been associated to arterial stiffness in observational studies, including young adults.^{17,18} Lipids, such as cholesterol and triglycerides, are strongly associated to arterial stiffness, as they are deposit components in the intima layer of the arterial wall.¹⁹ Serum calcium has been directly related to arterial stiffness as part of the atherosclerosis process, with the observation that the risk of cardiovascular disease increases in 10 years, estimated by the Framingham risk score.²⁰ Phosphorus had a low predictive value in the neural network; however, a study has related it to the arterial stiffness linked to the ankle-arm index, and with cardiovascular disease in healthy individuals, and it has been verified that it induces phenotypical transformation of aortic smooth muscle cells in vitro, into cells similar to osteoblasts.²¹

The tests included in the neural network have been frequently used in medical offices of primary care and specialized ones, so due to their high specificity and negative predictive value, as well as due to their high percentages of correct prognoses in CAVI values less than 9 in the clas-

sification table, they could be a means to determine the absence of arterial stiffness in patients attending medical offices, as well as in health campaigns, so using the multilayer perceptron could be a tool for a widespread use to determine the presence or absence of arterial stiffness based on the CAVI obtained by neural networks.

The limitations of this investigation were the origin of the source of information, which came from a secondary database, with the possibility of information and classification biases existing. According to the classification table, this neural network had a low percentage of correct prognoses to detect CAVI ≥ 9 , as well as low sensitivity and positive predictive values of 75%, so it is preferable as a tool to rule out the presence of arterial stiffness, as well as for initial screening, reducing the need for additional tests in unnecessary cases. Likewise, this neural network lacks variables that could have helped to a higher prediction capacity, such as glucose, LDL, HDL, VLDL, waist circumference, among others, so we suggest future investigations that include possible predictors that could not be obtained in this investigation as they were not available in the secondary database.

To conclude, the neural network of the multilayer perceptron type, based on primary care tests, had a high predictive value for LCAVI and RCAVI to rule out the presence of arterial stiffness.

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Position Statement

Joint opinion document on echocardiography and artificial intelligence

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ABSTRACT

Echocardiography is a key tool in cardiac assessment but faces challenges such as subjectivity in interpretation and dependence on image quality. AI, through techniques like machine learning and deep learning, enables the automation of processes such as image acquisition, quantification of parameters (ejection fraction, ventricular volumes), and suspicion of pathologies (hypertrophic cardiomyopathy, cardiac amyloidosis). Additionally, AI facilitates medical education through simulations that provide real-time feedback. Despite its advantages, challenges remain, including the lack of transparency in algorithms ("black box"), the need for external validation, and dependence on image quality. In conclusion, AI will not replace echocardiographers but will become an indispensable tool for optimizing diagnosis and clinical decision-making.

ABBREVIATIONS

AI: artificial intelligence
ML: machine learning
DL: deep learning
EF: ejection fraction

INTRODUCTION

Day by day more data are generated in medical practice: telemetry monitoring, auxiliary imaging tests, clinical histories and electronic prescription. However, the capacity of the brain to interpret so much information is limited, leading to resorting to new technologies increasingly. In such scenario, artificial intelligence (AI) appears as an essential tool that, in spite of appearing to have an advanced development, it is in its first stages in terms of humans and AI interaction.¹

Doppler echocardiogram is a fundamental tool in cardiovascular clinical practice, used for the structural and functional evaluation of the heart in real time. Its main limitations are inter and intraobserver variability, depending on the quality of the image obtained, as well as the time required to perform numerous measurements and calculations (Table 1). In this regard, AI enhances the capacity to process large volumes of information and it is positioning

as a key tool to reduce variability in interpretation and to optimize the diagnostic accuracy of evaluation (Figure 1).

AI has different branches, with the main ones in echocardiography being the following:

- **Machine learning (ML):** it allows computers to learn from large volumes of data, where human experts de-

TABLE 1.

Current challenges. Reproduced and translated under authorization by Dr. Roberto Lang. University of Chicago Medicine.

CHALLENGES IN ECHOCARDIOGRAPHY

- Large volume of patients
- Clinical guidelines
- Staff reduction
- Manual examination
- Interobserver variability
- Time-consuming tasks
- Differential diagnoses



FIGURE 1. Usefulness of AI in health care. Reproduced and translated under authorization by Dr. Roberto Lang, University of Chicago Medicine.

termine the set of characteristics to understand the differences between data input. Through mathematical algorithms, it identifies patterns, it identifies trends and improves its performance over time, facilitating the automation of complex processes; for example, the interpretation of images. Machine learning models are divided into three main categories: supervised learning (it uses sets of labeled data to train algorithms to classify data or predict results with accuracy) (Figure 3); unsupervised

learning (it uses algorithms to analyze and group sets of unlabeled data, discovering hidden patterns or data grouping not requiring human intervention) (Figure 4); semi-supervised learning (it offers a middle ground between supervised and unsupervised learning).

