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Summary

EDITORIAL

Public Health at the Center of Debate

La salud pública en el centro del debate

ANDRES ROSENDE

Cardiovascular diseases continue to be the leading cause of mortality worldwide and Argentina is no exception. (1) Despite significant progress in its reduction observed in the last decades, multiple factors have slowed the trend during recent years. (2) In this context, the COVID-19 pandemic broke out at the beginning of 2020, generating great uncertainty about the best policies to apply in order to prevent the collapse of the health system, with the ensuing increase in the number of deaths caused by the virus. Effectively, we have witnessed public discussions and the most diverse opinions, with greater or lesser degree of support. Infectologists, epidemiologists and intensive care specialists strolled along the television sets giving lectures, but also sociologists, anthropologists, political scientists, civil servants and politicians from all sectors exchanged their points of view, often not exempt from interests different from the welfare of the general population. As if this was not enough, journalists turned into "experts in pandemic management", "opinionologists" of all colors, colorful characters of the television prime time drinking allegedly unfailing beverages against the virus, and many other situations marked a time dominated by confusion and fear.

The reader of the study by Charask et al. (3) could jump to conclusions and state that the policies were wrong, impacting on the excess of all-cause mortality recorded by the vital statistics of the National Ministry of Health. (4) However, we will never know the counterfactual scenario of not having implemented them or having done so in a different direction, or with different intensity or duration. Would the same number of people have died? Or maybe less? Or perhaps more? Nobody would dare to predict it. Nevertheless, the association between the COVID-19 outbreak and the 15% increase in mortality due to myocardial infarction found by Charask et al., leaves no room for doubt.

Charask et al. reveal the sudden increase in specific mortality rate for myocardial infarction during the two years of Social, Preventive and Mandatory Isolation (SPMI) and its particular impact on women and subjects <60 years. At this point, other questions should be posed. Are these two circumstances related? Can we infer causality? Could the pandemic effect on infarct mortality have been avoided or at least mitigated?

Analyzing the causal mechanisms of the relationship between SPMI and the increase in mortality for myocardial infarction opens the gates to a complex and multidimensional scenario. What does this increase in infarct mortality really explain? Could it have been the massification of the COVID infection or the sanitary measures adopted in the SPMI context? Regardless the first option continues to be subject of investigation and debate, (5,6) we have all witnessed, in greater or lesser degree, the collateral damage generated by SPMI on the health system. Delays in consultation for fear of the virus, restrictions in displacement imposed by the authorities, an emergency system dedicated almost exclusively to the care of COVID-19 cases, cancellation of programmed diagnostic or therapeutic procedures, empty intensive care units for weeks, or even months, awaiting COVID-19 patients whose arrival was long delayed, and a marked alteration in ambulatory health services in charge of prevention through the control of risk factors, were among other causes faced.

The COVID-19 pandemic broke out in the midst of a sanitary context with huge structural challenges in multiple areas, and especially in that related to cardiovascular diseases and their risk factors. According to the last 2018 National Risk Factor Survey, carried out in subjects over 18 years of age, in Argentina there is a prevalence of 22.2% smoking, 66.1% overweight or obesity and 10.9% diabetes. In addition, an incidence

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of 39.5% hypercholesterolemia and 46.6% hypertension, with 32% underdiagnosis and a troubling lack of control in 4 out of 10 diagnosed patients has been encountered. (7) If we specifically approach ST-segment elevation myocardial infarction, we do not find detailed official statistics, though diverse independent studies performed in the country show an alarming reality. Even though early reperfusion therapy has the greatest impact on the reduction of morbidity and mortality in this context, , 4 out of 10 patients do not access it and among those who do through treatment with primary angioplasty or fibrinolytics, more than half are outside the recommended time window . (8-10) This shows not only the urgency to improve networks of care for opportune diagnosis and treatment, but also of strengthening public health policies aimed at controlling their risk factors and thus prevent or delay their emergence. (10,11)

This complex scenario discloses the enormous challenges of the Argentine health system in terms of prevention, diagnosis and opportune treatment of cardiovascular diseases and their risk factors. Thus, public health is placed at the center of the debate, highlighting the importance of health plan policies, which when delineating their objectives contemplate the cost of opportunity, in order to make them more efficient. It is necessary to learn from successes and mistakes made during this pandemic that surprised humanity, and whose real impact we are still understanding, to improve our position at the time of facing a similar health crisis that might occur in the future. (12,13) This implies working in extending population intervention policies to stop the silent pandemic of overweight and obesity, continue to reduce tobacco and alcohol consumption and salt intake, eradicate trans fats and promote environments favoring physical activity. At the same time, it is essential to strengthen primary healthcare, providing the resources and instruments that improve the diagnosis, treatment and control of risk factors such as hypertension, diabetes and hypercholesterolemia. (14) Finally, to work in the development and reinforcement of networks for the care of myocardial infarction with the aim of increasing the timely access to reperfusion therapies, without health coverage limitations, and ensuring an efficient secondary prevention. (11)

All the countries in the world have suffered the consequences of the COVID-19 pandemic and also the collateral damages of the measures adopted to face it. (15) Undeniably, some countries may have done it better than others, and the place Argentina will occupy in this sad ranking is still to be seen. At a time where public services and their management are at the center of debate in the light of a new government, it only rests to defend successful health policies and work to improve those with poor performance. It is imperative to support efficient universal health coverage, supported on data-based sanitary planning and guided by epidemiological priorities in the widest sense, with the purpose of providing more and better healthcare for all the population. The study by Charask et al. is undoubtedly an essential element in this debate, and disregarding its results, or not learn from them, would be a highly costly error for the health of the Argentine population.

Conflicts of interest

None declared.

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

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EDITORIAL

2023 Dr. Pedro Cossio Foundation Award

Premio Fundación Dr. Pedro Cossio 2023

JORGE LERMAN[MTSAC]

The 49th Argentine Congress of Cardiology was held with its usual success from October 19 to 21, 2023. The Scientific Committee of the Congress selected 4 works to contend for the 2023 Dr. Pedro Cossio Foundation Award. The winning work was:

Initial Diuretic Efficiency as Predictor of Diuretic Resistance and Clinical Outcome in Acute Decompensated Heart Failure.

Cristhian Scatularo, Luciano Battioni, Analia Guazzone, Guillermina Esperón, L. Corsico, Pablo Alcantara Costas, Hugo Grancelli

Acute decompensated heart failure (ADHF) is one of the most common causes of hospital admissions in the coronary care unit. It is usually defined as the new onset or worsening of symptoms or signs of congestion or systemic hypoperfusion. Early diagnosis and timely treatment are needed to prevent the high mortality associated with delayed treatment of this serious clinical condition. Loop diuretics are the cornerstone for achieving adequate decongestion and restoring clinical stability. The guidelines of the European Society of Cardiology (1) and the Consensus Statement on Heart Failure of the SAC (2) recommend the use of these drugs (class I), based on level of evidence C (experts opinion). This level of evidence is due to the limited evidence on mortality reduction with diuretics. The recently published ADVOR study suggests the benefit of adding acetazolamide, a carbonic anhydrase inhibitor, to loop diuretic therapy. (3) Other additional measures include oxygen therapy, vasodilators, pressor agents, inotropic drugs, or mechanical support. The severity of ADHF is related, among other parameters, to the intensity of diuretic treatment required to compensate for it and is worse when the dose of diuretic required is higher due to diuretic resistance (DR). (4) The efficacy of diuretic treatment can be assessed by measuring the urinary output or weight loss achieved. However, these individual factors may be inadequate surrogates of therapeutic effectiveness due to the presence of associated confounding factors. For this reason, the concept of diuretic efficiency (DE) was introduced. Diuretic efficiency is calculated by dividing the urinary volume or weight loss achieved (numerator) by the dose of intravenous diuretics administered (denominator). This marker has proved to be more consistent than its individual components and could provide better prognostic information. (5) The present study is a prospective, multicenter, and open analysis including 157 patients (56% men) with a median age of 74 years. The aim of the study was to assess whether the initial DE is correlated with and can predict patients' outcomes. The authors used the following definitions: 1) DR: requirement of furosemide ≥240 mg/day during the first 72 h of hospitalization; 2) DE: ratio of net fluid balance and cumulative amount of intravenous furosemide within the first 24 h. The exclusion criteria were creatinine ≥ 2.5 mg % or being on dialysis at admission, systolic blood pressure < 90 mm Hg, cardiogenic or septic shock, initial requirement of pressor or inotropic agents, mechanical ventilation (MV) or pregnancy. After bladder evacuation, an initial intravenous bolus of 40 mg of furosemide was given to patients within two hours of admission to the emergency department. In the first 24 hours after admission, all patients received intravenous boluses of 20 mg of furosemide every 8 hours. After the first day of hospitalization, the daily furosemide dose was adjusted (increased or decreased) every 24 hours, with evaluation of the extent of clinical congestion or daily diuresis (fluid balance threshold of -2000 mL/day). According to the protocol, up-titration of furosemide was performed by increasing the intravenous infusion. Down-titration of furosemide in the protocol allowed for shifting from intravenous to oral administration upon achieving an adequate response. The diuretic protocol was discontinued 72 h after enrollment or earlier in case of requirement of doses of furosemide ≥240 mg/day, tubular diuretic blockade (TDB), hypertonic saline (HS), renal replacement therapy (RRT),

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President of the Jury

inotropic drugs, pressor agents, or MV. The composite end point (CEP) was in-hospital mortality, readmissions for ADHF at 60 days or cardiovascular mortality at 60 days. Diabetes was present in 36%, atrial fibrillation in 43% and chronic kidney disease (CKD) in 20%. The etiologies were ischemic heart disease in 27%, valvular heart disease in 22%, and hypertension in 15%. Left ventricular ejection fraction (LVEF) was reduced in 43%, mildly reduced in 12% and preserved in 45%. The initial DE was -15 mL/mg (IQR -20 to -11) and there were no differences in DE across the entire spectrum of LVEF or between the different clinical types of ADHF. Diuretic resistance occurred in 13%. Worse DE value predicted the development of DR (OR 1.072; 95 % CI 1.015-1.130; p = 0.013). Patients with DE above -11 mL/mg were highly unlikely to develop DR [area under curve (AUC) 0.73; negative predictive value (NPV) 92.5% and positive predictive value (PPV) 30%]. Worsening renal function occurred in 22% of patients. Worse DE value was associated with a trend towards higher use of TDB (p = 0.07) and RRT (p = 0.06). Worse DE value was associated with the CEP (p = 0.025), mainly due to higher in-hospital cardiovascular mortality (OR 1.2; 95% CI 1.06-1.36; p = 0.0013), persistent congestion at 48 hours (p = 0.007), higher cumulative dose of furosemide at 72 h (p = 0.001) and worsening ADHF during hospitalization (p = 0.004). Cardiovascular mortality during hospitalization and at 60 days was 5.7 % and 6 %, respectively, and readmission rate due to ADHF at 60 days was 12%. In summary, the formula described above provides a simple, effective, and pragmatic method for measuring DE. This method can help identify cases of ADHF with a worse prognosis, allowing for more intensive diuretic treatment or other pharmacological or non-pharmacological therapeutic measures. This study contributes to the limited literature available on the vital benefits of diuretics in ADHF. Knowledge of the diagnostic tool described above would likely increase with greater and longer experiences.

The other candidates for the Cossio Award were:

Temporal Variability in Lp(a): Should we Repeat Testing?

María G. Matta, Laura Schreier, Augusto Lavalle-Cobo, Sebastián Garcia-Zamora, Agustina Ferraresi, Ángeles Madsen, Sofia Bellini, Guadalupe Ramos, Paula Roubicek, Pablo Corral.

Lipoprotein (a) or Lp(a), first described by the Norwegian Kar Berg in 1963, (6) consists of one molecule of cholesterol-rich LDL particle attached to one molecule of apolipoprotein(a) via a disulfide bond. Apolipoprotein(a) possesses structural homology with plasminogen, causing competitive inhibition of fibrinolysis. Thus, Lp(a) has prothrombotic and antifibrinolytic effects. In addition, Lp(a) can easily cross the endothelium and contribute to the development and growth of atherosclerotic plaques. It also increases the expression of pro-inflammatory cytokines and interleukines. This triple mechanism (proatherogenic, prothrombotic and proinflammatory) makes Lp(a) a novel risk factor for atherosclerotic cardiovascular disease that it is not considered in the different risk scores known. Elevated Lp(a) levels are strong independent predictors of myocardial infarction, aortic stenosis, heart failure, stroke, peripheral artery disease and cardiovascular mortality. (7) Its presence is genetically determined , with a strong familial tendency, and about 40 isoforms and several polymorphisms can be expressed. Additionally, there is a clear continuous association between Lp(a) concentration and the severity of each affection. (8) This association may vary according to ethnicity, diet, thyroid function, menopause, pregnancy, renal failure or inflammation. (8) In 80% of individuals, plasma Lp(a) levels are less than 70 nmol/L, and cardiovascular risk increases gradually beyond this limit. Plasma levels increase with statins while PSCK9 inhibitors decrease them. Currently, there is no treatment available to reduce Lp(a), but there are several ongoing phase I-II studies with antisense oligonucleotides and small mRNA. The European Atherosclerosis Society Consensus Statement on Lp(a) (8) and the SAC Consensus Statement on Cardiovascular Prevention (9) recommend universal measurement of plasma Lp(a) "at least once in a lifetime" (class I, level of evidence C). The aim of the authors of the work commented was to analyze the possible variability of Lp(a) over time in clinically stable patients. The secondary objective was to evaluate the causes of this variability. They conducted a prospective analysis of 740 Caucasian patients attending a lipid clinic from February 2018 to December 2022. For this investigation, they included 61 of these patients with at least two Lp(a) determinations taken within a minimum interval of 4 months. This interval was chosen empirically due to lack of evidence regarding measurement intervals. Normal values were defined as those below 70 nmol/L, borderline values as those between 70 and 125 nmol/L, and elevated values as those above 125 nmol/L. Mean age was 59.6 ± 13.0 years and 62.3% were men. Lp(a) variability was estimated by calculating the percentage change between the reference value and the measured value with the largest discrepancy. Forty-three percent of participants had Lp(a) > 70 nmol/L, less than 20% had a history of cardiovascular disease, and most were treated with statins. The study analyzed 171 determinations from 61 participants, ranging from a minimum of 4 months to a maximum of 48 months. Thirty-four participants had 2 determinations, thirteen had 3, eight had 4, five had 5 and one had up to 7. Twenty-one of the 61 participants (34.4 %) showed a variability ≥ 25 %. Five patients (38.46 %) were in the Lp(a) category < 70 nmol/L, 6 (54.54 %) were in the borderline Lp(a) range and 10 (27.02 %) were in the high Lp(a) category. Two patients in the lowest

category moved to a higher category, two in the borderline category moved to the highest category and one moved to the lowest category, and two of the 10 patients in the highest category moved to the borderline category. Thus, 7 (11.45%) participants moved to another category. One possible cause of these variations could be an increase in Lp(a) due to the initiation of statin treatment, discontinuation of PCSK9 inhibitors, or transition to menopause. The possibility of variations in LP(a) concentrations over time was suggested in a sub-study of the ARIC (Atherosclerosis Risk In Communities) program which demonstrated that patients with borderline high Lp(a) concentrations may have changes ≥ 20 nmol/dL over time, particularly if they are black, women, or have diabetes or hypertension. (10) Recently, Gaba et al. reported the results of the OCEAN(a)-DOSE study. In this phase 2, randomized trial of the Lp(a)-lowering small interfering RNA (siRNA) therapy olpasiran in 281 patients with atherosclerotic cardiovascular disease and Lp(a) >150 nmol/L, 51% of patients in the placebo arm experienced an upward or downward ≥ 50 nmol/dL change on repeated sessions. (11) These observations challenge the recommendations of guidelines and consensus statements, (8,9) in line with the paper being analyzed. Future studies should confirm or rule out this hypothesis. As a final comment, the recommendation to perform the measurement at least once is unclear. Only once? How many times? The answer is probably to repeat testing in borderline cases to determine whether there is a shift to the higher or lower category. It is yet to be determined whether these variations have any impact on the subsequent incidence of clinical events.

Novel Variables in Cardiopulmonary Exercise Testing with Additional Prognostic Value in Different Subtypes of Pulmonary Arterial Hypertension

Raul Ignacio Pasetto, Jorge Kriskovich, Celeste Lopez, María Lorena Coronel, Jorge Franchella

The use cardiopulmonary exercise stress test (CPET) provides some typical findings in patients with pulmonary hypertension (PH): low end-tidal carbon dioxide partial pressure ($ETPCO^2$), high ventilatory equivalent for carbon dioxide (VE/VCO^2), low oxygen pulse (VO^2/HR), and low peak oxygen consumption (peak VO^2). (12) A recent study conducted in our country, selected to receive the SAC Cossio Award in 2022, suggests that CPET could be used to reclassify patients with PH who are considered to be at low risk. In other words, to establish "high risk of low risk". (13) The aim of the study here analyzed was to establish the prognostic ability and cut-off points for new variables such as circulatory power (CP), (14) defined as the product of peak VO^2 by the peak systolic blood pressure reached during exercise, and ventilatory power (VP), calculated as the peak systolic blood pressure reached at peak exercise divided by VE/VCO^2 (peak SBP /VE/VCO^2). (15) It was carried out at Instituto de Cardiología de Corrientes and included 14 male patients with a mean age of 36 ± 14 years followed up for an average of 790 days. Seven patients had PH associated with congenital heart defects (4 with atrial septal defect and Eisenmenger's syndrome, one with tricuspid atresia, Fontan surgery and Eisenmenger's syndrome, 2 with pulmonic stenosis and one with tetralogy of Fallot). Six patients had idiopathic pulmonary arterial hypertension, and one had PH associated with connective tissue disease (systemic lupus erythematosus). On admission, 4 patients were in functional class (FC) I, 10 in FC II and none in FC III or IV. The primary end point was a composite of death, worsening FC or in-hospital admission for worsening PH. Four patients worsened their functional class, one of them had to be hospitalized, and there were no deaths. The mean duration of the CPET was 10.37 minutes, and the mean values of the variables were: peak VO^2 18.69 mL/kg/minute (49.15% of predicted peak VO^2); VE/VCO^2 47.96; VP 2.57 and CP 1902. The variables that demonstrated prognostic ability and their corresponding cut-off points are as follows: VE/VCO^2 42.5 (with a sensitivity of 75%, specificity of 66%, and an area under the curve of 0.8), peak $VO^2$15.35 mL/kg/min (with a sensitivity of 75%, specificity of 70%, and an area under the curve of 0.65), VP 2.3 (with a sensitivity of 75%, specificity of 78%, and an area under the curve of 0.77), and CP 1730 (with a sensitivity of 100%, specificity of 66%, and an area under the curve of 0.66). After multivariate analysis, PC still had the ability to predict the endpoint. This study adds novel information about the usefulness of CPET in PH. However, due to the limited number of patients included and the heterogeneity of the sample, it should be considered an exploratory investigation.