- **Deep learning (DL):** it is a subcategory of ML. It is based on artificial neural networks with multiple layers imitating the operation of the human brain. These networks enable the analysis of data in a hierarchical manner and to extract complex characteristics. Its capacity to detect subtle changes or changes invisible to the human eye in structures has revolutionized diagnostic accuracy in echocardiography.

Use of AI in echocardiography may occur in different aspects:

1. **Automation of image acquisition:** AI helps operators, including those with little experience, to obtain echocardiographic images of high quality. In this regard, algorithms guide, in real time, the position and angle of transducers, ensuring optimal views. This reduces inter-observer variability and it is particularly useful in environments with limited resources or where there are no specialists available.
2. **Acknowledgement and classification of echocardiographic views:** using different algorithms, the different echocardiographic views are identified and classified automatically, speeding up the work flow and minimizing human error.
3. **Automatic quantification:** AI enables the automatic measurement of parameters such as ventricular volumes, ejection fraction and transvalvular flows, among



FIGURE 2. Model of supervised learning. Reproduced and translated under authorization by Dr. Roberto Lang, University of Chicago Medicine.



FIGURE 3. Model of unsupervised learning. Reproduced and translated under authorization by Dr. Roberto Lang, University of Chicago Medicine.

ECOCARDIOGRAMA CONVENCIONAL



FIGURE 4. Current era of echocardiography. Reproduced and translated under authorization by Dr. Roberto Lang. University of Chicago Medicine.

EL FUTURO DE LA ECOCARDIOGRAFÍA?



FIGURE 5. Future of echocardiography. Reproduced and translated under authorization by Dr. Roberto Lang. University of Chicago Medicine.

others. This reduces the time of analysis and decreases inter and intraobserver variability. Thus, it is possible to assess, for instance, the systolic and diastolic function of the left ventricle or valve disease.

4. **Detection and diagnosis of pathologies:** AI allows to identify patterns associated with different heart diseases, such as hypertrophic cardiomyopathy, cardiac amyloidosis and pulmonary hypertension. These systems may alert clinicians about abnormal findings that could be overlooked in conventional evaluations.
5. **Education and training:** simulators have been developed based on AI that allow echocardiographers to be trained to practice with a wide variety of clinical cases. Algorithms offer feedback in real time on the quality of images and measurements made, improving the skills of image acquisition and interpretation.

Starting from the above items, it is possible to understand the mechanisms by which AI enables improving current practice, reaching an accuracy comparable to that of operators expert in the acquisition, interpretation and probability of etiological diagnoses of the different heart diseases (Figure 4). Recent studies suggest that AI also has a great potential to guide and predict results in transcatheter interventions.

Over the opinion article we will analyze how AI optimizes and will continue to optimize the performance of echocardiographic studies, improving diagnostic accuracy, minimizing mistakes and reducing interobserver variability, also called operator dependence, a key factor in this type of evaluation (Figure 5).

USE OF AI IN ECHOCARDIOGRAPHY

Measurement of diameters, volumes, ejection fraction and global longitudinal strain

Left ventricular systolic dysfunction is a frequent alteration originated by different pathologies. Its accurate evaluation is fundamental for the diagnosis, management and prognosis of cardiovascular diseases. Left ventricular ejection fraction (LVEF) is the most widely used parameter to assess systolic function and guide treatment. Echocardiographic evaluation presents limitations, such as visual analysis subjectivity and intra and interobserver variability, mainly influenced by the operator's experience.^{2,3,4}

Current technology allows to automatize echocardiographic measurements, decreasing the variability between experts and beginners. This increases efficacy and optimizes the workflow in echocardiography laboratories.⁵ Multicenter studies have evaluated independent software designed for an automatic detection of the endomyocardial edge, a technique that can be implemented not requiring AI. However, integrating AI-based algorithms has enabled optimizing this process, improving accuracy in the quantification of parameters such as 2D LVEF, left ventricular volumes and global longitudinal strain. These methods are particularly effective when image quality is moderate or good. However, in images with poorer quality, correlation with manual tracings reduces significantly.⁶

Besides the detection of the endomyocardial edge, the AI networks can precisely estimate global longitudinal strain, ventricular volumes, identify echocardiographic views and make accurate measurements in the ventricular mass and wall thickness.⁷ This was proven in the work by Salte et al., whose model based on ML can automatically identify the three traditional apical views and estimate the global longitudinal strain in different heart conditions. This approach reduced the processing time to just 15 seconds, in comparison to the 3 to 5 minutes required with traditional methods.⁸

AI thus offers a powerful tool to analyze echocardiographic images with precision and efficacy, improving diagnostic capacities and reducing the time needed for these tasks.

EVALUATION OF ALTERATIONS OF SEGMENTAL WALL MOTION IN ISCHEMIC HEART DISEASE

Segmental wall motion alterations are early indicators of ischemic heart disease and independent predictors of major adverse cardiovascular events.^{9,10,11} Although echocardiography is a key tool for diagnosis, a traditional evaluation based on visual interpretation presents significant limitations, including interobserver variability and dependency on operators experience.^{12,13} AI may help to overcome these challenges by integrating convolutional neural networks and DL models that would allow evaluating them with accuracy.^{9,10,11}

Several work groups have developed models with good results. Huang et al. developed a model based on convo-

lutional neural networks in three dimensions, analyzing echocardiographic videos, achieving 81.1% sensitivity and 81.6% specificity, proving its capacity to detect segmental motion alterations using both time and space information.⁹ Kusunose's work group proved that a DL model can have a precision comparable to experts in cardiology, with an area under the curve of 0.99 for segmental alterations.¹⁴ Another group developed an AI solution in real time that guides unspecialized operators and facilitates access to quality echocardiograms in different clinical scenarios.¹⁵ Lin et al. evaluated the performance of a model for automatic detection of anomalies in regional wall motion in patients suspected of myocardial infarction: they compared echocardiograms obtained with portable devices at the foot of the bed and standard devices. They developed an automated workflow that integrated the selection of views, ventricular segmentation, detection of wall motion alterations and quantification of cardiac function. The detection of motion anomalies showed an area under the curve of 0.88 and 0.91 in the studies obtained with portable and standard devices, respectively.¹² Other models are EC3D-Net and STGA-MS, which have displayed significant advancements in the automated detection of motion anomalies, exceeding conventional methods, improving diagnostic accuracy and reproducibility in the evaluation of ischemic myocardial dysfunction.^{10,11}

Stress echocardiography allows evaluating the development of segmental contraction anomalies after applying physical or pharmacological stress. There should be quality control in the interpretation of regional wall motion anomalies, as there is a greater interobserver variability than in normal studies.¹³ There are AI models showing a high diagnostic precision (84.4% sensitivity and 92.7% specificity) in an independent validation cohort, improving interobserver consistency and diagnostic confidence, increasing sensitivity by 10% and reaching an area under the ROC curve of 0.93.¹⁶ Although technology does not substitute clinical evaluation, its integration can improve efficiency and accuracy for the diagnosis of myocardial ischemia. Additional studies are required to evaluate its applicability in wider populations, but automation of analysis by AI may optimize diagnostic accuracy and reproducibility in evaluation.¹⁷

EVALUATION OF DIASTOLIC DYSFUNCTION AND HEART FAILURE WITH PRESERVED EF

Left ventricular diastolic dysfunction is a key factor in the pathophysiology of heart failure. However, its echocardiographic evaluation is complex and requires a multiparameter approach. There is no single variable with enough diagnostic precision for its detection, so currently it is advised to use an algorithm that combines multiple measurements.¹⁸

In recent years, different investigations were developed with the goal of evaluating the usefulness of AI in this field. The initial stresses, with its strengths and limitations, have

been previously analyzed in detail.¹⁹ The heterogeneity in AI techniques used and the methodological differences in diagnostic reference (whether the final echocardiographic report, the opinion of experts and the algorithms of clinical guidelines) have prevented obtaining definitive conclusions in these first studies.

However, more recent research has included a higher number of studies and a more homogeneous methodology. In a paper published in 2021, Tromp et al. showed that a DL algorithm was not only able to identify and classify the necessary echocardiographic views to assess ventricular function (systolic and diastolic), but also to perform automated measurements of key variables in the diagnosis of diastolic dysfunction, such as ventricular volumes and Doppler velocities (both of blood flow and of tissue).²⁰ These measurements showed a high coincidence with those performed by expert operators and were validated in multiple patient cohorts.