Do Patients with Pulmonary Embolism Associated with Active Cancer and Moderate or Severe Risk Score have Higher Risk of Adverse Outcome than Those Without Cancer?

José M. Bonorino, Jorge A. Bilbao, Nicolás A. Torres, Mateo Iwanowski, Emilia M. Spaini, Agustina F. Gallegos, José C. Santucci, Renzo Melchiori, María E. Aris Cancela, Horacio E. Fernández.

Venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) or pulmonary embolism (PE), is the third leading vascular disease after myocardial infarction and stroke. Its incidence increases with age as is almost eight times more common in subjects > 80 years than in those in their fifth decade of life. (16) The frequent association of cardiovascular diseases with cancer (the two leading causes of death in our environment) gave rise to the development of a new sub-specialty: cardio-oncology. (17) The association between cancer and PE was first recognized over a century ago by Armand Trousseau. (18) The incidence of PE in the general population is 0.1%, but

it is much more common in cancer patients, with a prevalence ranging from 2-15%. (19) This is especially true for metastatic tumors and is related to the type and primary location of the tumor (adenocarcinomas of the gastrointestinal tract, kidney, ovary, malignant brain tumors, and hematologic neoplasms), cancer staging, and antineoplastic treatment (chemotherapy, radiotherapy, and postoperatively). (20) The clinical presentation of PE varies widely, from mild cases that can be managed on an outpatient basis with a favorable outcome, to highly complicated cases with a high mortality rate. Several models have been described to quantify its severity and prognosis. The Pulmonary Embolism Severity Index (PESI) is one of the most extensively validated clinical scores. It is made up of 11 clinical variables with their corresponding scores. The scoring system categorizes patients into five classes based on their score. Class I (score < 65 points) has a mortality rate of less than 1.5%, while class V (score > 125 points) has a mortality rate between 10% and 25%. (21) The authors of this paper asked whether patients with PE and a moderate or severe PESI index (≥ 86 points) and active cancer have a worse outcome compared to those without cancer. For this reason, they conducted a single-center, retrospective and descriptive analysis of a prospective cohort attending Hospital Universitario Austral. Of 456 patients hospitalized between 2008 and 2022 with a diagnosis of PE, 209 had a PESI score ≥ 86. The study compared the incidence of in-hospital mortality (IHM), use of pressor agents (PA), and need for mechanical ventilation (VM) in patients with PE with and without cancer. Active cancer was defined as solid or hematological malignancies that have received chemotherapy and/or radiation treatment within the last year, or those without active treatment who are receiving palliative care. The population with PE and cancer was younger than the one without cancer (65 vs. 70 years, $p < 0.05$). The prevalence of hypertension was lower in patients with cancer (48% vs. 72%, $p < 0.05$) but the prevalence of diabetes was higher (19% vs. 8%, $p < 0.05$), respectively. A PESI score ≥ 86 was more frequent in patients with PE and cancer (100% vs. 84%, $p < 0.05$). There were no differences in IHM between both groups (12.7% vs. 8%, p = NS); however, the use of MV and PA was lower in patients with PE and cancer (9% vs. 34%, $p < 0.05$, and 11 % vs. 23%; $p < 0.05$, respectively). There were no deaths among patients with cancer (n = 24) or without cancer (n = 151) and PESI score < 86 points. In patients with cancer, PESI score < 86 vs. ≥ 86 points was not useful to predict IHM (0% vs. 12%, p = NS). The authors conclude that patients with PE and cancer and intermediate or high PESI scores are not at an increased risk of an unfavorable outcome. Mortality rate was not higher in this group and the need for MV and PA was lower. The small sample size likely contributed to the lack of statistical significance in the observed differences, as the trends exhibit wide variability. Several publications suggest different results. For example, Sorensen et al. analyzed 668 patients with PE and cancer from a Danish registry and reported 38% survival at one year in patients with cancer vs. 47% in the control group (RR 1.35, 95% CI 1.20 -1.50; $p < 0.001$). (22) Researchers from the University of Padua concluded that the presence of cancer significantly increases the risk of recurrent PE with poor vital prognosis (HR 1.72, 95% CI 1.31- 2.25]. (23) Recently, Rapezzi et al. published a study analyzing clinical trials with neutral or negative results. These situations suggest the possibility of a higher rate of total events than actually observed, smaller differences in the number of events between groups than calculated, or shorter follow-up periods than necessary. (24)

The jury of the 2023 Dr. Pedro Cossio Foundation Award was formed by the former presidents of the Argentine Society of Cardiology, Dr. Ana María Salvati and Dr. Ricardo Migliore, to whom I am grateful for their skilled and responsible participation.

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ORIGINAL ARTICLE

Initial Diuretic Efficiency as Predictor of Diuretic Resistance and Clinical Outcome in Acute Decompensated Heart Failure

Eficiencia diurética inicial como predictor de resistencia a diuréticos y evolución clínica en insuficiencia cardíaca aguda descompensada

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ABSTRACT

Background: In patients with acute decompensated heart failure (ADHF), early evaluation of diuretic efficiency (DE) could predict diuretic response and clinical outcome.
Objective: The aim of our study was to evaluate the association of DE with diuretic resistance (DR), in-hospital cardiovascular mortality, and readmission or cardiovascular mortality at 60 days in ADHF.
Methods: We conducted a multicenter and prospective study of patients hospitalized for ADHF. All patients received 40 mg of furosemide within two hours of admission and 20 mg every 8 hours in the first 24 hours. Subsequent adjustment of diuretic dose was left to the discretion of the investigator as determined by a pre-established protocol. DE was defined as the ratio of net fluid balance and cumulative amount of furosemide within the first 24 hours. Diuretic resistance was defined as requirement of furosemide infusion ≥240 mg/day during the first 72 hours. The clinical and biochemical variables were evaluated. The primary outcome was a composite of in-hospital cardiovascular mortality, and cardiovascular mortality or readmissions for ADHF at 60 days.
Results: The cohort was made up of 157 patients; median age was 74 years and 56 % were men. Diuretic efficiency was –15 mL/mg (interquartile range, IQR, –20 to –11). Diuretic resistance was evident in 13 % of patients, 8 % required sequential diuretic blockade, and 4 % required renal replacement therapy. Worsening renal function occurred in 22 % of patients. Cardiovascular mortality during hospitalization and at 60 days was 5.7 % and 6 %, respectively. Readmission rate for ADHF at 60 days was 12 %. Worse DE was associated with DR (p = 0.013), while patients in DE quartiles above -11 mL/mg were highly unlikely to develop DR (area under curve, AUC, 0.73, negative predictive value, NPV, 92.5 %). Worse DE value was associated with the composite endpoint (p = 0.025), higher in-hospital cardiovascular mortality (p = 0.003), persistent congestion at 48 hours (p = 0.007), higher cumulative dose of furosemide at 72 hours (p = 0.001) and worsening HF during hospitalization (p = 0.004).
Conclusion: Low initial DE was associated with DR, persistent congestion, and higher in-hospital cardiovascular mortality in ADHF, and constitutes a useful parameter to detect those patients who could benefit from early intensive diuretic treatment.

Keywords: Heart failure – Furosemide – Diuresis – Mortality

RESUMEN

Introducción: En pacientes con insuficiencia cardíaca aguda descompensada (ICAD) la eficiencia diurética (ED) evaluada en forma precoz podría predecir la respuesta a diuréticos y la evolución clínica.
Objetivo: Nuestro objetivo fue evaluar la asociación de la ED con la resistencia a diuréticos (RD), la mortalidad cardiovascular intrahospitalaria, y la mortalidad cardiovascular y las reinternaciones a 60 días en la ICAD.
Material y métodos: Estudio prospectivo y multicéntrico que incluyó pacientes internados por ICAD. Recibieron 40 mg de furosemida dentro de las 2 horas del ingreso y 20 mg cada 8 horas en las primeras 24 horas. El escalamiento diurético posterior quedó a criterio del investigador según un protocolo preestablecido. Se definió la ED como balance hídrico/dosis de furosemida en las primeras 24 horas y la RD como el requerimiento de infusión de furosemida ≥240 mg/día en las primeras 72 horas. Se evaluaron variables clínicas y bioquímicas, y el punto final combinado (PFC) de mortalidad cardiovascular intrahospitalaria, y mortalidad cardiovascular y reinternaciones por ICAD a 60 días.
Resultados: Se incluyeron 157 pacientes, mediana de edad de 74 años, 56 % hombres. La ED fue –15 mL/mg (rango intercuartílico, RIC, –20 a –11). Se evidenció la RD en el 13 % de los pacientes, el 8 % requirió bloqueo tubular y el 4 % terapia de reemplazo renal. El 22 % desarrolló empeoramiento de la función renal. La mortalidad cardiovascular intrahospitalaria fue del 5,7 % y en el seguimiento

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a 60 días, del 6 %. Las reinternaciones por ICAD a 60 días fueron del 12 %. Una peor ED se asoció al desarrollo de RD (p = 0,013) y los pacientes con ED superior a –11 mL/mg tuvieron mayor probabilidad de no desarrollar RD (área bajo la curva, AUC, 0,73; valor predictivo negativo, VPN, 92,5 %). Una peor ED se asoció al PFC (p = 0,025), mayor mortalidad cardiovascular intrahospitalaria (p = 0,003), persistencia de congestión a 48 horas (p = 0,007), mayor dosis de furosemida a 72 horas (p = 0,001) y empeoramiento de la ICAD en la internación (p = 0,004).
Conclusión: La ED inicial baja se asoció a la RD, la dificultad en la descongestión y una mayor mortalidad cardiovascular intrahospitalaria en ICAD. Es un parámetro útil para detectar pacientes que podrían beneficiarse de un tratamiento diurético intensivo precoz.

Palabras clave: Insuficiencia cardíaca – Furosemida – Diuresis - Mortalidad

INTRODUCTION

Acute decompensated heart failure (ADHF) is usually defined as the new onset or worsening of symptoms or signs of congestion or systemic hypoperfusion, requiring early diagnosis and timely treatment. (1,2) Intravenous loop diuretics are the cornerstone to achieve proper decongestion and clinical stability in this condition. Effective response to these drugs is necessary for in-hospital progress and during the vulnerable phase. (3-5)

Identifying patients with diuretic resistance (DR) is clinically relevant because it is associated with higher mortality and readmission risk. However, there is currently no standard definition of DR during hospitalization for ADHF. (6-10) Patients with DR may benefit from alternative decongestive treatments in addition to intravenous furosemide, making early detection crucial. (11-17)

The urinary output achieved, and the absolute dose of diuretics have been classically considered to be variables related to the response to decongestive treatment, DR, and prognosis, (6-10) However, these individual factors could be inadequate surrogates of the therapeutic effectiveness since there are multiple associated confounding factors, such as the degree of congestion, disease severity and the subjective nature of the treating physician. (6-10)

Diuretic efficiency (DE), considered as the urinary output or weight loss achieved divided by the amount of intravenous diuretics administered, is a parameter that has shown a clear association with diuretic response and the clinical course in patients with ADHF. (18-20) Therefore, measuring DE, defined as the ratio of the net fluid balance during the first 24 hours and the dose of furosemide given, could be an objective parameter to help identify patients with DR who are likely to have a worse clinical outcome. This can facilitate the implementation of more effective decongestion strategies.

The aim of this study was to evaluate the usefulness of DE within the initial 24 hours in ADHF patients as a predictor of DR, in-hospital outcome, and readmission rate due to decompensation or cardiovascular mortality at 2 month-follow up, considered the vulnerable phase.

METHODS

Study design and objective

We conducted a prospective, multicenter, and open study including consecutive patients > 18 years admitted to the coronary care unit (CCU) due to ADHF. Initial DE was defined as the ratio of net fluid balance and cumulative amount of intravenous furosemide within the first 24 hours. The initial DE of the patients included was calculated, and we also evaluated the clinical, biochemical, and echocardiographic variables on admission and at 72 hours, and the occurrence of clinical events during hospitalization and at 60 days. The variables evaluated are defined in the Appendix.

Population

- Inclusion criteria: patients > 18 years hospitalized in the CCU due to ADHF,
- Exclusion criteria: creatinine (Cr) levels ≥ 2.5 mg/dL or on dialysis on admission, systolic blood pressure < 90 mm Hg, cardiogenic or septic shock, requirement of pressor or inotropic agents, mechanical ventilation (MV) or pregnancy. Those patients who did not sign the informed consent form or who were enrolled in other clinical trials with pharmacological intervention were also excluded.

Protocol of diuretic treatment

The strategy of diuretic treatment during the first 72 hours of hospitalization in the CCU was determined by a pre-established protocol (Figure 1). After bladder evacuation, an initial intravenous bolus of 40 mg of furosemide was given to patients within two hours of admission to the emergency department. In the first 24 hours after admission, all patients received intravenous boluses of 20 mg of furosemide every 8 hours. After the first day of hospitalization, the daily furosemide dose was adjusted (increased or decreased) every 24 hours, with evaluation of the extent of clinical congestion or daily diuresis (fluid balance threshold of -2000 mL/day), according to the pre-established protocol and to the discretion of the treating physician. According to the protocol, up-titration of furosemide was performed by increasing the intravenous infusion. Down-titration of furosemide in the protocol allowed for shifting from intravenous to oral administration upon achieving an adequate response. The diuretic protocol was discontinued 72 hours after enrollment or earlier in case of requirement of doses of furosemide ≥240 mg/day, tubular diuretic blockade (TDB), hypertonic saline (HS), renal replacement therapy (RRT), inotropic drugs, pressor agents, MV , or in the event of a significant clinical complication as determined by the investigator.

Outcome measures

Diuretic resistance (DR): requirement of furosemide ≥240 mg/day during the first 72 hours of hospitalization.
Composite end point: in-hospital mortality, readmissions for ADHF at 60 days or cardiovascular mortality at 60 days.
Secondary end points:

- Cardiovascular mortality during hospitalization

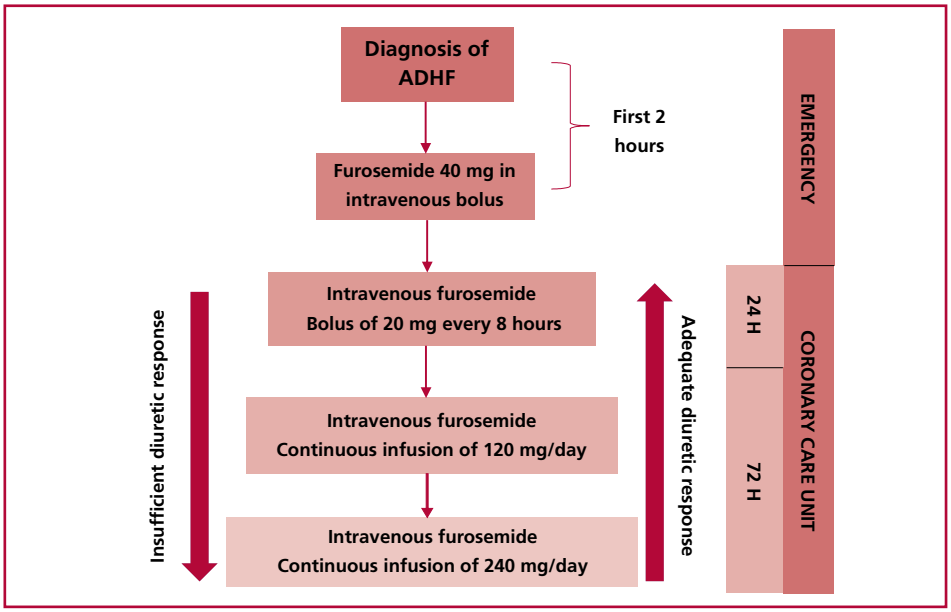


Fig. 1. Strategy of diuretic dose adjustment during the first 72 hours of hospitalization as determined per protocol according to the evaluation of the treating physician.

Abbreviations: ADHF (acute decompensated heart failure)

- Cardiovascular mortality at 60 days.
- Readmissions for ADHF at 60 days.
- Persistent clinical congestion at 48 hours after inclusion.
- Cumulative furosemide dose required at 72 hours after inclusion.
- Weight change at 72 hours after inclusion.
- Worsening renal function (WRF) at 72 hours after inclusion..
- Change in N-terminal pro B-type natriuretic peptide (NT-proBNP) levels at 72 hours after inclusion.
- Change in E/e' ratio and pulmonary artery systolic pressure (PASP) at 72 hours after inclusion.
- Requirement of TDB with > 1 diuretic, HS or RRT during hospitalization
- Worsening ADHF during hospitalization
- Requirement of inotropic drugs or MV during hospitalization
- Length of CCU stay

Data collection, ethical aspects, and sources of funding

The clinical and biochemical variables and the relevant images were collected. Patient recruitment started once the protocol was approved by the Committee on Ethics of the Argentine Society of Cardiology. All the subjects gave their informed consent to be included in the study. Data were recorded in a printed form customized for the study, and then incorporated into a single electronic database by the principal investigator. Data confidentiality was maintained in compliance with the Personal Data Protection and Patient Rights Act, ensuring that the identification of each individual participant is not possible. None of the authors have disclosed any conflicts of interest, and this study was not funded.

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD), or median and interquartile range (IQR), according to their distribution. Categorical variables were expressed as absolute and relative frequencies. Continuous variables were compared using the Student's t test or the Mann-Whitney U test, according to their distribution. Proportions were analyzed using the chi-square test or the Fisher's exact test, as applicable according to the frequency of the values expected. The association of the initial DE with the end points was analyzed, with adjustment for predetermined variables: age, chronic kidney disease (CKD), hypoalbuminemia, ambulatory use of furosemide, left ventricular ejection fraction (LVEF), and sepsis. In addition, the distribution of the endpoints was evaluated according to the calculated quartiles of the initial DE. A ROC curve was constructed to evaluate the ability of DE to predict DR, and the sensitivity and specificity of the quartile with the worst DE value (25th percentile) were evaluated. The alpha error was set at 5% to establish statistical significance. All the statistical calculations were performed using SPSS 21.0 software package.