That same year, Pandey et al. published a study where they evaluated another DL algorithm designed to identify subgroups in high and low risk of diastolic dysfunction.²¹ Their findings were validated in external cohorts, including populations from the TOPCAT (Spironolactone for Heart Failure with Preserved Ejection Fraction) and the RELAX-HF (Effects of Serelaxin in Patients with Acute Heart Failure) trials: it was observed that patients classified as in high risk presented a higher rate of adverse events in follow-up (mortality and hospital admission due to decompensated heart failure), higher neurohormonal activation and less capacity for exercise. Furthermore, the neural network-based model predicted elevated filling pressures with higher accuracy (area under the ROC curve) in comparison with the algorithm of the American Society of Echocardiography from 2016.

In 2023, two large-scale studies were published. Chen et al. analyzed 1304 echocardiographic studies with the goal of developing an AI-based model, capable of identifying echocardiographic views, detecting the presence of diastolic dysfunction and establishing degree of severity. The model validation by comparison with human experts validation showed an excellent consistency.²² On the other hand, Ackerman et al. analyzed more than 5000 patients exclusively using the apical four-chamber view. Its AI model showed an outstanding diagnostic performance, with an area under the curve (AUC) of more than 97% in the derivation cohort and 95% in the validation cohort for the identification of diastolic dysfunction.²³ Subsequently, in 2024, the same group from the Mayo Clinic published a follow-up study with a 3.4-year median, where it was proven that patients identified by the algorithm as patients with a probability of presenting diastolic dysfunction had a higher risk of mortality and hospitalization by heart failure over an observation period. These findings reinforce the prognostic usefulness of AI in risk stratification and early identification of patients with higher clinical vulnerability.²⁴

In spite of advancements, there are still key challenges

that should be solved before a routine implementation of AI in clinical practice. Among them, the following stand out: the need to define which of the multiple AI approaches is the most appropriate for this issue, validation in population groups that have not been studied yet, the management of "indeterminate" results, a lack of validation with more rigorous gold standards (such as invasive measurement of filling pressures and ventricular relaxation time, Tau), the evaluation of reproducibility, and last but not least, the financial impact entailed by the integration of these algorithms in echocardiography devices.

STUDIES FOR HEART VALVE DISEASES

Although echocardiography constitutes the method of choice for the diagnosis of heart valve diseases, there are still underdiagnosed cases, partly due to access limitations and variability in the acquisition and interpretation of images. The introduction of portable ultrasound devices has improved accessibility to this tool, although a proper training is still required to guarantee diagnostic quality studies. In this scenario, AI is transforming the evaluation and management of heart valve diseases, optimizing image acquisition and reducing operator dependence. In comparative studies, the diagnostic accuracy of nurses with no previous experience in echocardiography to assess aortic and mitral valve disease reached values of more than 92% in comparison to expert echocardiographers, showing the potential of these technologies to enhance echocardiography applicability in different clinical fields.²⁵

In a scenario of assessment of valve diseases, AI can provide assistance with:

- 1. Acquisition:** a proper visualization of chambers, valves, jets and Doppler signals requires training, so algorithms were developed to guide image acquisition. When comparing new nurses vs expert echocardiographers, the accuracy of the former to assess aortic or mitral valve diseases was more than 92%.²⁵
- 2. Identification:** just as with left ventricular images, AI not just allows reading data obtained from raw valve images, but also automatic measurements. This will be translated into shorter times in the management of valve diseases due a reduction in time to establish a diagnostic probability, thus decreasing interobserver variability to determine severity (currently, approximately 61% for mitral regurgitation). There are algorithms that can detect mitral and tricuspid valves with 98% and 90% accuracy, respectively; others are capable of identifying continuous-wave Doppler signal with 98% accuracy.^{26,27} In a study with 256 patients, AI had an excellent diagnostic capacity compared with measurements made by humans in terms of maximum velocity of the aortic valve ($r=0.97$), mean gradient ($r=0.94$), aortic valve area ($r=0.88$), systolic volume ($r=0.79$), velocity time integral of the left ventricular outflow tract ($r=0.89$), aortic velocity time integral ($r=0.96$) and left ventricular outflow tract diameter ($r=0.76$).^{27,28}

3. **Segmentation:** it refers to identifying a structure in an image, allowing automatizing the evaluation of diameters and annulus, valve or Doppler function. There are algorithms trained with mitral valve images, which obtained a variable accuracy, from modest to good (0.48-0.79) and an error rate close to 6% for perimeter measurement and 12% for the valve area.²⁹ In regard to Doppler, in a study, an algorithm was trained with 1132 patients with mitral regurgitation from mild to severe, and it was validated with 295 patients, achieving an accuracy close to 90% for each category of severity; another publication reported a correlation of 0.9 between an algorithm and an expert for the measurement of velocities, gradient and velocity time integral of Doppler signals.³⁰
4. **Identification of severity:** it is based on identifying data exceeding human perception. In a cohort of 139 patients, it was possible to identify the severity of mitral regurgitation with an accuracy greater to 99%; another study could identify rheumatic diseases with 77% accuracy.^{31,32} These algorithms also allow identifying mitral prosthetic valves with an area under the curve of 98%.

It not only allows to improve a current evaluation, but also add clinical, genetic and laboratory information, and data from auxiliary tests, achieving decision-making in a much shorter time.

There are models using ML developed for aortic valve disease: a study from the Cleveland Clinic identified phenotypes of aortic aneurysm in 656 patients with bicuspid valve, allowing associating them with predominant valve disease.^{33,34,35,36} Another 3 studies were designed to identify groups in high risk within the range of aortic stenosis:

- Casaclang-Verzosa et al. described the progression of mild to severe stenosis in 346 patients using 79 clinical and echocardiographic variables. They showed 2 subgroups of moderate aortic stenosis (one male and with less EF; another with lower velocities, but greater left ventricular mass and atrial volumes) and their response after valve replacement.
- Sengupta et al. analyzed a cohort of 1052 patients with mild or moderate aortic stenosis and a group with severe low-flow low-gradient aortic stenosis. They found a group in higher risk with higher calcium score, elevated biomarkers, gadolinium uptake, incidence of valve replacement and pre- and post-surgical death. The validation model showed better discrimination and reclassification than current methods.
- Finally, Kwak et al. developed a model based on 398 patients with moderate to severe aortic stenosis, incorporating 11 clinical variables, of laboratory and echocardiographic, with the aim of identifying patients that may not benefit from an intervention. Through data analysis, they identified three differentiated subgroups, among which one presented high cardiovascular mortality, while another showed high total mortality. These findings suggest that the last subgroup may require an alternative therapeutic approach, highlighting the po-

tential of AI in risk stratification and personalization of management strategies.

USEFULNESS IN TRANSCATHETER INTERVENTIONS IN STRUCTURAL HEART DISEASE

Transcatheter interventions in structural heart disease have exponentially increased due to population ageing and technological advancements, such as transcatheter aortic valve implant, left atrial appendage closure, atrial septal defect closure and procedures on atrioventricular valves. These interventions have turned into the first-line treatment for multiple pathologies, and AI has emerged as a key tool in the optimization of these procedures, improving selection of patients, preoperative planning, execution, post-implant monitoring and follow-up, contributing to optimizing clinical outcomes.^{37,38}

In this scenario, AI, by supervised learning, predicts results and facilitates early diagnoses by reducing the time of image processing and inter and intraobserver variability through the analysis of large data volumes. By means of unsupervised learning, it identifies hidden patterns, classifies patients according to specific phenotypes and risks, and determines different outcomes and therapeutic responses.³⁷

The selection of patients for heart valve interventions is based on symptoms and echocardiographic findings, while the indication of left atrial appendage closure is based on the risk of stroke or bleeding.³⁷ Through ML (with a technique called cluster analysis), hidden patterns can be discovered within data and patients can be classified into phenotypes with different clinical outcomes. In aortic stenosis, for instance, this technique helps to identify patients that may benefit from transcatheter treatment.^{36,37,38} Furthermore, in atrial fibrillation, it allows to estimate the risk of stroke and evaluate specific anatomical variabilities of the left atrial appendage to facilitate the indication of percutaneous closure.

On the other hand, supervised ML is an alternative to conventional statistics to establish a prognostic probability and thus generate stronger models.³⁹ Nevertheless, AI algorithms are not free from biases, as they depend on data quality, relevance and integrity for their training.

In computed tomography (CT), DL is used to automatically segment and quantify aortic valve calcification; a key datum for diagnosis and mortality prediction.⁴⁰ In the cases of severe aortic stenosis with low flow and low gradient, where echocardiographic results can be misleading, calcium score by echocardiography based on AI has proven to be useful with clinical decision-making.