Ethical considerations

The protocol was evaluated and approved by the Committee on Ethics of the Argentine Society of Cardiology through the PRIISA.BA platform of the Ministry of Health of the City of Buenos Aires. Since this survey was anonymous and self-administered, participants were not required to give informed consent. The survey was conducted following national and international ethical standards for research on human subjects, as the Declaration of Helsinki revised in 2013, National Ministry of Health resolution 1480/2011, law N° 3301 of the city of Buenos Aires, and ANMAT regulation 6677/10 and amendments 4008 and 4009. Data privacy among respondents was protected through anonymity in the electronic survey.

RESULTS

A total of 157 patients were included; median age was 74 years (IQR 62-83), and 56 % were men. Diabetes was present in 36 %, atrial fibrillation in 43 % (n = 68) and CKD in 20 % (n = 31). The etiologies were ischemic heart disease in 27 % (n = 43), valvular heart disease in 22 % (n = 35) and hypertension in 15 % (n = 24). LVEF was reduced in 43 % (n = 67),

mildly reduced in 12 % (n = 19), and preserved in 45 % (n = 71). The remaining baseline characteristics of the population are described in Table 1.

The initial DE was -15 mL/mg (RIC -20 to -11) and there were no differences in the DE across the entire spectrum of LVEF (p=0.8) or between the different clinical types of ADHF (p=0.3). Diuretic resistance was evident in 13 % (n= 20) of the cohort, 8 % (n= 13) required TDB, 1 patient required HS and 4 % (n= 6) required RRT. Worsening ADHF occurred in 13 % (n = 20) and WRF in 22 % (n = 35), while 10 % (n = 16) required pressor or inotropic drugs and 4 % (n = 6) required MV during hospitalization. Length of stay in the CCU was 5 days (IQR 4-8). In-hospital cardiovascular mortality was 5.7 % (n = 9) and cardiovascular mortality during the 60-day follow-up was 6.4 % (n = 10). Twelve percent (n = 19) of the patients were readmitted for ADHF at 60 days.

Worse DE predicted the development of DR (OR 1.072; 95 % CI 1.015-1.130; p= 0.013), and was associated with a trend towards higher use of SDB (p = 0.07) and RRT (p = 0.06) adjusted for predetermined variables (age, CKD, hypoalbuminemia, ambulatory use of furosemide, LVEF and sepsis) (Figure 2). The distribution of the end points by DE quartiles is described in Table 2. The ROC curve analysis indicated that patients with DE quartiles above -11 mL/mg are highly unlikely to develop DR, with an AUC of 0.73 (95% CI 0.59-0.87, p=0.001), sensitivity of 60 %, specificity of 80 %, negative predictive value of 92.5 % and positive predictive value of 30 % (Figure 3).

Worse DE value was associated with the composite endpoint, mainly due to higher in-hospital cardiovascular mortality (OR 1.20; 95 % CI 1.06-1.36; p=

Table 1. Baseline characteristics of the population.

Variable	
Age (years), median (IQR)	74 (62 - 83)
Male sex, n (%)	88 (56)
Hypertension, n (%)	121 (77)
Diabetes, n (%)	57 (36)
Previous atrial fibrillation, n (%)	68 (43)
Chronic kidney failure, n (%)	31 (20)
Etiology of heart failure, n (%)	
Ischemic heart disease	43 (27)
Valvular heart disease	35 (22)
Hypertension	24 (15)
Others	55 (35)
Functional class (NYHA), n (%)	
I	53 (34)
II	84 (54)
III	16 (10)
IV	4 (2)
Previous heart failure treatment, n (%)	
Beta blockers	104 (66)
ACEI/ARB	85 (54)
ARNI	11 (7)
Aldosterone antagonists	49 (31)
iSGLT-2	4 (2.5)
Oral furosemide	59 (38)
Previous dose of furosemide (mg), median (IQR)	40 (20-40)
Clinical presentation of heart failure, n (%)	
Pulmonary congestion	92 (58)
Acute pulmonary edema	28 (18)
Right ventricular-predominant heart failure	37 (24)
NT-proBNP on admission (pg/mL), median (IQR)	3939 (2200-6300)
Ejection fraction (%), median (IQR)	48 (30-59)
Preserved (LVEF ≥50 %), n (%)	71 (45)
Mildly reduced (LVEF between 41 % and 49 %), n (%)	19 (12)
Reduced (LVEF ≤40 %), n (%)	67 (43)

Abbreviations: ARB: Angiotensin II receptor blocker; ACEI: angiotensin-converting enzyme inhibitor; ARNI: angiotensin receptor neprilysin inhibitor; iSGLT-2: sodium-glucose co-transporter 2 inhibitor; IQR: interquartile range; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association

0.003), with no significant differences in the rate of cardiovascular mortality or readmissions for ADHF at 60-day follow-up.

Worse DE was associated with persistent congestion at 48 hours (OR 1.10; 95 % CI 1.03-1.18; p = 0.007), higher total cumulative dose of furosemide administered at 72 hours (p = 0.001), lower weight loss at 72 hours (p = 0.0001) and worsening of ADHF during hospitalization (OR 1.11; 95 % CI 1.03-2; p = 0.006). Similarly, worse DE was associated with a trend toward a lesser percentage decrease in NT-proBNP at 72 hours after inclusion (p = 0.09), with no differences in the reduction of the E/e' ratio and PASP. Patients with the worst DE value presented greater requirement of pressor agents (OR 1.18; 95 % CI 1.04-1.33; p = 0.008) and greater but not significant requirement of inotropic agents (OR 1.05; 95 % CI 0.98-1.13; p = 0.12) during hospitalization, with no differences in the rate of WRF, MV and length of stay in the CCU (Figure 2).

Patients in the lowest quartile of DE value (less than -11 ml/mg) were at a higher risk of developing DR and had a worse prognosis during hospitalization. Furthermore, decongestion was less effective, and a more complex diuretic strategy was required for these patients compared to those in higher DE value quartiles (Table 2).

DISCUSSION

In this study, measuring DE within the initial 24 hours proved effective in assessing diuretic responsiveness to furosemide in ADHF. It also helped identify patients with DR who will exhibit reduced clinical decongestion and will require a higher dose of furosemide in the first 72 hours. Additionally, the initial DE predicted the development of events during the entire hospitalization, mainly worsening ADHF, use of vasoactive drugs, and in-hospital mortality.

Discrimination of events by quartiles of DE revealed that a DE value better than -11 mL/mg was associated with a low probability of developing DR. Moreover, patients in the quartile with worse values suffered from more complications and required more intense diuretic therapy. The calculation of DE within the initial 24 hours of hospitalization can prove valuable in daily practice to identify patients who are at greater risk of developing DR and may benefit from a more aggressive diuretic treatment that could improve their clinical outcome. This potential clinical usefulness should be evaluated through future randomized studies.

While there is evidence to suggest that urinary output is adequate for evaluating the response to diuretic therapy, it should be noted that it depends on the dosage of furosemide administered, fluid intake, and the level of congestion. It has been reported that the overall amount of furosemide given to patients is a predictor of their clinical outcome during hospitalization. (6-10) However, this may be influenced by the bias resulting from the severity of ADHF and the criteria of the treating physician. Therefore, relying solely on either urinary output or cumulative diuretic dose would not completely measure the patient's inherent reaction to diuretic treatment. Currently, measuring natriuresis soon after furosemide administration has emerged as a useful parameter for evaluating diuretic response. Although this approach facilitates dynamic optimization of treatment, serial measurement is required, and the method may not be available in all the centers. (21-28)

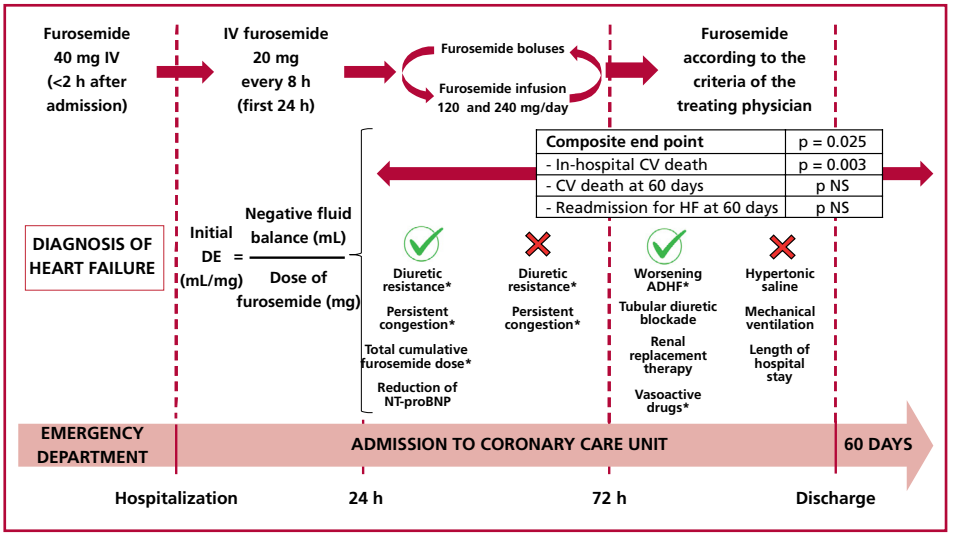


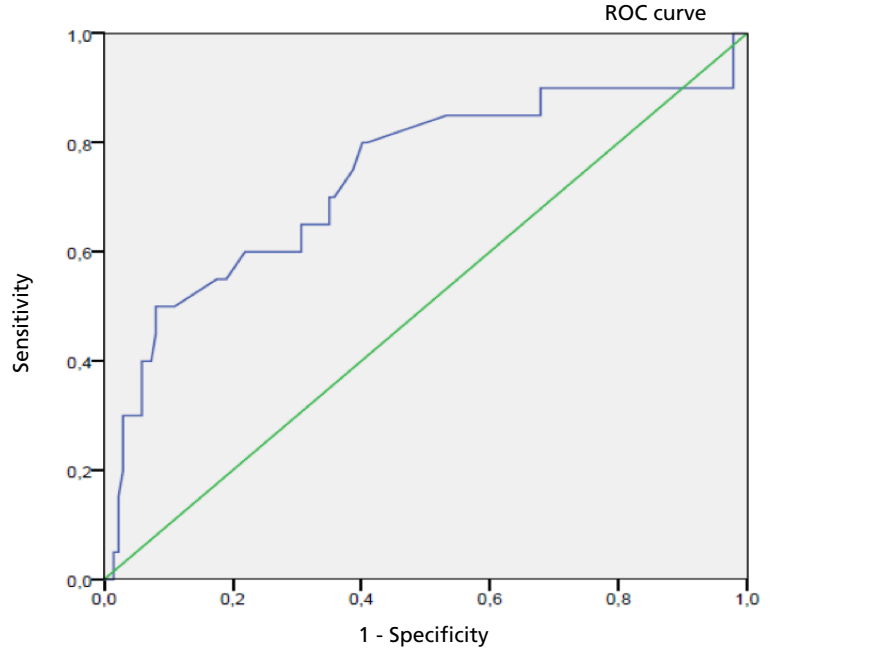
Fig. 2. Graphical summary: diuretic protocol used and results of the study.

Abbreviations: ADHF: acute decompensated heart failure; CV: cardiovascular; DE: diuretic efficiency; IV: intravenous; NS: non-significant; PASP: pulmonary artery systolic pressure
*p value < 0.05

Table 2. Distribution of end points by initial diuretic efficiency quartiles.

	DE Quartile 1 (> -20 mL/mg) N = 46	DE Quartile 2 (-20 to -15.1 mL/mg) N = 39	DE Quartile 3 (-15 to -11 mL/mg) N = 35	DE Quartile 4 (< -11 mL/mg) N = 37
CEP, n (%)	8 (17.4)	7 (18.4)	6 (17)	14 (38)*
In-hospital CV mortality, n (%)	0 (0)	3 (7.7)	0 (0)	6 (16.2)*
CV mortality at 60 days, n (%)	5 (10.9)	1 (2.9)	1 (2.9)	3 (9.7)
Readmissions for ADHF at 60 days, n (%)	5 (10.9)	3 (7.9)	5 (14.3)	6 (16.2)
Diuretic resistance (furosemide ≥240 mg/day), n (%)	2 (4.3)	2 (5.1)	5 (14.3)	11 (29.7)*
Persistent congestion at 48 h, n (%)	3 (7)	3 (7)	4 (11)	13 (35)*
Cumulative furosemide dose at 72 hours (mg), median (IQR)	176 (60-1120)	206 (60-1740)	275 (60-1740)	524 (60-3000)*
Weight loss at 72 h (kg)	–5 (–7 to –3)	–4 (–5 to –2)	–3 (–5 to –2)	–3 (–4 to –2)*
Sequential diuretic blockade, n (%)	2 (4.3)	3 (7.7)	1 (3)	7 (19)*
Hypertonic saline, n (%)	0 (0)	0 (0)	0 (0)	1 (2.7)
Renal replacement therapy, n (%)	1 (2.2)	0 (0)	1 (3)	4 (11)*
Worsening ADHF, n (%)	2 (4.3)	5 (12.8)	3 (8.6)	10 (27)*
Percent NT-proBNP reduction, median (IQR)	56 (73-36)	53 (62-31)	49 (70-40)	41 (61-7)*
Length of stay in the CCU (days), median (IQR)	6.3 (2-21)	7.3 (2-24)	6 (3-23)	10.6 (3-86)*

Abbreviations: ADHF: acute decompensated heart failure; CCU: coronary care unit; CV: cardiovascular; DE: diuretic efficiency; CEP: composite end point (in-hospital CV mortality, CV mortality and readmissions at 60 days); IQR: interquartile range.
Quartile 1 is the quartile with the best DE and quartile 4 is the quartile with the worst DE
* p value < 0.05 between quartile 4 and the rest of the cohort



Area	Typical error	Asymptotic sig.	95% CI lower limit	95% CI upper limit
0.735	0.069	0.001	0.599	0.871

Abbreviations: CI: confidence interval; ROC: receiver operating characteristic; ROC curve (sensitivity vs. 1-specificity)

Fig. 3. Discrimination ability of diuretic efficiency to predict the development of diuretic resistance according to the analysis of the ROC curve.

In our cohort, we excluded more severely ill patients, such as those with Cr ≥ 2.5 mg %, cardiogenic or septic shock, and those requiring MV. These patients have multiple factors that can interfere with the diuretic response and the clinical course, necessitating higher diuretic doses. Thus, our study indicates that low initial DE is associated with adverse events even in ADHF patients with milder clinical presentations. Despite the association of CKD, hypoalbuminemia, and previous use of oral furosemide with DR, (6-10) it is important to note that the initial DE remains an independent predictor of both DR and in-hospital mortality, even after adjusting for these variables.

Previous experiences have shown that DE is associated with an increased risk of readmission for ADHF and mortality within 60 days of discharge from hospitalization for ADHF. This is a critical period when the risk of clinical events is elevated. (18-20) However, in the current cohort, this association could not be established, likely due to the low rate of events during the vulnerable stage. Notably, the exclusion of patients with the highest clinical severity by protocol may have contributed to this finding.

In this analysis, we found no correlation between the initial DE and the occurrence of WRF, as indicated by an increase in serum Cr levels or a reduction in the estimated glomerular filtration rate. This finding may be because WRF included patients with persistent congestion despite increasing diuretic doses and poor prognosis (true WRF or acute renal injury), alongside those with clinical improvement during diuretic treatment and a favorable course (pseudo WRF). (29-35) However, the diuretic response (DE) is not exclusively determined by renal function. It also relies on left and right ventricular function, volemia, and several other factors that affect the pharmacokinetics and pharmacodynamics of diuretics in ADHF. (1-5)

Our study demonstrated that patients with better DE had a greater reduction of NT-proBNP within the initial 72 hours of hospitalization. This finding is consistent with multiple analyses indicating that NT-proBNP levels decrease during decongestive treatment, and this is associated with a better prognosis during hospitalization and the vulnerable stage. (1,2,36,37) However, to date, there is no evidence to support therapeutic guidance through serial measuring of this biomarker. (1,2,36,37)

There was no correlation found in this cohort between DE and improvement in the dynamic measurement of the E/e' ratio, PASP, and inferior vena cava diameter through echocardiography despite the evidence supporting the efficacy of this method in identifying residual congestion and optimizing diuretic treatment. (38-41)

There are some limitations to this study. We could not measure intra-abdominal pressure or central venous pressure, which are variables related to the development of DR. (6-10) The presence of ultrasound lung comets was not examined during the periodic evaluation of congestion, despite being a proven useful tool in the diagnosis and therapeutic management of congestion. (42,43) At present, we do not haved longer-term follow-up, in which there could be an association of initial DE with clinical events as demonstrated in previous experiences. (18-20)

CONCLUSION

In patients hospitalized for ADHF, initial DE was associated with the development of DR, persistent congestion, higher cumulative dose of furosemide and higher in-hospital cardiovascular mortality. Diuretic efficiency is a useful parameter to detect those patients who could benefit from early intensive diuretic treatment and thus achieve better clinical outcome

Conflicts of interest

None declared.

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

Source of funding

None.

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APPENDIX

1. Operative definition of variables

- **Acute decompensated heart failure (ADHF):** clinical syndrome characterized by new onset or worsening of symptoms and signs of tissue congestion associated with elevated intracardiac filling pressures. (1,2) Acute decompensated heart failure will be considered in the presence of one sign (pulmonary rales, acute pulmonary edema, third heart sound on auscultation, central venous pressure >16 cm of water, jugular venous distension, hepatojugular reflux, peripheral edema, or hepatomegaly) and one classic symptom of congestion (orthopnea, paroxysmal nocturnal dyspnea, or NYHA FC III-IV). Neither echocardiographic nor biochemical criteria were considered for the diagnosis of AHF.
- **Worsening ADHF:** worsening of signs and symptoms of congestion in patients hospitalized for ADHF and receiving diuretic treatment, requiring up-titration of the diuretic dose. (1, 2)
- **Cardiogenic shock:** syndrome characterized by tissue hypoperfusion (cold extremities, altered sensorium, oliguria <0.5 mL/kg/min, lactate levels > 2 mEq/L) and hypotension (baseline systolic blood pressure < 90 mm Hg or a drop > 40 mm Hg from baseline systolic blood pressure) secondary to low cardiac output (CI < 2.2 l/min/m2 and pulmonary capillary wedge pressure > 18 mm Hg, as measured by Swan-Ganz catheter), and requiring treatment with inotropic drugs. (1,2)
- **Worsening renal function:** based on the AKIN criteria, it is defined as an increase ≥ 0.3 mg/dL in the serum creatinine or a decrease in creatinine clearance > 25 % compared with the baseline value according to the CKD-EPI formula (29-35).
- **Systemic inflammatory response syndrome (SIRS):** set of clinical manifestations resulting from the systemic inflammatory cascade requiring the presence of at least two of the following 4 criteria for diagnosis: body temperature > 38°C or < 36°C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute or PaCO2 < 32 mm Hg; or white blood cell count > 12 000 cells/cm^3 or < 4000 cells/cm^3. (44)
- **Sepsis:** presence of SIRS in the setting of infection. (44)
- **Septic shock:** signs of systemic hypoperfusion and hypotension (baseline systolic blood pressure < 90 mm Hg or a drop > 40 mm Hg from baseline systolic blood pressure) despite adequate fluid resuscitation and requiring treatment with pressor agents (norepinephrine, epinephrine, vasopressin), in the setting of sepsis. (44)
- **Tubular diuretic blockade:** concurrent use of furosemide plus thiazide diuretics or mineralocorticoid receptor antagonists. The doses of diuretics are spironolactone 50 mg/day, eplerenone 50 mg/day or hydrochlorothiazide 50 mg/day, or greater. (1,2)
- **Hypertonic saline:** sodium chloride between 3 % to 7.5 % given in IV infusion over 60 minutes. (1,2)
- **Renal replacement therapy:** dialysis, ultrafiltration, and hemodiafiltration (1,2).
- **E/e' ratio:** ratio of peak diastolic mitral inflow velocity (E-wave) measured in the apical 4-chamber view (B-mode) to peak diastolic mitral annulus velocity (e' wave) measured in the septum and lateral annulus in the apical 4-chamber view (B-mode) by tissue Doppler imaging. For patients with atrial fibrillation (AF), it is recommended to take three measurements and average the results. An average E/e' ratio >14 in patients in sinus rhythm and >11 in those with AF will be considered as an increase in filling pressures. (38-41).
- **PASP:** pulmonary artery systolic pressure estimated by adding the tricuspid valve pressure gradient to the right atrial pressure (based on inferior vena cava collapsibility). A PASP ≥ 36 mm Hg is considered elevated. (38-41)

ORIGINAL ARTICLE

Acute Myocardial Infarction Mortality in Argentina During the COVID-19 Pandemic. Ministry of Health Vital Statistics Data

Mortalidad del infarto agudo de miocardio en la Argentina durante la pandemia de COVID-19. Datos oficiales de las estadísticas vitales del Ministerio de Salud

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ABSTRACT

Background: During the COVID-19 pandemic, health care centers and especially intensive care units worldwide were saturated by cases of acute respiratory failure produced by the SARS-CoV-2 virus. Social preventive and mandatory isolation (SPMI), established by law N° 27 541 since March 20, 2020, and extended by Decree N° 260/20 to December 31, 2021, determined home confinement, and during this period coronary angioplasties and central cardiac surgeries decreased. The hypothesis of our study was that during the pandemic acute myocardial infarction (AMI) mortality increased in Argentina, as this is a time-dependent disease, mainly with out-of-hospital mortality.

Objectives: The aim of this study was to evaluate general and COVID-19 mortality in the population ≥20 years during the pandemic and analyze the trend of overall and divided by age and sex AMI mortality.

Methods: Vital statics published by the Ministry of Health of Argentina were analyzed, considering the pandemic period as the two SPMI years and 2019 as the pre-pandemic period. Overall and AMI gross and specific rate of mortality were considered as (number of deaths taking place in the Argentine population during 1 year / total population in the same zone at midyear) × 1000, respectively. Deaths for AMI were those contemplated in the International Classification of Diseases 10th revision (ICD-10) as I21, I22. The mortality trend was analyzed with linear trend of proportions (Chi2 for trends; significant p <0.05) using Epi-Info software, and including the ≥20-year population. In the analysis by age the population was divided into ≥ or < 60 years.

Results: During the pandemic mortality increased by 26% with respect to 2019 (p<0.001) (table). Deaths for COVID-19 were 53 222 and 84 698 for 2020 and 2021, respectively. AMI mortality increased by 15%, with a greater number of deaths in the young and female population.

Table 1. Overall results comparing the years 2020 and 2021

Argentina: vital statistics	2019 (pre-pandemic)	2020 (pandemic)	2021 (pandemic)	Odds Ratio (Chi² for trends)	p
Total population ≥ 20 years	30 417 141	30 822 573	31 224 154		
Mortality ≥ 20 years	325 486	367 807	423 112		
% mortality	1.07	1.19	1.35	1.26	<0.001
Gross mortality rate	10.7	11.93	13.55		
AMI deaths	17 789	18 881	20 901	1.15	<0.001
Specific mortality rate	0.58	0.62	0.67		
Male	10 246	10 492	11 719	1.12	<0.001
Female	7 471	8 227	9 064	1.19	<0.001
≥ 60 years	16 161	16 197	18 010	1.09	<0.001
< 60 years	1 628	2 684	2 891	1.73	<0.001

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Conclusions: During the pandemic there was a great increase in mortality, attributable to COVID-19, and increased mortality for acute myocardial infarction, especially in women and in patients <60 years, probably due to secondary SPMI effects.

Key words: Cardiac Anatomy – Myocardium - Cardiac Fulcrum - Myocardial Support - AV node.

RESUMEN

Introducción: En todo el mundo, durante la pandemia de COVID-19 los centros asistenciales y especialmente los cuidados intensivos se vieron saturados por los casos de insuficiencia respiratoria aguda producidos por el virus SARS-CoV-2. El aislamiento social, preventivo y obligatorio (ASPO) establecido por Ley N° 27.541 desde el 20 de marzo de 2020, y ampliado por el Decreto N° 260/20 hasta el 31 de diciembre de 2021, determinó el confinamiento en domicilio. Durante el mismo se observó una disminución de las angioplastias coronarias y cirugías cardíacas centrales. La hipótesis de nuestro trabajo es que hubo un incremento de la mortalidad por el infarto agudo de miocardio (IAM) en la Argentina en el periodo de pandemia, dado que es una patología tiempo dependiente y cuya mortalidad es mayormente extrahospitalaria.
Objetivos: Evaluar el incremento de la mortalidad general y por COVID-19 en la población ≥20 años en el periodo de pandemia y analizar la tendencia de mortalidad del IAM en forma global y segregada por edad y sexo.
Material y métodos: Se analizaron las estadísticas vitales publicadas por el Ministerio de Salud de la Argentina. Se consideró período de pandemia de acuerdo con los 2 años del ASPO, y prepandemia al año 2019. Se consideró tasa bruta y específica de mortalidad al (número de defunciones acaecidas en la población de la Argentina durante 1 año / población total en la misma zona a mitad del mismo año) x 1000, global y por IAM respectivamente. Las defunciones por IAM son las consideradas en el ICD-10 como I21, I22. La tendencia de mortalidad se analizó por el análisis lineal de tendencias de proporciones (Chi² de tendencias; p significativa <0,05) con Epi-info y se incluyó a la población ≥20 años. En el análisis por edad se dividió a la población en ≥ o < 60 años.
Resultado: La mortalidad en pandemia se incrementó un 26% con respecto al año 2019 (p<0,001) (tabla). Las defunciones por COVID-19 fueron 53 222 y 84 698 para los años 2020 y 2021 respectivamente. La mortalidad por IAM se incrementó un 15%, con un aumento mayor en jóvenes y mujeres.

Tabla 1. Resultados generales comparando los años 2020 y 2021.

Argentina: estadísticas vitales	2019 (prepandemia)	2020 (pandemia)	2021 (pandemia)	Odds Ratio (Chi² de tendencias)	p
Población total ≥ 20a	30 417 141	30 822 573	31 224 154		
Mortalidad ≥ 20a	325 486	367 807	423 112		
% mortalidad	1,07	1,19	1,35	1,26	<0,001
Tasa bruta de mortalidad	10,7	11,93	13,55		
Muertos por IAM	17 789	18 881	20 901	1,15	<0,001
Tasa específica de mortalidad	0,58	0,62	0,67		
Varones	10 246	10 492	11 719	1,12	<0,001
Mujeres	7 471	8 227	9 064	1,19	<0,001
≥ 60 años	16 161	16 197	18 010	1,09	<0,001
< 60 años	1 628	2 684	2 891	1,73	<0,001

Conclusiones: En la pandemia hubo un fuerte incremento de la mortalidad, atribuible al COVID-19, y un incremento de la mortalidad por infarto agudo de miocardio en especial en mujeres y menores de 60 años, probablemente atribuible a los efectos secundarios del ASPO.

Palabras clave: Pandemia de COVID-19 - Infarto agudo de miocardio - Estadísticas vitales de Argentina

INTRODUCTION

The COVID-19 pandemic, originated by the SARS-CoV-2 virus, has had a profound impact in medical care and mortality worldwide. (1) In Argentina, as in many other countries, the implementation of "Social preventive and mandatory isolation (SPMI)", according to Law No 27 541, aimed at stopping virus propagation, but also generated secondary effects in medical care of other severe diseases. (2) Acute myocardial infarction (AMI), a condition that requires immediate medical care, is one of these critical diseases with greater morbidity and mortality risk, and whose early diagnosis and treatment save lives.

During the pandemic, medical centers, including intensive care units, were surpassed by patients with acute respiratory failure due to COVID-19. However, in Argentina this situation occurred later, but generated an immediate effect in the population who refused to attend the emergency rooms for fear of contagion, with delays in consultation and a strong reduction in revascularization treatments. This combination of fear and then strong increase in the demand could have led to delays in AMI care, with significant impact in the increase of mortality. (3,4)

This study was carried out based on official data provided by the Ministry of Health of Argentina, with the aim of analyzing whether the COVID-19 pandemic was associated with a significant increase in total

and AMI mortality in the Argentine population. (5-7) In addition, it examined differences in mortality according to age and gender, to understand how different population groups could have been dissimilarly affected by the secondary effects of the pandemic.

METHODS

Vital 2019-2021 statistics published by the Ministry of Health of Argentina were analyzed (see Supplementary material). The two SPMI years were considered as the pandemic period and 2019 as the pre-pandemic year. Gross and specific rate of mortality were considered, as (number of deaths taking place in the Argentine population during 1 year / total population in the same zone at midyear) × 1000, overall and by AMI respectively. Deaths for AMI were those contemplated in the International Classification of Diseases 10th revision (ICD-10) as I21, I22. The mortality trend was analyzed with linear trend of proportions (Chi^2 for trends; significant $p < 0.05$) using Epi-Info software, and including the ≥20-year population. In the analysis by age the population was divided into ≥ or < 60 years.

Ethical considerations

The study waived the ethics committee evaluation (MSAL Resolution 1480/11) as it was an epidemiological study analyzing sources of secondary data with no identification information on the deceased.

RESULTS

Table 1 shows 26% increase in overall mortality during the pandemic compared with the year 2019 ($p<0.001$). This increase was mainly attributed to deaths caused by COVID-19: 53 096 and 84 480 cases in 2020 and 2021, respectively. Gross mortality increased by 13.5% (see Figures 1 and 2), which represents an absolute difference of 2.85 additional deaths per 1000 inhabitants compared with the period prior to the pandemic. In addition, AMI mortality increased by 15% compared with the pre-pandemic year ($p<0.001$), following the same trend as overall mortality. The specific mortality rate for AMI was 0.67, which represented an absolute increase of 9 more deaths per 100 000 inhabitants in 2021 (see Figures 3 and 4).

Additionally, mortality for AMI increased by 19% in women compared with men ($p<0.001$), together with a marked increase of 73% mortality in patients <60 years ($p<0.001$) (see Table).

DISCUSSION

Overall and AMI mortality

Recent estimations of the World Health Organization (WHO) reveal that the total number of deaths associated directly or indirectly with the COVID-19 pandemic between January 2020 and December 2021, termed as "excess mortality", reached approximately 14.9 million cases. (8,9) In accordance with these data, the Ministry of Health of Argentina reported an overall increase in mortality during the pandemic, with a peak of 26% in the first semester of 2021. (10) These data totally agree with our own findings, despite our study population includes subjects ≥20 years.

Our research shows a significant increase of 15% in AMI mortality with respect to the pre-pandemic period, equivalent to an absolute value of 67 deaths per 100 000 inhabitants in 2021. Although there is lack specific statistical data on the incidence of AMI in Argentina, we base our conclusions on the REGIBAR study performed in Bariloche in 2017 by Calandrelli et al. (11) This study reported an incidence of ST-segment elevation and non-ST-segment elevation myocardial infarction of 128 cases per 100 000 inhabitants and 46.7% lethality, with 90% of out-of-hospital deaths. When contextualizing these results, we observed that mortality passed from 45% in the pre-pandemic year to 52% in 2021, confirming and agreeing with the findings of the Bariloche study.

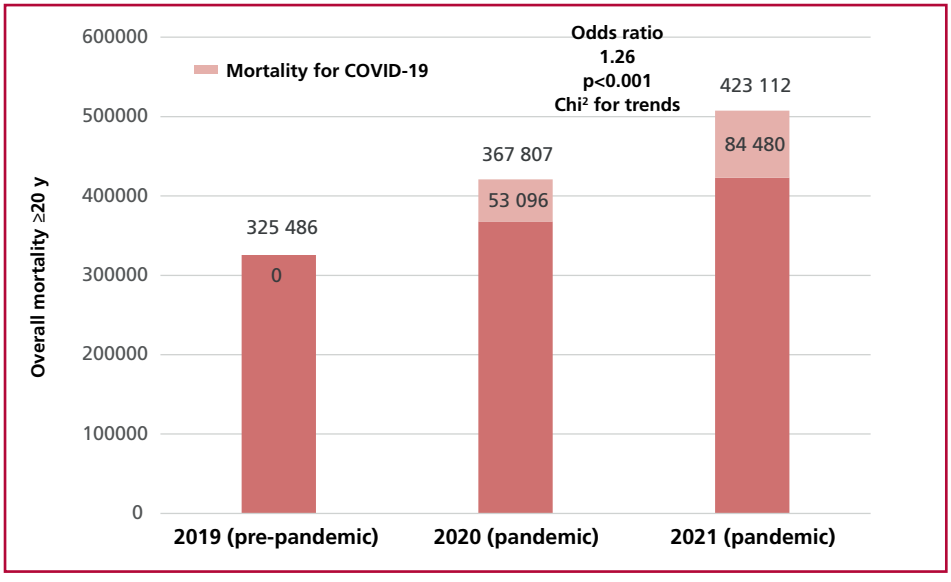
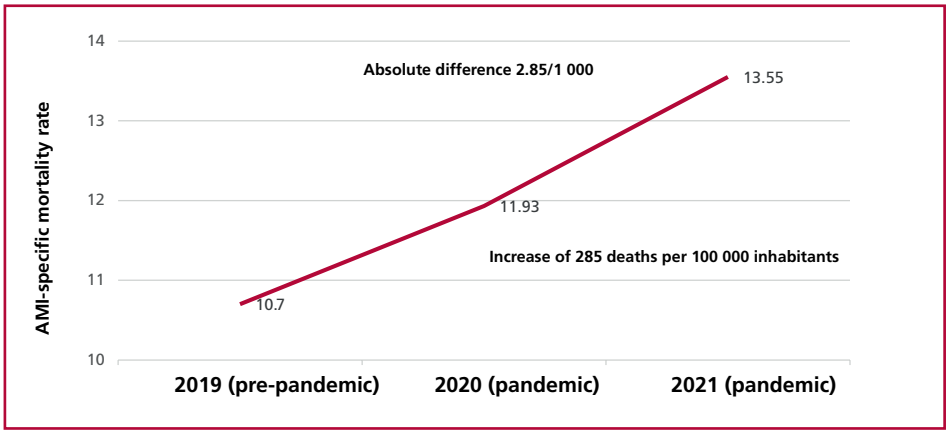
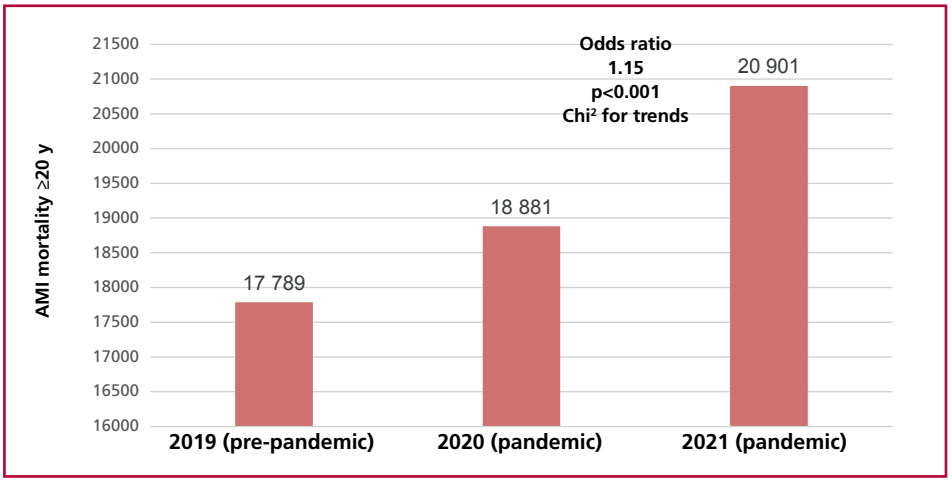


Fig. 1. Increase of overall mortality with respect to the pre-pandemic period (2019) Mortality increased by 26% especially due to COVID-19 deaths.



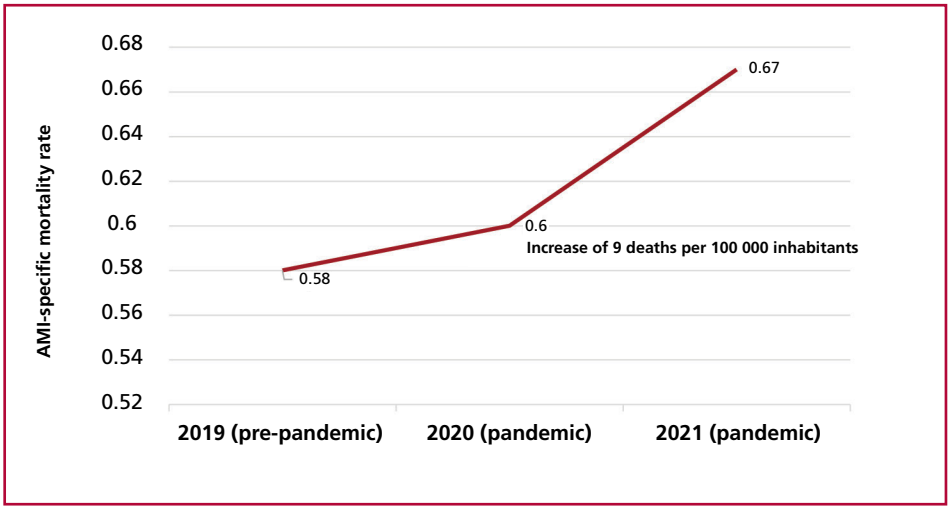
AMI: acute myocardial infarction

Fig. 2. Increase of gross mortality rate with respect to 2019 and number of deaths per 100 000 inhabitants.