An algorithm based on more than 530,000 echocardiograms was developed, which improves the detection of severe aortic stenosis, exceeding the limitations of conventional measurements of the left ventricular outflow tract.⁴¹ However, the complexity of DL algorithms requires a high capacity for computational processing, including graphic processing and computing units in the cloud.⁴²

ML has also revolutionized the planning of transcath-

eter interventions by the generation of computational 3D models, which enable selecting devices in a more precise manner and predict performance.⁴³ This has been validated in procedures like transcatheter aortic valve implant, Mitra-Clip, left atrial appendage (LAA) closure and transcatheter mitral valve replacement (TMVR). Particularly, a CT-based model has proved to accurately predict the deformation and apposition of the LAA closure device, improving the procedure's planning.⁴⁴

During intervention, use of AI facilitates the automatic identification of anatomical structures by the fusion of fluoroscopic images with echocardiography or CT. This integration has been used in transcatheter aortic valve implant (TAVI) and LAA closure, reducing the time of the procedure and exposition to radiation.⁴⁵ Furthermore, AI-assisted planning with augmented reality enables the generation of 3D holograms in real time, optimizing visualization and the positioning of the device.⁴⁶

In the follow-up in the short term, supervised ML has proven to predict in-hospital mortality with greater accuracy after TAVI and TMVR in comparison with traditional models.⁴⁷ Likewise, AI has exceeded the conventional score systems (EuroSCORE, STS) in the prediction of survival within 30 days after TAVI.⁴⁸ An efficient model was described, to predict the need for pacemaker implant after TAVI, a frequent complication, by the integration of clinical, electrocardiographic and echocardiographic data.⁴⁹

AI-based automated quantification has also significantly reduced the time of analysis per patient.⁵⁰ As to the prediction of hospital stay after TAVI, an ML model has identified novel predictors, as the duration of the procedure, the need for physiotherapy and results according to the day of the week when the intervention is made.

IDENTIFICATION OF MYOCARDIAL DISEASES

The classification and diagnosis of myocardial diseases in early stages, when patients are still asymptomatic, represent a critical area where computational science may contribute great benefits. In clinical practice, these patients may remain undiagnosed for long periods, and only receive treatment when the disease has progressed to advanced stages. This has implications not just in the prognosis and quality of life of patients, but also in the reduction of future hospital costs.

Left ventricular hypertrophy is a frequent finding in clinical practice and is associated to adverse cardiovascular events such as arrhythmias, myocardial ischemia, heart failure and sudden cardiac death.^{51,52} A study made by Zhang et al. proved that convolutional neural networks can identify echocardiographic windows and provide specific measures, such as wall thickness and left ventricular mass.⁷

From the point of view of etiological diagnosis, echocardiography is often not enough, and more complex studies are required for an accurate diagnosis. Between the main etiologies that present as ventricular hypertrophy, we find hypertension, hypertrophic cardiomyopathy, aortic steno-

sis, chronic kidney disease and cardiac amyloidosis. Other less frequent etiologies include myocarditis, sarcoidosis and storage diseases, such as Fabry or Danon, besides mitochondrial cardiomyopathies.

Myocardial texture is difficult to evaluate and quantify by simple observation from a physician.⁵³ In this regard, AI has shown its capacity to differentiate myocardial hypertrophy secondary to hypertension from hypertrophic cardiomyopathy and uremic cardiomyopathy. It has been observed that hypertrophic cardiomyopathy presents a more homogeneous pattern of numerical values distribution in algorithmic analysis, which could be useful for etiological differentiation.⁵⁴

In traditional echocardiographic in the evaluation of cardiac amyloidosis, although multiple suggestive findings can be identified, none has proven to be specific or sensitive enough to establish a definitive diagnosis. Besides, certain echocardiographic characteristics require advanced analysis with specialized software, which entails more processing time and it is usually applied in cases with an already confirmed diagnosis.⁵⁵

A study in academic centers used a model based on echocardiographic videos with four-chamber views, achieving a high diagnostic accuracy (C-statistic of 0.96), superior to that of experts in detection of amyloidosis. They emphasized that the model had a better performance in the detection of cardiac amyloidosis by transthyretin than by light chains.⁵⁶ Another DL model could identify subtle changes in ventricular geometry, allowing the differentiation of cardiac amyloidosis from ventricular hypertrophy.⁵⁷ Even the FDA (Food and Drug Administration) approved the EchoGo® Amyloidosis AI software for the detection of cardiac amyloidosis by echocardiography. This system has shown a high diagnostic performance, with an area under the ROC curve of up to 0.93 and a negative predictive value of more than 85%. Its sensitivity is consistent between the different types of amyloidosis. Besides, it exceeded conventional analysis in patients older than 60 years with heart failure and increase in left ventricular wall thickness, with an area under the ROC curve of 0.93 in comparison to 0.73.