AMI: acute myocardial infarction

Fig. 3. Increase of AMI mortality



AMI: acute myocardial infarction

Fig. 4. Increase of infarct mortality with a peak in 2021. AMI mortality rate.

The data provided by the Ministry of Health vital statistics do not identify in-hospital and out-of-hospital mortality. However, in line with the REGIBAR study, demonstrating that 90% of AMI deaths are out-of-hospital, the combination of this trend with the marked decrease in procedures such as coronary angioplasties and central cardiac surgeries during the pandemic, together with the delayed times of patient consultation, suggest that excess mortality could be due to a collateral SPMI effect, especially considering that survival in AMI is time-dependent. (12,13)

An additional aspect deserves to be considered when approaching the increase in mortality, focusing on the direct consequences of the COVID-19 infection in the cardiovascular system. Recent investigations underline the virus capacity to directly affect the heart, with inflammatory and procoagulant responses that contribute to cardiovascular complications, evidenced by subendocardial injury and a marked increase of mortality in this group of patients. (14,15) The relationship between the COVID-19 infection and preexisting cardiovascular conditions has been the subject of extensive attention in the scientific literature. Data from observational studies and meta-analyses suggest that patients with underlying cardiovascular diseases could face a substantially higher risk of severe complications and mortality for COVID-19, in addition to stimulating prothrombotic states. (16,17) Moreover, it is essential to consider the possibility of erroneous AMI diagnoses, as these might be confused with myocarditis, a well-documented phenomenon in the present pandemic. (18) This overlapping in the clinical presentations highlights the complexity in the identification between acute cardiovascular events and complications derived from the viral infection, adding a level of difficulty when approaching specific mortality associated with AMI.

Female subgroups and subjects below 60 years of age

The higher increase of female mortality is an aspect that deserves analysis. Although the underlying causes were not explored in this study, prior investigations have suggested that women tend to present atypical AMI symptoms compared with men, hampering diagnosis and the search for adequate medical care. Social and cultural barriers can also influence in the lower inclination of women to seek medical care, which could have been exacerbated during the pandemic, as well as the lack of knowledge that the main cause of female death is cardiovascular, as shown by Dr. del Sueldo et al. in a recently published survey in 1500 women, who perceived cancer as the main health problem, and where only 16% considered cardiovascular causes as the leading cause of death. (19)

The impact of SPMI and the pandemic in younger groups also merit attention. The pronounced increase of AMI mortality in patients below 60 years agrees with a recent publication from the Centers for Disease Control and Prevention (CDC), showing that in younger and middle-age groups, AMI-associated mortality increased by 5.3% and 3.4%, respectively. Hypothetically, this could be attributed to different factors, as the perception of lower risk of cardiovascular disease in young populations, or the concern of hospital viral exposition. These trends are similar to reports on health behavioral changes during the pandemic, as the reduction of physical activity and the increase of an unhealthy diet, especially in the young population. (20-22)

Limitations

Death certificates have a strong limitation to confirm the cause of death in case this is not dubious, due to the lack of necropsies.

Infarct classification in the out-of-hospital setting is always speculative.

The incidence of AMI in Argentina is unknown.

We cannot rule out if only SPMI has been the cause of a greater prevalence of AMI deaths, or if a direct damage caused by COVID-19 could have played a role, due to the cytokine release syndrome, deregulation of the renin-angiotensin system, destabilization of the atherosclerotic plaque or coagulation disorders.

CONCLUSIONS

The present study highlights how a health crisis of great magnitude, as the COVID-19 pandemic, can have a significant impact on AMI mortality. The answers of Public Health, though necessary to control virus propagation, should also carefully consider the involuntary collateral effects in the care of other critical diseases. The adaptation of strategies to balance virus restraint with the provision of adequate medical care is essential to minimize unforeseen negative consequences in situations of crisis. This study contributes to the growing understanding of the complex interactions between cardiovascular medical care and global health crises.

Conflicts of interest

None declared.

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

Financing

None.

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ORIGINAL ARTICLE

Burnout Survey among SAC Cardiologists

Encuesta burnout (¿estás quemado?) en Especialistas de Cardiología SAC

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ABSTRACT

Background: Healthcare professionals are exposed to an occupational phenomenon as a result of chronic stress in the workplace, called burnout syndrome (BOS). Burnout has become currently one of the most important psychosocial occupational hazards, and generates significant healthcare costs.
Objective: The aim of our study was to evaluate the subjective perception of the prevalence of BOS among cardiologists of the Argentine Society of Cardiology (SAC) using Maslach Burnout Inventory (MBI), and the differences between sexes.
Methods: We conducted an observational, cross-sectional study using an anonymous survey distributed among SAC members in April 2023. The information collected included the subjective impression of BOS (feeling "burned out"), sex, age and years of practice. The participants could optionally complete the MBI (subscales) to establish the diagnosis of BOS.
Results: A total of 756 professionals participated in the survey; 51.4% were women. Sixty-two percent of the participants were > 40 years old, and 61% had been practicing medicine for more than 10 years. Of all the physicians surveyed, 94.4% completed the MBI, with women more likely to do so than men (96.6% vs. 91.3%, p < 0.001).
The prevalence of BOS, assessed by a high MBI score (≥ 67), was 75%, while 69% reported feeling burned out (p<0.001).
Of those who felt burned out (69%), 96.8% completed the MBI, and 78% of them received a diagnosis of BOS based on high MBI scores.
Of the 31% who did not feel burned out, 89.3% completed the MBI. BOS was diagnosed in the emotional exhaustion subscale in 24%, in the depersonalization subscale in 18%, and in the personal accomplishment subscale in 10%.
The diagnosis of BOS made by high MBI score was more common in survey participants under 40 years than in older participants (50% vs. 28%, p < 0.001) and in professionals who have been practicing medicine for less than 10 years (45% vs. 20% in those with more years of practice, p<0.001).
Women were more likely to experience BOS according to their own perception (77% vs. 56%, p<0.001) and MBI score (80% vs. 74%, p<0.001), specifically in the emotional exhaustion (37% vs. 29%, p<0.001) and personal accomplishment (37% vs. 41%, p<0.001) subscales, with no differences by sex in the depersonalization sphere.
Conclusion: BOS was found to be prevalent among the surveyed cardiologists, particularly in female participants, as indicated by both their own perception and the MBI assessment. In addition, 1 out of 4 professionals surveyed who did not feel "burned out" tested positive for BOS.
Given the high prevalence of BOS among cardiologists, coordinated and sustained prevention and intervention actions should be undertaken to change this reality that negatively impacts both patient and physician health.

Key words: Cardiologists - Burnout - Exhaustion - Risk - Prevention

RESUMEN

Introducción: Los profesionales de la salud se encuentran expuestos a un fenómeno ocupacional que resulta del estrés crónico en el ámbito laboral llamado síndrome de burnout (SBO). Este se ha convertido en uno de los riesgos laborales psicosociales más importantes en la sociedad actual y genera costos significativos en el ámbito de la salud.
Objetivo: Evaluar la prevalencia de SBO por percepción subjetiva y mediante la aplicación del inventario del síndrome del Desgaste Ocupacional "Burnout" de Maslach (MBI) en los especialistas de cardiología del padrón de la Sociedad Argentina de Cardiología (SAC), y las diferencias acordes al sexo.
Material y métodos: Estudio observacional, de corte transversal, mediante una encuesta anónima realizada en abril de 2023 a los especialistas del padrón SAC. Se recabaron datos sobre impresión subjetiva de SBO (sentirse "quemado"), sexo, edad, tiempo de ejercicio profesional. Fue opcional completar el inventario MBI (subescalas) para establecer el diagnóstico de burnout.
Resultados: Participaron 756 profesionales, 51,4 % fueron mujeres. El 62 % tenían más de 40 años y el 61 % tenía más de 10 años de ejercicio profesional. Del total de médicos encuestados, el 94,4 % eligió realizar el test de Maslach (MBI), siendo esto más frecuente en las mujeres (96,6 % vs 91,3 %, p<0,001).

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La prevalencia de SBO por un MBI de alto puntaje (≥ 67puntos) fue del 75 % y la prevalencia de percepción de SBO fue del 69 % (p< 0,001).
De los que se autopercibieron "quemados" (69 %), el 96,8 % contestó el inventario MBI y se confirmó el diagnóstico de SBO por MBI de alto puntaje en el 78 %.
De los que se autopercibieron "no quemados" (31 %), el 89,3 % completó el inventario MBI con diagnóstico de SBO en la subescala cansancio emocional (24 %), despersonalización (18 %) y realización personal (10 %) más allá de no tener la impresión subjetiva de estar "quemado".
Los menores de 40 años tuvieron más SBO por MBI de alto puntaje (50 % vs 28 %, p= 0,001) al igual que los profesionales con menos de 10 años en el ejercicio de su profesión (45 % vs 20 % en aquellos con tiempo mayor, p<0,001).
El SBO fue más prevalente en las mujeres que en los hombres, tanto por autopercepción (77 % vs 56 %, p<0,001) como por el inventario de Maslach (80 % vs 74 %, p=0,001), específicamente en la subescala agotamiento emocional (37 % vs 29 %; p<0,001) y realización personal (37 % vs 41 %, p<0,001), sin diferencias por sexo en la esfera de despersonalización.
Conclusión: El SBO tiene alta prevalencia entre los cardiólogos encuestados, principalmente en mujeres, tanto por autopercepción como por aplicación del inventario MBI. Por otro lado 1 de cada 4 profesionales encuestados que no se autopercibían "quemados" tuvieron un test positivo para SBO.
Teniendo en cuenta la alta prevalencia de SBO entre los especialistas en cardiología es imperioso realizar acciones de prevención e intervención concertadas y sostenidas para transformar esta realidad que impacta desfavorablemente tanto en la salud de los pacientes como en la de los propios médicos.

Palabras claves: Cardiólogos - Burnout - Agotamiento - Riesgo -Prevención

INTRODUCTION

A mounting body of evidence indicates that healthcare professionals are exposed to an occupational phenomenon as a result of chronic stress in the workplace. (1,2) Burnout has become one of the most important psychosocial occupational hazards today and generates significant health care costs. (3,4)

Burnout syndrome (BOS) is an individual response to chronic work stress that develops progressively and can eventually become chronic, resulting in detrimental health effects. (5) From a psychological point of view, this syndrome causes damage at cognitive, emotional, and attitudinal levels, which affects the performance of the individual and their environment. (6) However, it is not a personal problem, but a consequence of certain characteristics of the work activity. (7)

The term was introduced in the psychological sphere by Freudenberger, (7) who described burnout as a state of exhaustion, fatigue and frustration due to a professional activity that fails to produce the expected expectations. Later, Maslach (8) introduced the concept of burnout in the scientific literature and defined it as a gradual process of fatigue, cynicism and reduced commitment among social care professionals. Years later, after conducting numerous empirical studies, Maslach and Jackson (9) revised the concept of burnout to generate a more rigorous and operational definition, and defined burnout as a psychological syndrome that can occur in caregivers and is characterized by emotional exhaustion, depersonalization, and a reduced sense of professional efficacy. Empirical studies indicate that exhaustion and depersonalization constitute the core or key dimensions of BOS at work, while lack of professional accomplishment is considered an antecedent of burnout, or even a consequence. Maslach's and Jackson's description of exhaustion is widely accepted in scientific literature and the Maslach Burnout Inventory (MBI) is the most objective and validated tool to diagnose BOS. Although there are no cut-off scores to determine the presence or absence of clinical burnout, it is defined by high levels of emotional exhaustion and depersonalization and low levels of personal accomplishment. The MBI scores for the diagnosis of burnout are classified in low (1-33), medium (34-66), and high (67-99). (10,11)

Burnout syndrome greatly affects both the personal and work lives of workers, as well as the economy and public health of nations. For this reason, the World Health Organization (WHO) has added burnout in the 11th Revision of the International Classification of Diseases (ICD-11) as an occupational phenomenon (12) and urged countries to conduct regular surveys to establish its prevalence among physicians, (13) which ranges from 35% to 60% across various medical specialties.

In the last Medscape Cardiologist Lifestyle, Happiness & Burnout Report 2023, 29% of cardiologists in the United States said they felt burned out and 14% were burned out and depressed. (14) Due to the significance of this subject and the absence of local data among cardiologists, we decided to conduct the current investigation. The aim of our study was to evaluate the subjective perception of the prevalence of BOS among the Argentine Society of Cardiology (SAC) cardiologists, using Maslach Burnout Inventory (MBI), and the differences between sexes.

METHODS

We conducted an observational, cross-sectional study using an anonymous survey with closed questions developed in REDCap. The participation was voluntary. The information collected included the subjective impression of BOS (feeling "burned out"), sex, age, years of practice, and risk factors (hypertension, family history, diabetes, dyslipidemia, and cardiovascular disease). The participants could optionally complete the MBI to establish a diagnosis of BOS through the assessment of the subscales (emotional exhaustion, depersonalization and personal achievement).

The survey was distributed via email, WhatsApp and different social networks (Instagram and Facebook, among others) to cardiologists included in the register of SAC members. The access to the survey was through an online link, which was opened during April 2023. The distribution message on social networks stated that the survey was limited to cardiologists exclusively. The survey is published in the Appendix.

Statistical analysis

Qualitative variables are expressed as percentages and were compared using the chi-square test or Fisher's test, as appropriate. Quantitative variables are expressed as median and interquartile range (IQR) and were compared using the Mann Whitney test.

The diagnosis of BOS was made using a score ≥ 67 points in the MBI. The percentage of males and females who responded the survey was analyzed, as well as the proportion categorized by sex with their subjective impression of BOS and burnout in the different subscales. The total score obtained in the MBI was analyzed, along with the score of each of its components (subscales) by sex, age, years of practice and subjective perception.

Multivariate analysis was performed to determine whether stress, measured objectively by the MBI, is a predictor of cardiovascular disease after controlling for classic confounders (hypertension, diabetes, dyslipidemia, etc.).

A two-tailed p value < 0.05 was considered statistically significant.

Ethical considerations

The protocol was evaluated and approved by the Committee on Ethics of the Argentine Society of Cardiology through the PRIISA.BA platform of the Ministry of Health of the City of Buenos Aires. Since this survey was anonymous and self-administered, participants were not required to give informed consent. The survey was conducted following national and international ethical standards for research on human subjects, as the Declaration of Helsinki revised in 2013, National Ministry of Health resolution 1480/2011, law N° 3301 of the city of Buenos Aires, and ANMAT regulation 6677/10 and amendments 4008 and 4009. Data privacy among respondents was protected through anonymity in the electronic survey.

RESULTS

A total of 756 professionals participated in the survey; 51.4% were women. Sixty-two percent of the participants were > 40 years old, and 61% had been in the profession for more than 10 years.

Of all the physicians surveyed, 94.4% completed the MBI, with women more likely to do so than men (96.6% vs. 91.3%, $p < 0.001$).

The rate of BOS, assessed by a high MBI score (≥ 67), was 75%, while 69% reported feeling burned out ($p < 0.001$). (Figure 1)

Of those who felt burned out (69%), 96.8% completed the MBI, and 78% of them received a diagnosis of BOS based on high scores. Of the 31% who did not feel burned out, 89.3% completed the MBI. Burnout syndrome was diagnosed in the emotional exhaustion subscale in 24%, in the depersonalization subscale in 18%, and in the personal accomplishment subscale in 10%. (Table 1).

Those who felt burned out completed the MBI more often than those who did not feel burned out (96.8% vs. 89.3%, $p < 0.001$).

The diagnosis of BOS made by high MBI score was more common in survey participants under 40 years than in older participants. Similarly, professionals who have been practicing medicine for less than 10 years had a higher prevalence of BOS compared to those with more years of practice (Table 1).

Women were more likely to experience BOS according to their own perception (77% vs. 56%, $p < 0.001$) and MBI score (80% vs. 74%, $p < 0.001$) (Figure 2). This was particularly true in the emotional exhaustion (37% vs. 29%, $p < 0.001$) and personal accomplishment (37% vs. 41%, $p < 0.001$) subscales. No differences by sex were found in the depersonalization sphere. (Figure 3)

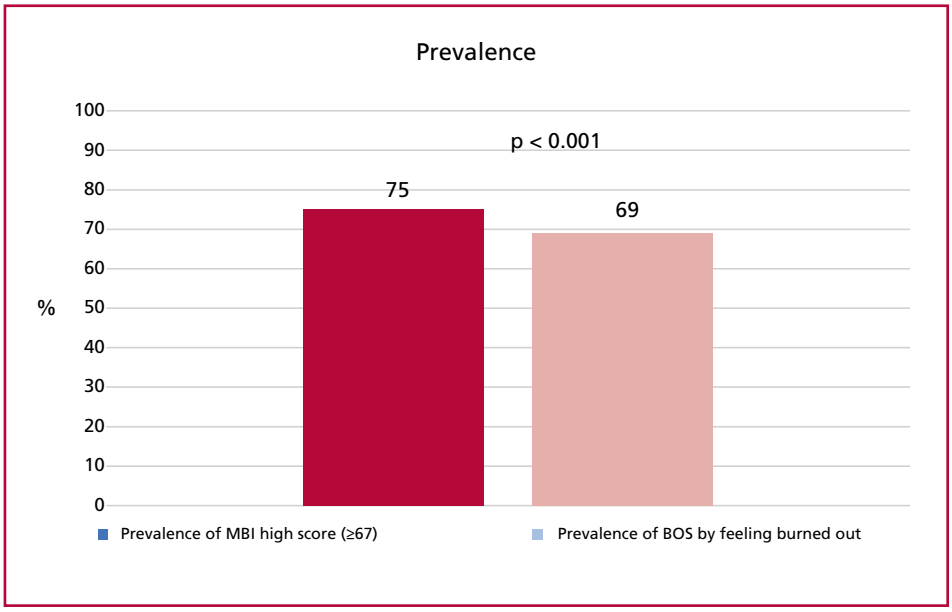
As for traditional risk factors for cardiovascular disease, hypertension was reported by 17% of respondents, more frequently in men (25.7% vs. 9%, $p < 0.001$). There were no differences in the prevalence of diabetes (5.2%) between men and women. Dyslipidemia was more common in men (31% vs. 17%, $p < 0.001$), but the history of cardiovascular disease was similar in men and women (14%). We could not determine how BOS affects cardio-metabolic health by analyzing survey data, as most of the data did not show any significant results.