In patients with heart failure and preserved EF, with predominance of right congestion symptoms, the differential diagnosis includes restrictive cardiomyopathy and constrictive pericarditis. In this scenario, echocardiography is considered the first-line study for the diagnosis of constrictive pericarditis.^{58,59} However, its accuracy depends on the quality of the study and the experience of the operator, and additional studies may be required, like CT, MRI or hemodynamic evaluation.^{60,61,62}

In 2016, Sengupta et al. carried out a pilot study using speckle-tracking and AI by a classifier of associative memory to differentiate constrictive pericarditis of restrictive cardiomyopathy, obtaining an area under the curve of 0.89, above the conventional echocardiographic variables.⁶³ A more recent study used a DL model to differentiate constrictive pericarditis from restrictive cardiomyopathy sec-

ondary to amyloidosis, reaching an area under the curve of 0.97 with four-chamber view and external validation with area under the curve of 0.84.⁶⁴

EDUCATION IN ECHOCARDIOGRAPHY

AI has become an invaluable tool to improve the acquisition and interpretation skills for echocardiographic images; particularly in training echocardiographers. AI-based simulators allow students to practice with a wide variety of clinical cases; from common scenarios up to complex and rare situations, which enriches their experience and training for real practice.

One of the most significant advancements in this field is the capacity of AI to offer feedback in real time. Algorithms may evaluate the quality of images acquired by the students, guiding them in the correct position and angulation of the transducer to obtain optimal views. Moreover, these systems can offer suggestions to improve the acquisition technique and point out common mistakes, accelerating the learning process and reducing dependency on the constant supervision by an instructor. This capacity is particularly useful in environments with limited resources, where access to experts in echocardiography can be scarce.

Another outstanding aspect is use of AI for image interpretation. DL models can analyze echocardiographic studies and compare the findings of students with those of experts, offering an objective evaluation of their performance. This not only improves the diagnostic accuracy of students, but also lets them get familiar with quality standards and best practices in the interpretation of studies. Moreover, AI can generate automated reports that work as study and reference material, facilitating reviews and continuous learning.

In brief, AI is revolutionizing education in echocardiography by providing interactive, personalized and accessible tools that improve the training of health care professionals. As these technologies continue evolving, they are expected to play an even more important role in preparing highly trained echocardiographers and in the reduction of variability for image acquisition and interpretation.

LIMITATIONS

The clinical application of AI in echocardiography faces multiple challenges that have to be approached before a widespread adoption. One of the main ones is the “black box” problem in algorithms; i.e. the lack of transparency in the internal operation of complex models, particularly those based on DL, which makes it difficult to interpret results and understand the criteria used for models to establish a diagnostic probability. This, evidently, can generate mistrust for a clinical use.

The quality of echocardiographic images is still a determinant factor in the performance of all these algorithms. Thus, image acquisition variability, influenced both by the experience of operators and by the technical features of the device, can affect model accuracy. This highlights the need for strategies to optimize data quality.

Another clinical aspect is the lack of standardization and external validation of many models, which raises questions about its applicability in clinical practice and in different populations of patients. Most studies that have evaluated AI in cardiology have been retrospective and require validation in multicenter studies in a large scale to demonstrate its usefulness in real clinical scenarios.

Finally, some models, mainly of ML, depend on data previously labeled by doctors, which may introduce inherent biases and systematic errors in the interpretation of findings. This dependency on human classification underscores the need to develop strategies to minimize the impact of these biases on algorithm training.

CONCLUSIONS

AI is revolutionizing the field of echocardiography, offering tools that improve diagnostic accuracy, reduce interobserver variability and optimize workflow in cardiac imaging laboratories. From the automatic quantification of parameters such as ejection fraction and global longitudinal strain, to the evaluation of heart valve diseases and the detection of segmental wall motion alterations in ischemic heart disease, AI has shown a significant potential to transform clinical practice. However, significant challenges persist, like the need for external validation of algorithms, the interpretability of AI models and the dependency on image quality.

The future of AI in echocardiography will depend on its effective integration in the clinical environment, combining automation with human supervision to guarantee accurate and reliable interpretations. As technical and methodological challenges are overcome, AI may transform echocardiography into an even more powerful tool, optimizing cardiovascular diagnosis and contributing to a more personalized and efficient medicine.