DISCUSSION

The impact of physician burnout on the quality and efficiency of patient care is becoming increasingly recognized. In fact, the American Heart Association states that physician well-being is crucial for ensuring quality patient care and academic activities. (15,16) A hostile work environment, no control over workload, and insufficient documentation time are independently associated with higher rates of burnout among cardiologists. (17) The consequences of burnout are not insignificant and include lower-quality patient care, higher rates of medical error, decreased productivity, and decreased patient satisfaction. The consequences of physician exhaustion include broken personal relationships, substance use, depression, and even suicide. (18-20)

In the Medscape Cardiologist Lifestyle, Happiness, and Burnout Report 2022, (21) 47% of U.S. cardiologists were burned out, particularly among female cardiologists (55% vs. 40%). On the other hand, the Medscape Report 2023 (BOS 29%) showed no sex differences in job burnout. (14) Bureaucratic tasks were cited as the primary cause of burnout among cardiologists in both 2022 and 2023. Physicians overall mostly chose positive coping mechanisms such as exercise, meeting with family and/or friends, and getting more sleep. (14,21)

In the paper "Burnout and Career Satisfaction Among U.S. Cardiologists" by the American College of Cardiologists, more than one-quarter of respondents (26.8%) reported being "burned out". (13)



MBI: Maslach Burnout Inventory; BOS: burnout syndrome

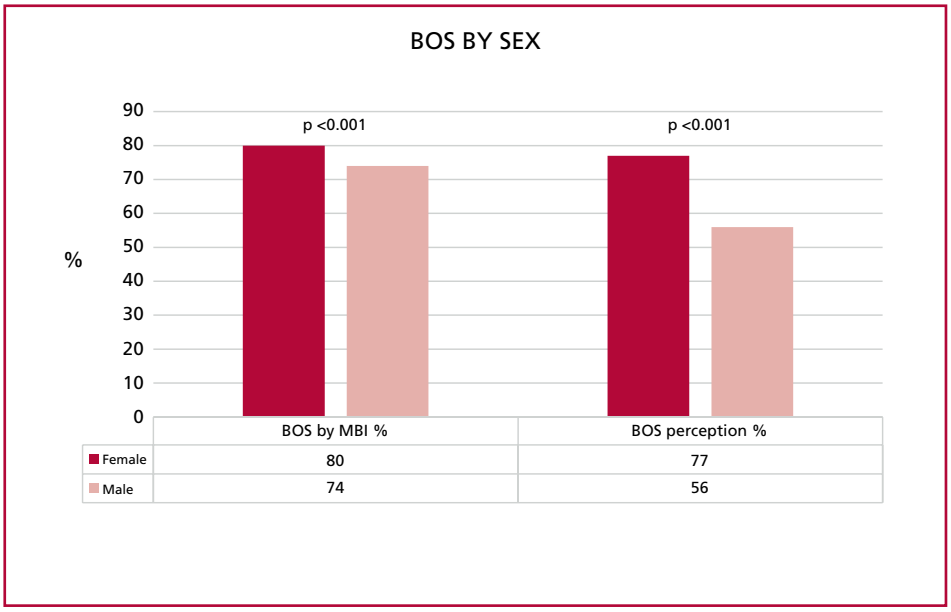
Fig. 1. Prevalence of BOS.

Table 1. Not burned out vs. burned out by high score (≥ 67)

	MBI score ≤ 66 (n= 192	MBI score ≥ 67 n= 568	p
Female sex, %	45	54	0.032
Male sex, %	55	46	
Age, %			
<30 years	4	8	
31- 40 years	15	36	
41-50 years	25	27	
51-60 years	33	19	
> 60 years	47	10	
Age > 40 years, %	72	50	<0.001
Diabetes, %	4.7	5,4	0.732
Hypertension, %	22	16	0.056
Dyslipidemia, %	32	21	0.003
BMI, median (IQR 25-75)	25 (23-27,7)	25 (23-28)	0.909
> 10 years of practice, %	80	55	<0.001
Cardiovascular disease, %	18	13	0.072
Burnout perception, %	35	78	<0.001
Emotional exhaustion subscale, median (IQR 25-75)	14 (9-21)	39 (31-46)	<0.001
Depersonalization subscale, median (IQR 25-75)	2,5 (1-6)	9 (4-15)	<0.001
Personal accomplishment subscale, median (IQR 25-75)	41 (32-46)	38 (32-43)	0.003

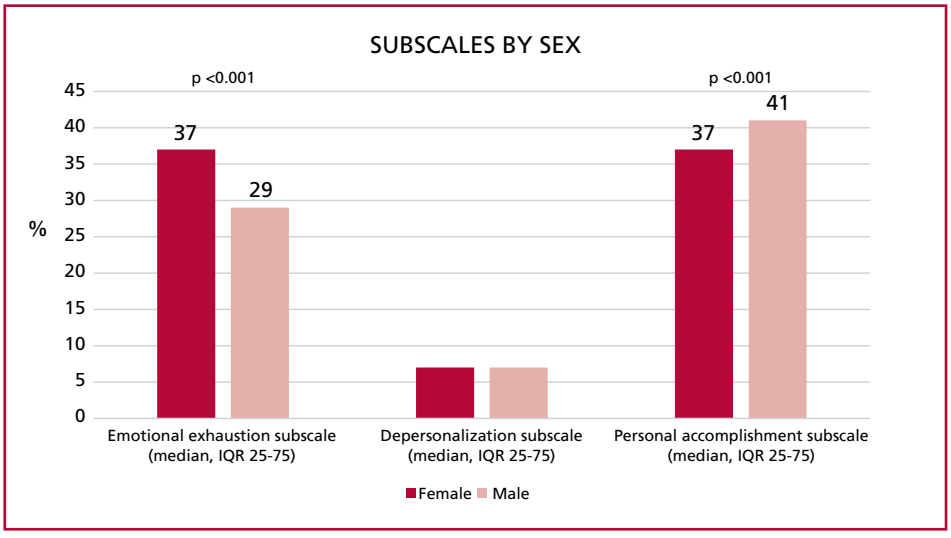
MBI: Maslach Burnout Inventory; IQR: interquartile range

Fig. 2.



MBI: Maslach Burnout Inventory; BOS: burnout syndrome

Fig. 3.



IQR: Interquartile range

Our data indicates a greater rate of BOS, both subjectively (69%) and as determined by MBI (75%), and like in other countries, it is more prevalent among women. Female doctors face a multitude of responsibilities and tasks assigned by men (multitasking), apart from their work overload. This situation can worsen self-awareness and self-regulation, adversely affecting cognitive, emotional, social, and physiological health predictors. (22-24)

It is unclear why burnout is more prevalent in this study compared to the cited reports, although the likely drivers of burnout include low pay, unrealistic efficiency/productivity targets, limited time for each patient visit, high administrative burden, the need for moonlighting, job insecurity, loss of autonomy associated with intense work, financial stress, and increasing negative opinions towards physicians. (25, 26) In terms of the perception of workplace well-being, a recent survey conducted on labor equity, gender violence, and cardiovascular risk factors among Argentine cardiologists included in the register of the Argentine Society of Cardiology, (27) revealed that 66% of specialists believed their workload was excessive, with no significant differences between genders. Furthermore, over half (66%) reported that their remuneration was not commensurate with their professional and academic training, particularly among female specialists.

According to our report, participants under the age of 40 and those with less than 10 years of practice had a higher prevalence of burnout syndrome diagnosed by a high MBI score. This data aligns with prelimi-

nary figures from a recent survey on 250 cardiology residents, in which 8 out of 10 (83%) considered the possibility of emigrating to practice their profession in another country. Insecurity, poor working conditions, low wages and a high workload are some of the underlying reasons. (28)

Occupational burnout among physicians is primarily attributable to problems in the practice environment rather than to new regulations or professional roles. Aspects of the practice environment contribute to the distress experienced by individual physicians. These dimensions have been well characterized and include stereotypes: physicians should be insensitive to normal human limitations (i.e., superhuman), work should always come first, and seeking help is a sign of weakness. These mindsets lead many physicians to engage in unhealthy levels of self-sacrifice manifested by excessive work hours, anxiety about missing something that would benefit their patients, and prioritizing work over personal health. (26)

Several studies conducted in different fields have revealed another disorder called the "impostor phenomenon", which describes a psychological experience of intellectual and professional fraudulence in both men and women. This phenomenon can be structured in the individual as a real syndrome associated with both personal (e.g., low emotional well-being, problems with work-life integration, anxiety, depression, suicide) and professional (e.g., impaired job performance, occupational burnout) consequences. (29,30) Medical students seem to be more exposed, with 1 in 4 students experiencing the impostor phenomenon, and those who experience it are at higher risk for professional burnout. (31)

Burnout appears to be a risk factor for psychiatric problems, such as depression, anxiety disorders, substance use, post-traumatic stress disorder, and neurocognitive problems, as well as family and relationship problems. (32)

The scientific literature suggests that implementing individual-centered and structural/organizational strategies can result in clinically significant decreases in physician burnout. (33,34)

CONCLUSION

BOS was found to be prevalent among the surveyed cardiologists, particularly in female participants, as indicated by both self-perception and the MBI assessment. In addition, 1 out of 4 professionals surveyed who did not feel "burned out" tested positive for BOS. Interestingly, compared with other studies, burnout rates were higher among cardiologists. Our data necessitate improving our efforts to determine the causes of burnout and design solutions at the individual and organizational levels. Defining the outlines of burnout provides us with a common language and a space to discuss this emerging scourge in the field of medicine today. We can utilize this comprehension of burnout to further develop interventions, explore them, and effectively tackle them to promote better health for everyone.

Conflicts of interest

None declared.

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

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APPENDIX

MASLACH BURNOUT INVENTORY (MBI)

- Author: Christina Maslach (San Francisco, United States - 1946)
- Coauthors: Susan E. Jackson & Michael P. Leiter
- Published: 1981 - 2016
- Origin: United States
- Study variable: Burnout syndrome
- Components evaluated: Emotional exhaustion, depersonalization, cynicism, personal accomplishment
- Administration: healthcare workers (cardiologists)
- Number of items: 15-22 (according to the component)
- Type of items: 7-point Likert scale

Item	Value
Never/Not once	0
Rarely/Several times per year	1
Sometimes/At least once a month, or less	2
Often/Several times per month	3
Frequently/Once a week	4
Usually/Several times per week	5
Always/ Every day	6

- Subscales for the MBI-HSS form

Subscale	Code	Items	Number of items	Score per item	Score per subscale	Sign of burn out
Emotional exhaustion	EE	1, 2, 3, 6, 8, 13, 14, 16, 20	9	From 0 to 6	From 0 to 54	> 26
Depersonalization	DP	5, 10, 11, 15, 22	5	From 0 to 6	From 0 to 30	> 9
Personal accomplishment	PA	4, 7, 9, 12, 17, 18, 19, 21	8	From 0 to 6	From 0 to 48	< 34

- Assessment

Subscale	Low level	Moderate level	High level
Emotional exhaustion	From 0 to 18	From 19 to 26	From 27 to 54 (*)
Depersonalization	From 0 to 5	From 6 to 9	From 10 to 30 (*)
Personal accomplishment	From 0 to 33 (*)	From 34 to 39	From 40 to 56

(*): Burnout syndrome symptoms

The Maslach Burnout Inventory is a questionnaire for the evaluation of the work environment. It evaluates the burnout syndrome, which is a type of chronic stress experienced by workers subjected to heavy and routine work. The usual manifestation is that their attitude towards their job changes.

This questionnaire was designed by Christina Maslach and Susan Jackson in 1981 to assess job burnout in human service professionals. However, there are other versions of the inventory that assess workers in the education field and various other occupations.

ORIGINAL ARTICLE

Predictors of Mild Cognitive Impairment in a Hypertensive Population

Predictores de riesgo de deterioro cognitivo leve en una población de hipertensos

VALENTINA D. MÁS[1], MARÍA N. RIVERO[1], PAOLA M. SPÓSITO[1], XIMENA CUBA[1], MARIO LLORENS[1]

ABSTRACT

Background: Cognitive status is considered a biomarker of vascular brain damage caused by hypertension (HTN). Screening for mild cognitive impairment (MCI) is essential in patients with HTN.
Objective: The aim of this study was to evaluate the presence of predictors of MCI in hypertensive patients.
Methods: We conducted an observational and cross-sectional study between 2015 and 2023. All the patients > 18 years treated in a clinic and who were evaluated with the Montreal Cognitive Assessment (MoCA) were included. A score < 24 in the MoCA test was considered abnormal. Patients with motor or sensory impairment, psychiatric disorders, or illiteracy were excluded. Qualitative variables are presented as absolute frequencies and percentages, and the chi-square test was used to analyze their association. Quantitative variables are expressed as mean ± standard deviation and were compared with the independent samples t-test. All the variables with statistical significance in the univariate analysis through forward selection were included in the multiple logistic regression analysis. A p value < 0.05 was considered statistically significant.
Results: A total of 129 patients were included (women-to-men ratio 2:1; mean age 60 years); 79.1% had stage 3 HTN, time from HTN diagnosis was > 20 years in 30.4%, 52.7% had complete primary education, 89.4% had overweight/obesity, 36.4% were smokers and 29.7% had mixed dyslipidemia. A score ≥ 24 in the MoCA was present in 65.1% and 34.9% had a score < 24. The logistic predictor model identified time from HTN diagnosis, mixed dyslipidemia and cerebrovascular disease as predictors of abnormal MoCA. A tertiary educational level had a protective effect.
Conclusions: Identifying predictors of cognitive impairment is a priority to take preventive actions. In this study, time from HTN diagnosis, mixed dyslipidemia, cerebrovascular disease and educational level were associated with cognitive impairment.

Key words: Mild cognitive impairment - Hypertension - Montreal Cognitive Assessment

RESUMEN

Introducción: El estatus cognitivo es considerado un biomarcador del daño vascular encefálico en la hipertensión arterial (HTA). Es fundamental en pacientes con HTA la pesquisa del deterioro cognitivo leve (DCL).
Objetivo: Valorar la presencia de factores predictores de DCL en pacientes hipertensos.
Material y métodos: Estudio observacional, transversal, en el periodo 2015-2023. Se incluyeron pacientes mayores de 18 años, asistidos en policlínica que hubieran realizado la Evaluación Cognitiva de Montreal (MoCA). Se consideró valor de MoCA alterado uno < 24. Se excluyeron pacientes con dificultades motoras, sensoriales, enfermedad psiquiátrica, analfabetismo. Las variables cualitativas se presentan como frecuencias absolutas y relativas, y para el estudio de asociación se utilizó test de Chi cuadrado. Las variables cuantitativas se presentan como media y desviación estándar, y el estudio de diferencias se realizó con test T de Student para muestras independientes. En el análisis de regresión logística múltiple se colocaron aquellas variables significativas en el análisis univariado por el método Forward. Nivel de significación alfa = 0,05.
Resultados: 129 pacientes, mujeres: hombres 2:1; edad promedio 60 años. El 79,1 % tenía HTA grado 3, 30,4 % presentaban más de 20 años de evolución de HTA. El 52,7% tenía escolarización primaria. Un 89,4 % presentaba sobrepeso-obesidad, el 36,4 % tabaquismo, 29,7 % dislipidemia mixta. Un 65,1% presentó un valor de MoCA ≥ 24 y el 34,9 % un valor < 24. En el modelo predictor logístico, las variables evolución en años de HTA, dislipidemia mixta, y enfermedad cerebrovascular fueron predictoras de riesgo de MoCA alterado. El nivel educativo terciario fue factor protector.
Conclusiones: La identificación de factores predictores de daño cognitivo es prioritaria para una acción preventiva. En este estudio las variables tiempo de evolución de la HTA, dislipidemia mixta, enfermedad cerebrovascular y nivel educativo permitieron predecir mayor riesgo de DCL.

Palabras clave: Deterioro cognitivo leve - Hipertensión arterial - Evaluación cognitiva de Montreal

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INTRODUCTION

Most countries worldwide are experiencing growth in both the size and the proportion of older persons in the population. According to the United Nations, population aging is poised to become one of the most significant social transformations of the 21st century, affecting all sectors of society. Uruguay began its aging process at the beginning of the 20th century, earlier than other countries in the region. Nowadays, along with Cuba they are the two countries in the region with the highest incidence of elderly population. (1).

The World Health Organization (WHO) has been leading international action plans under the framework of the "United Nations 2021–2030 Decade of Healthy Aging" program. The goal is to promote healthy aging, which aims to develop and maintain functional capacity to enable well-being in old age. Functional ability is closely related to intrinsic capacity, defined as "composite of all physical and mental capacities of an individual". (2) The intrinsic capacity framework includes cognitive ability and is a significant aspect of the "WHO Integrated Care for the Elderly" (ICOPE) program. (3)

Dementia, a major neurocognitive disorder, is one of the leading causes of disability and dependency among older people worldwide. In high-income countries, individuals with dementia face a mortality risk that is two-and-a-half times higher. Nonetheless, it is underdiagnosed, and when it is diagnosed, it is typically in advanced stages. Lack of understanding of the disease, combined with stigma, creates barriers to early diagnosis and the immediate care that patients need. There is a misconception that memory problems are a normal part of aging and that nothing can be done about them. (4)

The onset of dementia is preceded by mild cognitive impairment (MCI) and subjective memory or cognitive complaint (CC). Mild clinical impairment is a clinical syndrome characterized by impairment in memory or other cognitive function, without significant impairment in the ability to perform activities of daily living. It is a defined clinical-pathological entity, which identifies subjects who are in an intermediate state between normal aging and dementia. The course of MCI is variable and can progress to dementia, remain stable or regress, which defines it as an important diagnostic and therapeutic target. (5-7)

The criteria for the diagnosis of MCI are frequent memory complaints, abnormal memory on cognitive testing (adjusted for age and education level), normal activities of daily living, and absence of dementia. (5,6)

The Montreal Cognitive Assessment (MoCA) is a screening tool for MCI with good results in the international literature that has been translated into several languages and validated in numerous countries. The results have shown high internal consistency and predictive validity. (8) This tool evaluates 6 cognitive domains (memory, visuospatial skills, executive functions, attention/concentration/working memory, language, and orientation). The total possible score is 30 points. A score < 26 indicates MCI, with a sensitivity of 89 % and specificity of 75%. In a cohort of 137 patients treated at Hospital Maciel in Montevideo, Uruguay, a MoCA cut-off point < 24 was associated with a sensitivity of 88.9% and specificity of 78.9% to detect MCI. (9)

Environmental and genetic factors have been described in the pathogenesis of MCI, both in its onset and progression. Environmental factors include low educational level, depression in the elderly, hearing loss, social isolation, and cardiovascular risk factors (CRF) such as hypertension (HTN). It is estimated that over 80% of patients with HTN are not adequately controlled. Uncontrolled and untreated HTN is associated with cognitive impairment and dementia. (10,11)

Cognitive status is internationally considered a biomarker of vascular brain damage caused by HTN. The 2023 European Society guidelines for the management of HTN recommend performing cognitive function testing as part of the clinical evaluation of hypertensive patients. Therefore, it is important to have appropriate screening tests available during medical visits. Thirty percent of hypertensive patients without involvement of other organs present vascular brain damage and cognitive impairment. The time from HTN diagnosis, HTN stage and variability of blood pressure levels, and the loss of the physiological dipper pattern are associated with impaired cognitive function. (12,13)

For this reason, the aim of this study was to evaluate the presence of predictors of MCI in a hypertensive population.

METHODS

We conducted a descriptive, observational, and cross-sectional study between May 2015 and January 2023 at the Hypertension Clinic of Hospital Maciel in Montevideo, Uruguay. Patients treated in the Clinic sign a general informed consent form, which is then recorded anonymously in the database.

All the patients > 18 years evaluated with the MoCA were included. Patients with motor or sensory impairment, psychiatric disorders, or illiteracy were excluded.

The following variables were analyzed:

- Sex: men and women.
- Age: in years
- Educational level: defined by the years of education completed. The educational levels are categorized as follows: incomplete primary education (less than 6 years completed), complete primary education (6 years completed), incomplete secondary education (between 7 and 11 years completed), complete secondary education (12 years completed), incomplete tertiary education, and complete tertiary education (depending on whether the corresponding syllabus has been completed).
- HTN: systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg.
- Time from HTN diagnosis: in years.
- Stage of HTN (according to ESC 2018): stage 1, SBP 140-159 and/or DBP 90-99 mm Hg; stage 2, SBP 160-179

and/or DBP 100-109 mm Hg; and stage 3, SBP > 179 and/or DBP > 109 mm Hg.
- Weight: in kg, measured with office scale.
- Height: in cm, measured with portable stadiometer.
- Overweight: body mass index (BMI) between 25 and 30 kg/m^2.
- Obesity: BMI > 30 kg/m^2.
- Diabetes mellitus (DM): fasting glycemia ≥ 126 mg/dl or incidental finding of glycemia > 200 mg/dL.
- Mixed dyslipidemia: total cholesterol > 190 mg/dL and/or LDL cholesterol > 115 mg/dL and/or HDL cholesterol < 40 mg/dL in men or 46 mg/dL in women and triglycerides > 150 mg/dL. (14)
- Pre-existing cardiovascular disease: history of ischemic heart disease (IHD), heart failure (HF), lower extremity peripheral artery disease, stroke and/or transient ischemic attack (TIA), documented in the medical record.
- CC: frequent memory loss reported by patients or caregivers.
- Cognitive impairment: according to the optimal cut-off point for the study population.
  A score < 24 in the MoCA was considered abnormal.

Statistical analysis

Qualitative variables are presented as absolute frequencies and percentages, and the chi-square test was used to analyze their association. Quantitative variables are expressed as mean ± standard deviation and were compared with the independent samples t-test. All the variables with statistical significance in the univariate analysis through forward selection were included in the multiple logistic regression analysis. All statistical calculations were performed using STATA 17.0 software package. A p value < 0.05 was considered statistically significant.

Ethical considerations

The study was evaluated and approved by the Institutional Review Board of Hospital Maciel and was conducted following the National Statement 158/19 for research on human subjects and the Declaration of Helsinki revised in 2000. Data confidentiality was maintained, and all the patients signed an informed consent form to be included in the database.

RESULTS

A total of 129 patients were included. Mean age was 60.0 ± 1.1 years and 68.2% (n = 88) were women. The majority of patients (79.1%) had HTN stage 3, and time from HTN diagnosis was > 20 years in 30.4%.

In terms of educational levels, 52.7% reported incomplete or complete primary education. Regarding CRF, 89.4% had overweight or obesity, 36.4% were smokers, and 29.7% had dyslipidemia. A score ≥ 24 in the MoCA test was present in 65.1% and 34.9% had a score < 24 points.

On univariate analysis, there were no differences between the two groups, abnormal MoCA and normal MoCA, in terms of sex, HTN stage, overweight or obesity, smoking habits, peripheral artery disease, IHD, HF, and atrial fibrillation.

The variables with statistically significant differences on univariate analysis are presented in Table 1. Multivariate logistic regress analysis identified the independent predictor variables that are shown in Table 2.

The final predictor model was made up of time from HTN diagnosis > 20 years, the presence of mixed dyslipidemia, stroke/TIA, and tertiary education level. The presence of a subjective complaint was only observed in the univariate model, but it lost statistical significance in the multivariate model.

DISCUSSION

Hypertension is the primary CRF for cognitive impairment. The age at diagnosis and the time from HTN diagnosis are significant predictors of cognitive impairment. The longer the time from HTN diagnosis, the worse the performance in both executive functions and immediate logical memory. (15-17) In the study population, time from HTN diagnosis >20 years was the main predictor of abnormal MoCA.

Hypertension has been associated with reduced abstract reasoning (executive dysfunction), slowing of mental processing speed, and, less frequently, memory deficits. (18)

Muela et al. reported that the HTN stage and educational level were the best predictors of MCI in patients with hypertension. The most affected cognitive domains were language, processing speed, visuospatial abilities, and memory. (19)

The 2023 European Society guidelines for the management of HTN recommend screening hypertensive patients > 65 years using short cognitive screening tests, such as the Mini-Mental State Examination. However, the guidelines place greater emphasis on the MoCA. A MoCA score below 24, or below 26 and subjective complains of memory loss should lead to referral to a neurologist or a geriatrician. (12)

Most of the population included in this study has stage 3 hypertension according to the 2018 ESC guidelines, probably because they are treated in clinic specialized in managing difficult cases of hypertension. However, in this study HTN stage had no significant differences between the groups with normal and abnormal MoCA. A tertiary educational level had a protective effect is this study. A high level of education is widely used as an indicator of "cognitive reserve", defined as individual ability to make flexible and efficient use of available neuronal networks in the active model (10) to cope with pathology. Patients with cognitive impairment with higher cognitive reserve have an increased capacity to cope with reduced white matter integrity and thus modulate structural brain changes. (20)

The prevalence of CRF is higher in patients with cognitive impairment compared to those who are cognitively normal. There is significant evidence linking CRF and subclinical atherosclerosis to brain health. This evidence suggests that cerebrovascular and neurodegenerative diseases often coexist and contribute to the development of dementia. Therefore, a history of stroke or TIA can be a predictor of increased risk.

Variables	Abnormal MoCA < 24 (n = 45)	Normal MoCA ≥ 24 (n = 84)	p
Educational level, n (%)			
Incomplete primary education	16 (35.6)	13 (15.5)	
Complete primary education	9 (20.0)	30 (35.7)	
Incomplete secondary education	10 (22.2)	22 (26.2)	<0.001
Complete secondary education	2 (4.4)	2 (2.4)	
Incomplete tertiary education	1 (2.2)	5 (6.0)	
Complete tertiary education	2 (4.4)	7 (8.3)	
No data	5 (11.1)	5 (6.0)	
Age, years, mean ± SD	66.1 ± 1.6	56.8 ± 1.3	<0.001
Time from HTN diagnosis, years, n (%)			
< 5 years	6 (18.9)	18 (31.6)	
5 to 10 years	7 (21.9)	12 (21.1)	<0.001
11 to 20 years	2 (6.3)	17 (29.8)	
> 20 years	17 (53.1)	10 (17.5)	
Mixed dyslipidemia, n (%)	14 (37.8)	25 (6.4)	<0.001
Diabetes, n (%)	16 (41.0)	22 (26.5)	0.029
Established CV disease, n (%)	20 (55.6)	28 (38.4)	0.003
Stroke/TIA, n (%)	12 (33.3)	14 (19.2)	0.004
Cognitive complaint, n (%)	21(56.8)	30(40.5)	0.047

CV: cardiovascular; HTN: hypertension; MoCA: Montreal Cognitive Assessment; SD: standard deviation; TIA: transient ischemic attack

Table 1. Differences between patients with abnormal MoCA and normal MoCA.

Table 2. Multivariate model to predict MCI. Independent predictors

Variable	OR	95% CI
Tertiary educational level	0.43	(0.19 - 0.71)
Time from HTN diagnosis > 20 years	5.33	(2.28 - 7.31)
Mixed dyslipidemia	2.07	(1.06 - 4.89)
Stroke/TIA	1.82	(1.25 - 3.89)

CI: confidence interval; HTN: hypertension; MCI: mild cognitive impairment; OR: odds ratio; TIA: transient ischemic attack

(21) In this population, only mixed dyslipidemia was found to be a cardiovascular risk factor to predict worse cognitive function. This may be due to the relatively low number of patients.

Cognitive complaints are a common reason for consultation, representing a significant number of patients treated in memory care units worldwide. Jonker et al. (2000) found an incidence of 25-56%. In 2005, the percentage of CC at Karolinska Memory Clinic in Huddinge, Sweden, was 38%. (22,23) Cognitive complaints are considered a stage preceding MCI and a risk factor for dementia. In a Japanese cohort of 3672 participants, CC were associated with a higher risk of dementia in cognitively intact participants but not in those with cognitive impairment (HR 4.95, 95% CI 1.52–16.11, p = 0.008). (24)

In the study population, CC only appeared as a predictor in the univariate model but lost statistical significance in the multivariate model. Wang et al. did not find any association between CC and dementia. They evaluated 543 individuals from a rural area twice during a 3-year period. In both evaluations, CC was associated with poorer performance on neuropsychological tests but not with cognitive impairment over time. (25) Based on the evidence provided by the Rotterdam study, it is possible that the characteristics of a population living in a rural setting with a low level of education may have reduced the predictive value of CC. Overall, most longitudinal studies suggest a modest positive association between CCs and future deterioration. (26) Identifying subjects at this preclinical stage would have dual utility: developing new therapeutic strategies to delay the onset of the disease and reducing the worldwide prevalence of dementia in the next 40 years. (27)

Study limitations

The study population may be biased because they are patients attending a specialized clinic with a high percentage of patients who have stage 3 hypertension and are overweight or obese.

CONCLUSIONS

Identifying predictors of cognitive impairment is a priority in preventing the development and progression of vascular dementia. Time from HTN diagnosis, mixed dyslipidemia, cerebrovascular disease, and educational level were associated with cognitive impair-

ment. In the future, it will be necessary to determine which group of individuals would be candidates for early intervention.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Predictive Capacity of Different Surgical Risk Scores in Infective Endocarditis

Capacidad predictiva de diferentes puntuaciones de riesgo quirúrgico en la endocarditis infecciosa

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ABSTRACT

Background: Infective endocarditis (IE) is a life-threatening disease that may require surgical treatment. Despite being fundamental in decision making, surgical scores were not generated specifically to stratify the risk of this disease.
Objectives The objective of this study was to: To evaluate the predictive capacity of surgical risk scores adjusted for IE.
Methods: Single-center observational and retrospective study of 270 patients > 18 years, hospitalized for active IE from 06/2008 to 02/2023, of which 70 (26%) underwent central cardiac surgery. Device-associated endocarditis and patients who did not undergo cardiac surgery were excluded. The surgical risk scores analyzed were: EuroSCORE II, EURO-IE, STS-IE and PALSUSE (Prosthesis, Age >70, large cardiac destruction, Staphylococcus, Urgency, Female gender, EuroScore >10). The predictive capacity of each score was evaluated using the C statistic, calculating the area under the curve of the sensitivity/1-specificity relationship with their respective 95% confidence intervals (CI), and statistical significance.
Results: The median age (interquartile range, IQR) was 60 years (48-67) and the number of days of hospitalization were 23 (17-39). Forty-one patients (58.57%) had a prosthetic valve. Regarding the causative germs, Staphylococcus was responsible for 30% of the infections. The main indications for surgical treatment were heart failure (44%), abscess (19%) and prosthetic dysfunction (12%). Annular abscess was observed in 28.57% of patients. Urgent surgery was performed in 45.71% and emergency surgery was performed in 7.14%. Hospital mortality was 21.42%. The predictive capacity of all scores was statistically significant, except for the STS-IE. The STS-IE score presented an area under the curve (AUC) of 0.586 (95% CI 0.429-0.743). The EuroSCORE II, an AUC of 0.685 (95% CI 0.541-0.830); the EURO-IE presented an AUC of 0.695 (95% CI 0.556-0.834) and the PALSUSE an AUC of 0.819 (95% CI 0.697-0.941).
Conclusions: The results of this study suggest that the PALSUSE score was a better predictor of surgical risk in patients with active IE, compared to the Euroscore II, EURO-IE and STS-IE scores.

Keywords: Infective Endocarditis - Heart Valve Surgery - Mortality - Risk Score

RESUMEN

Introducción: La endocarditis infecciosa (EI) es una enfermedad potencialmente mortal que puede requerir tratamiento quirúrgico. A pesar de ser fundamentales en la toma de decisiones, los puntajes de riesgo quirúrgico no fueron generados específicamente para estratificar el riesgo de esta enfermedad.
Objetivo: Evaluar la capacidad predictiva de los puntajes de riesgo quirúrgico ajustados a la EI.
Material y métodos: Estudio unicéntrico observacional y retrospectivo de 270 pacientes mayores de 18 años que cursaron internación por EI en actividad desde 06/2008 hasta 02/2023, de los cuales 70 (26%) fueron sometidos a cirugía cardíaca central. Se excluyeron las endocarditis asociadas a dispositivos, y los pacientes que no se sometieron a cirugía cardíaca. Los puntajes de riesgo quirúrgico analizados fueron: EuroSCORE II, EURO-IE, STS-IE y PALSUSE (Prótesis, Edad >70, (Large) gran destrucción, *Staphylococcus*,Urgencia,Sexo femenino,EuroSCORE>10). La capacidad predictiva de cada puntaje se evaluó por medio del estadístico C, calculando el área bajo la curva de la relación sensibilidad/1-especificidad, con sus respectivos intervalos de confianza (IC) 95%, y su significación estadística.
Resultados: La mediana (rango intercuartílico, RIC) de edad fue de 60 años (48-67) y la de los días de internación fue de 23 (17-39). Cuarenta y un pacientes (58,57%) tenían una válvula protésica. Respecto a los gérmenes causales, el *Staphylococcus* fue responsable del 30% de las infecciones. Las principales indicaciones de tratamiento quirúrgico fueron la insuficiencia cardíaca (44%), el absceso (19%) y la disfunción protésica (12%). Se objetivó absceso anular en el 28,57% de los pacientes. La necesidad de cirugía de urgencia fue del 45,71% y de emergencia del 7,14%. La mortalidad hospitalaria fue del 21,42%. La capacidad predictiva de todos los puntajes

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fue estadísticamente significativa, excepto el STS- IE . El STS-IE presentó un área bajo la curva (ABC) de 0,586 (IC 95% 0,429-0,743). El EuroSCORE II, un ABC de 0,685 (IC 95% 0,541-0,830); el EURO-IE presentó un ABC de 0,695 (IC 95% 0,556-0,834) y el PALSUSE un ABC de 0,819 (IC 95% 0,697-0,941).
Conclusiones: Los resultados de este estudio sugieren que el score PALSUSE fue mejor predictor de riesgo quirúrgico en pacientes con EI activa, en comparación con los puntajes Euroscore II, EURO-IE y STS-IE.

Palabras clave: Endocarditis infecciosa - Cirugía cardíaca valvular - Mortalidad - Puntuación de riesgo

INTRODUCTION

Infective endocarditis (IE) is a potentially fatal cardiovascular disease. During 2019, the estimated global incidence of IE was of 13.8 cases per 100 000 subjects per year, and IE accounted for 66 300 deaths. (1)Although it is a relatively rare pathology, it has a great impact on the morbidity and mortality of patients. (2-4) In this context, medical treatment alone is often inadequate and must be combined with surgical intervention. However, in critically ill patients, cardiovascular interventions can be challenging and have poor outcomes. (5) According to the EIRA III registry, the median length of hospital stay in patients admitted for IE was 28 days and during that period, surgery was indicated for 56.9% of the patients, with 22% mortality rate of the operated patients. (4)

The risk of surgical treatment during the active phase of IE is strongly influenced by pre-existing comorbidities. (6,7) Currently, the decision to indicate surgery must be made by the endocarditis team (made up of cardiologists, imaging specialists, cardiovascular surgeons, infectologists and microbiologists), (8) considering the urgency of the clinical condition, the perioperative risk, the potential for recovery from infection and the associated long-term prognosis of the patient. (9,10) For this reason, it is crucial to have precise tools to predict the outcome of the intervention.

Risk prediction scores for cardiovascular surgery (e.g., STS or EuroSCORE II) may not be ideal for IE, a rare situation in the population that originated these risk scales. (11-13) Therefore, there are scores specifically designed for this pathology, which include the STS-IE, the PALSUSE score and the EURO-IE, among others. These scoring systems have been developed based on retrospective data and their performance is variable. (13-15)

Taking this into account, choosing the appropriate score to predict mortality in a specific population of patients with IE constitutes a fundamental tool for decision making. The objective of the present work was to analyze the group of patients who undergo cardiovascular surgery for active IE, to reveal the complications related to the procedure and to evaluate the capacity of different risk scores to predict them.

METHODS

An observational and retrospective study was carried out in patients admitted between June 2008 and February 2023, with a diagnosis of definite or possible IE, according to the Duke criteria, (16) in the Hospital Universitario Fundación Favaloro, a referral center for cardiovascular surgery of the Autonomous City of Buenos Aires, Argentina. Those over 18 years of age who were hospitalized for active IE were included, and those undergoing central cardiac surgery were taken into account for the evaluation of risk scores. Patients with IE associated to devices (pacemakers, cardiodefibrillators or resynchronizers) and IE in percutaneously implanted valves were excluded.

Anthropometric data, laboratory values, clinical characteristics, and hospital outcomes were collected prospectively from the medical records. Acute renal failure (ARF, increase in serum creatinine ≥0.3 mg/dL in 48 hours), the requirement for hemodialysis (HDL), complete atrioventricular block (CAVB), stroke, transient ischemic attack (TIA), reoperation, and surgery-related infection were considered post-surgical complications.