In conclusion, AI will not replace echocardiographers, but will turn into an indispensable ally for more accurate and personalized clinical decision-making.

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In Memoriam

Dr. Roberto Lang

(1951- 2025)

In this issue of the Revista of the Argentine Federation of Cardiology we published what will surely be the last article by Dr. Roberto Lang, at least in Argentine cardiology literature. The scientific production of Dr. Lang is unlimited. Right now, several of his papers are being published in several scientific journals all over the world. Surely this will be his last paper, because today, June 11 2025, Roberto flew as high as his dreams, leaving hundreds of the friends and disciples he made during his extensive and prolific medical career, devoted to the development of ultrasound in cardiology, with unmatched creativity and drive: heartbreaking.

Artificial intelligence in echocardiography was the last field where he delved with the strength of his ideas and his usual academic quality. From his position as Director of the Noninvasive Cardiac Imaging Laboratory and the Cardiac Imaging Center of the University of Chicago Medical Center; Professor of Radiology and Medicine in the Section of Cardiology, Carlson Professor of Medicine, he made his dreams rise through initiatives that revolutionized the practice of cardiological diagnosis. He published more than 500 scientific papers, which jointly with his recommendations and clinical practice guidelines express the result of his tireless work.

Roberto was not just a distinguished cardiologist, mentor and educator of hundreds of cardiologists throughout the world, but also a great human being. Sensitive, honest, loyal, generous and a great friend to his friends. I can attest to his sympathy, loyalty and high sense of friendship, as I could enjoy them for over 25 years. From the start, I shared with him his passion for innovation, which randomly led us to a focus group on development of contrast in ultrasound, in Newport Beach, a long



Professor Roberto Lang
MD FASE FACC FESC

time ago; as well as the emergence and unstoppable progress of new echocardiographic techniques. His generosity opened doors, not just for me but for many other Argentinians, to participate in the birth of 3D echocardiography, automatism applied to the quantification of the different cardiac functions, the determination of normal values in different countries and different races, the definition of how to use all tools for cardiological diagnosis.

He opened the doors of his laboratory, and those of his heart as well, to many young and not so young colleagues who wanted to learn from his experience and ideas, with unlimited generosity.

He tried to "give back" to his beloved Argentina what he thought was needed to realize its potential. He travelled thousands of kilometers to be in person, not just in the most outstanding conferences, but also in academic courses and careers, where young Argentinians and South Americans were training with great effort, not seeking material compensations. The Master's Degree on Ultrasound in Cardiology from the Universidad Nacional de la Plata is a testament of it since its inception.

Roberto is gone, but his legacy remains unforgettable in the hundreds of disciples trained around the world. His eternal journey started today and will be as boundless as his dreams and as high as his brilliant ideas and his sound work.

Roberto is gone, but his legacy is infinite! It will last in each of his friends and disciples, in his patients and in many others that will benefit from these achievements in the field of medicine. Thank you very much, dear friend!

Dr. Ricardo Ronderos

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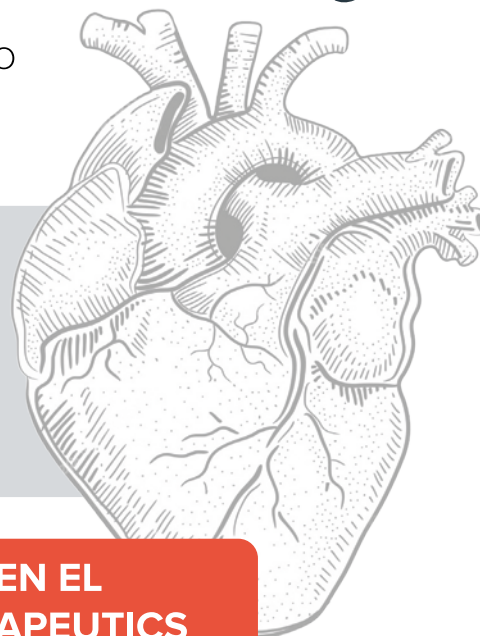
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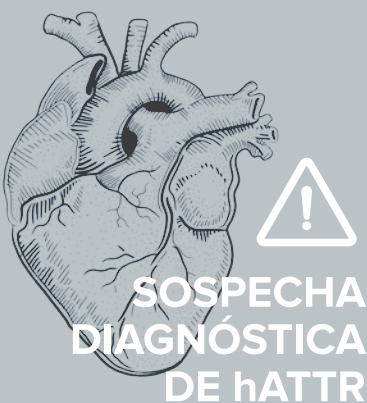
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