Four risk scores specifically designed to predict in-hospital mortality after cardiovascular surgery were used (Table 1): EuroSCORE II, (11) modified EuroSCORE (EURO-IE), (13) the Society for Thoracic Surgery risk score for infective endocarditis (STS-IE) (14) and the PALSUSE scoring system. (15)

The different risk scores were compared in their predictive capacity for in-hospital mortality. Alternatively, we evaluated whether these scores were useful for predicting major complications defined as stroke, ARF, HDL, reoperation, infections, CAVB, pacemaker requirement; major complications or death; or prolonged hospitalization defined as greater than 30 days.

Statistical analysis

Quantitative variables were expressed as mean±standard deviation (SD) or median and interquartile range (IQR), according to the normal distribution evaluated by the Shapiro-Wilk test. Qualitative variables were expressed as number and percentage. Comparisons between groups were made with the Student t test for continuous variables and using the Chi2 test or Fisher's exact test for categorical variables. The Hosmer-Lemeshow test was used to evaluate the goodness of fit of the risk scores. The discrimination capacity of the models was measured by the C statistic and the receiver operating characteristic (ROC) curve, with the respective area under the curve of the sensitivity/1-specificity relationship, their 95% confidence intervals (CI) and statistical significance. The discrimination ability of the area under the curve (AUC) was considered excellent (AUC 0.90–1), good (AUC 0.80–0.90), reasonable (AUC 0.70–0.80), poor (AUC 0.60–0.70) or null (AUC 0.50–0.60). The De Long test was used to compare risk scores. A two-tailed p value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 16 (SPSS Inc, Chicago, Illinois, USA), and R version 4.3.1.

Ethical considerations

The protocol was evaluated and approved by the Institution's Ethics Committee.

Table 1. Risk scores for infective endocarditis

EuroSCORE II	EURO-IE	STS-IE	PALSUSE
Age	Previous cardiac surgery	Previous CABG	Prosthetic valve endocarditis
Gender	Critical preoperative situation	Urgency (No cardiogenic shock)	Age>70
Insulin-requiring diabetes	Creatinine clearance	Emergency/Cardiogenic Shock	Intracardiac destruction
COPD	NYHA >1	Preoperative Balloon/Inotropes	Staphylococcus spp
Extra cardiac arthropathy	Age	Multivalvular surgery	Emergency surgery
Creatinine clearance	Emergency surgery	Insulin-requiring diabetes	Female gender
Active endocarditis	Fistula	Non-insulin-requiring diabetes	EuroSCORE>10%
Previous cardiac surgery	Staphylococcus spp	Hypertension	
Pulmonary hypertension	Pulmonary hypertension	Chronic lung disease	
Recent heart attack (<90 days)	Emergency surgery	Active endocarditis	
Angor functional class		Kidney failure or Creatinine >2	
Functional class of dyspnea		mg/dL	
Reduced mobility		Arrhythmia	
Critical preoperative situation		Previous valve surgery	
Ejection fraction			
Surgical priority			
Associated intervention			
Thoracic aorta surgery			

CABG: Coronary artery bypass grafting; COPD: Chronic obstructive pulmonary disease; NYHA: New York Heart Association scale.

RESULTS

In the analyzed period, 270 patients were admitted with a diagnosis of active IE, of whom 70 required valve surgical treatment. Table 2 shows the characteristics of this population. Patients undergoing surgery were younger: 60 (IQR 48-67) vs. 69 (IQR57-76) years; p=0.001, with a more frequent prosthetic valve involvement (58.5% vs. 42%; p=0.01), and a higher percentage associated with dyspnea (42.8% vs. 19.5%; p=0.001) and heart failure (55.7% vs. 28.5%; p<0.0001). On the other hand, patients who did not undergo surgical treatment had a higher prevalence of neoplastic diseases (11.5% vs. 1.4%; p<0.0001). A similar frequency of previous endocarditis and previous predisposing procedure was observed.

Regarding the group undergoing valve replacement, the presurgical ultrasound showed that 18.5% of the population had a reduced left ventricular ejection fraction (LVEF), with mild to moderate dysfunction in 17.1% and severe in 1.4% of cases. Vegetation was observed in 77% (n=54), located in the aortic valve in 66.6%,of cases, in the mitral valve in 31.5% of cases and only 1 patient with mitro-aortic location. Prosthetic IE represented 58.6% of cases, and aortic involvement was the most frequent (80.5%). This location was also the most common among native IE (55%). The presence of abscesses was observed in 28.6% of cases, again aortic location was the most prevalent (70%). The indications for surgical treatment were heart failure (44.3%), abscess (18.6%), prosthetic dysfunction (11.5%), persistent fever (7.2%), recurrent embolism (4.3%). %), sepsis (2.9%), and others (11.2%).

The median hospital stay of the operated patients was 23 (IQR 17-39) days; 40% stayed more than 30 days, and 4.2% more than 60 days. Postoperative complications in order of frequency were: ARF (32.9%), CAVB (22.9%), HDL (11.4%), stroke (8.6%), requirement for reoperation (8.6%), infection (8.6%), others (24.3%). In-hospital mortality was 21.4%, 4.3% mortality within 48 hours after surgery. Of the deceased patients, 53.5% had ARF, while 27.5% of the survivors presented this complication (p NS). Similarly, more patients who died were complicated with HDL (33% vs. 5.5%; p<0.01). *Staphylococcus* spp was the most frequently found germ (30%).

In the individualized analysis of the prediction scores, PALSUSE presented as the most frequent variables: prosthetic valve involvement (58.9%), urgency (45.6%), intracardiac destruction (34.3%), EuroSCORE>10% (32.9%), rescue of Staphylococcus spp. (30%), female gender (21.4%) and age over 70 years (20%). The most frequent variables of STS-IE were: presence of active endocarditis (100%), arterial hypertension (68.6%), previous cardiovascular surgery (57.2%), urgency (45.7%) and renal failure (31.5%). Regarding the EURO-IE and EuroSCORE II scores, the most frequent shared variables were previous cardiovascular surgery (57.2%), age ≤60 years (45.7%), urgency of the intervention (45.7%) and New York Heart Association functional class (CF NYHA) >1 (41.4%). Among the specific variables, the presence

	Surgical treatment (n=70)	Medical Treatment (n=200)	p
Age	60 (48-67)	69 (57-76)	0.001
Male sex	55 (78,5%)	145 (72.5%)	0.346
Hospitalization days	23 (17-39)	19 (12-36)	0.294
Diabetes Mellitus	16 (22.8%)	44 (22%)	0.868
Chronic renal failure	9 (12.8%)	25 (12.5%)	1.000
Prosthetic valve	41 (58.5%)	84 (42%)	0.018
Previous endocarditis	10 (14.2%)	28 (14%)	1.000
Predisposing prior procedure	24 (34.2%)	53 (26.5%)	0.221
Fever	58 (82.8%)	163 (81.5%)	0.858
Dyspnoea	30 (42.8%)	39 (19.5%)	<0.001
Leukocytes/mm^3	9700 (6600-11900)	8900 (6550-12750)	0.566
Anemia	53 (75.7%)	158 (79%)	0.614
Driving disorder	12 (17.1%)	29 (14.5%)	0.568
Heart failure	39 (55.7%)	57 (28.5%)	<0.0001
Acute kidney failure	14 (20%)	44 (22%)	0.865
Sepsis	5 (7.1%)	31 (15,5%)	0.101
Embolism	17 (2.2%)	31 (15.5%)	0.104
Persistent fever	10 (14.2%)	26 (13%)	0.838
Anticoagulation	19(27.1%)	55 (27.5%)	1.000
Cancer	1(1.4%)	23 (11.5%)	0.007
Previous cardiovascular disease	55 (78.5%)	149 (74.5%)	0.523
Splenomegaly	8 (11.4 %)	9 (4.5 %)	0.048

Table 2. Comparative analysis of patients with active IE, whether or not undergoing surgical treatment.

of fistula (34.3%), *Staphylococcus* spp. (30%) and mitral valve involvement (25.7%), are added as the most frequently present in EURO-IE, and a LVEF greater than 50% (81.4%) in the EuroSCORE II.

All models presented good goodness of fit: the Hosmer-Lemeshow test did not show statistical significance for any of the proposed scores (PALSUSE df=4, p=0.912; EuroSCOREII df=8, p=0.175; STS-EI df=7 , p=0.200; EURO-EI df=8, p=0.595). Figure 1 shows the ROC curves for mortality corresponding to the four scores. The PALSUSE score was the one that showed the highest AUC (AUC 0.819, 95% CI 0.697-0.941; p<0.001), behaving as a score with good discrimination capacity for mortality. Although they retained statistical significance, EuroSCORE II (AUC 0.685, 95% CI 0.541-0.830; p=0.029) and EURO-IE (AUC 0.695, CI 0.556-0.834; p 0.022), showed poor discrimination capacity. The STS-IE score was not useful as a discriminative tool (AUC 0.596, 95% CI 0.429-0.743; p=0.310). In the comparison between scores, PALSUSE showed a statistically significant difference with respect to STS-IE in predicting mortality (p<0.001), while when compared with EuroSCORE II and EURO-IE, the benefit of this score was of borderline statistical significance (p=0.05).

Table 3 shows the results of the different scores in predicting prolonged hospitalization, major complications, and major complications or death. Regarding prolonged hospitalization, EuroSCORE II and STS-IE had poor discriminatory power, while it was null for EURO-IE and PALSUSE. On the other hand, STS-IE had a reasonable power for discrimination of major events, albeit poor in the rest of the scores. The predictive capacity of the 4 scores for major complications or death was reasonable.

DISCUSSION

The treatment of IE is a challenge due to the complexity of this disease and the critical condition in which patients must face it. (4) Surgery can be curative, especially for those cases where medical treatment is ineffective; (8) hence, it is important to have a reliable tool to determine its risk. (5) Surgical risk prediction scores for general cardiovascular surgery may lose accuracy in less common diseases such as IE. For this reason, several specific scoring systems have been developed for this disease.(13-15) In our series, the PALSUSE score showed better ability to predict hospital death, therefore, it could be a good resource for decision making, a result similar to that published by other series. (5,17)

The evaluated population shares similar characteristics to the population registered in EIRA III, which is the largest series of studies on IE in Latin America, (4) although it is relevant to highlight that our population presented a greater proportion of patients with prosthetic valve IE, which may be related to the characteristics of our center. The mortality observed in our series is similar to the mortality detected in other reg-

Table 3. Results of the different scores in predicting prolonged hospitalization, major complications and major complications and death.

Name	AUC	CI 95%	p
Prolonged hospitalization EuroSCORE II	0.696	0.556-0.835	0.01
Prolonged hospitalization STS-IE	0.652	0.505-0.799	0.04
Prolonged hospitalization EURO-IE	0.517	0.336-0.667	0.83
Prolonged hospitalization PALSUSE	0.503	0.352-0.647	0.99
Major Complications EuroSCORE II	0.690	0.530-0.849	0.01
Major Complications STS-IE	0.788	0.658-0.918	<0.001
Major Complications EURO-IE	0.633	0.488-0.778	0.08
Major Complications PALSUSE	0.615	0.472-0.758	0.14
Major complications or death EuroSCORE II	0.720	0.591-0.849	0.002
Major complications or death STS-IE	0.742	0.622-0.863	0.001
Major complications or death EURO-IE	0.705	0.584-0.827	0.004
Major complications or death PALSUSE	0.727	0.606-0.848	0.001

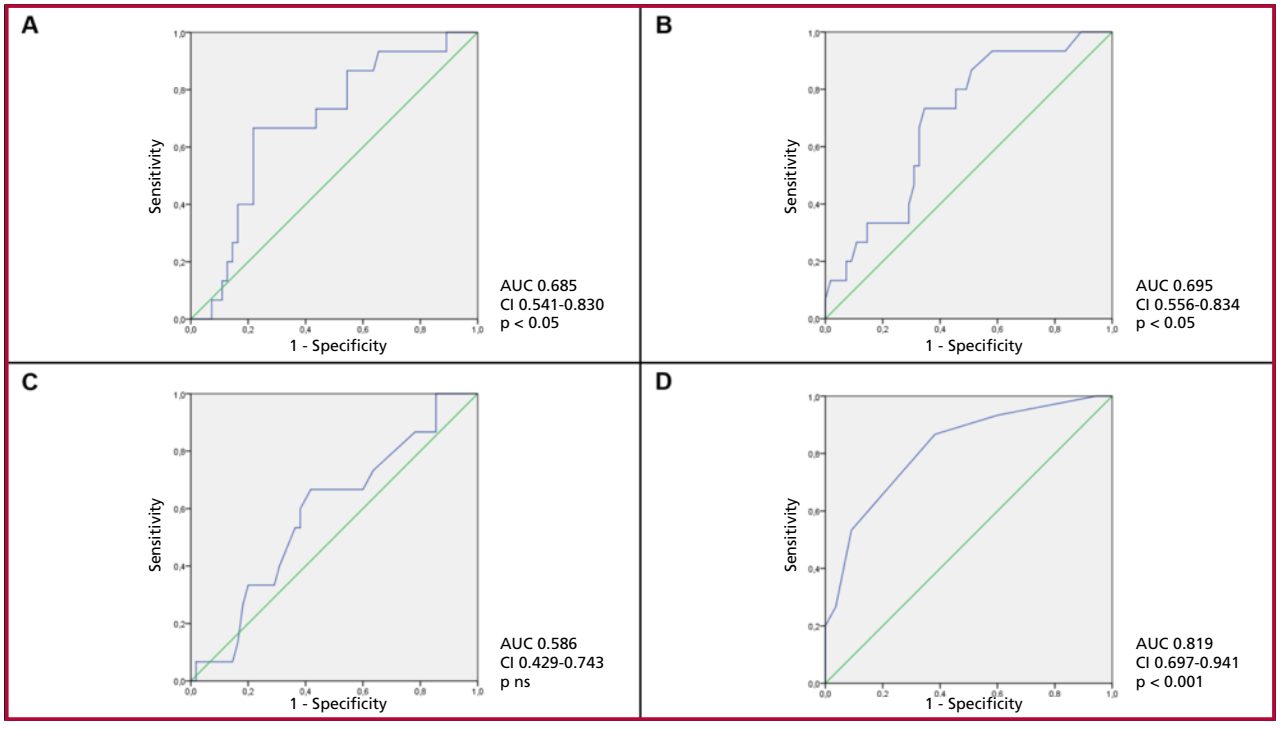
AUC: area under curve; CI:confidence interval.

istries (4,5). In the EIRA III registry, the mortality of patients undergoing surgical treatment was 22%, (4) while the series reported by Gatti et al. was 25.6%. (5)

In our work we performed a comparison of 4 surgical risk scores to predict mortality. Firstly, not all the compared scores were designed to evaluate surgical mortality in patients with IE, since EuroSCORE II evaluates the risk of cardiac surgery in general. (11) There is controversy based on the validity of this score to estimate surgical risk in IE. Patrat-Delon et al. conclude in their work that EuroSCORE II underestimates the surgical risk of IE since it does not evaluate variables that behave as independent predictors of mortality such as the presence of a prosthetic valve, septic shock or large vegetations. (18) While, in other series, EuroSCORE II was a useful tool to predict the surgical risk of this disease. (19)

Secondly, PALSUSE is a composite score, since within its 7 variables is the EuroSCORE, possibly generating an advantage in risk prediction. (15) It is worth clarifying that PALSUSE variables behaved as independent mortality factors in other series. In the study carried out by Costa et al, age, intracardiac destruction and prosthetic valve IE were independent

Fig. 1. ROC curve for the different risk scores predicting mortality. (A) EuroSCORE II. (B) EURO-IE. (C) STS-IE. (D) PALSUSE.



AUC: Area under the curve; CI: Confidence interval 95%.

predictor variables of mortality, (20) as well as the presence of heart failure, which, although not included as a dichotomous variable in PALSUSE, was the main indication for emergency surgery in our study. This fact could justify the good discrimination capacity for mortality that PALSUSE possesses.

It is important to note that ARF and the requirement for HDL were more frequent among patients who later died. This finding is in line with the presence of renal function assessment in the majority of the scores evaluated. Stahl et al. describe how renal failure prior to complex surgery is a predictor of mortality. (21) It is relevant to highlight that, although PALSUSE does not directly evaluate renal function, this is assessed in EuroSCORE.

The risk scores evaluated did not have a good predictive capacity for prolonged hospitalization and major complications. This finding should not be surprising, as has already been mentioned, most of these scores have been designed for the prediction of mortality, and mortality may precisely be a factor that censors the appearance of other complications. Therefore, we consider that these results do not invalidate the use of these scores, which are tools recommended by various consensus documents. (8,17,22)

Limitations

The retrospective design and the participation of a single center constitute the major limitations of our study. Furthermore, the number of patients analyzed could be considered low, since it is a rare pathology, which is only operated on in a fraction of patients. Furthermore, the study cohort has been under prospective follow-up for 15 years. We must take into account that the constant evolution of indication, recommended treatments, implementation of surgical techniques and post-operative care of cardiovascular surgeries can influence the results.

CONCLUSION

The surgical morbidity and mortality of IE depend on a variety of pre-, intra-, and postoperative factors. It is a serious, potentially fatal pathology, in which the option of surgical treatment carries a high risk. In this sense, recognizing specific risk prediction tools becomes an urgent need. The PALSUSE score was shown to be the most accurate in predicting in-hospital death and should be considered together with other risk prediction strategies for decision making in patients with IE. We consider that due to the importance and severity of the disease, research in this field should remain active; therefore, the multicenter registries in our environment are of fundamental relevance. Future studies may assess the prospective importance of these findings.

Conflicts of interest

None declared.

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

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ORIGINAL ARTICLE

Acute Myocardial Infarction in Argentina. Third ARGEN-IAM-ST Registry Report and 8-Year Mortality Behavior

Infarto de miocardio en la Argentina. Tercer reporte del registro ARGEN-IAM-ST y comportamiento de la mortalidad en 8 años

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ABSTRACT

Background: The continuous Argentine ST-segment Elevation Acute Myocardial Infarction (ARGEN-IAM-ST) registry presents its third general report.
Objective: The aim of this study was to evaluate the main ST-segment elevation myocardial infarction (STEMI) markers of care and its complications in the continuous ARGEN-IAM-ST registry, and assess the outcome of reperfusion therapy and mortality in the last 8 years.
Methods: This was a national, prospective, multicenter study, including STEMI patients with up to 36-hour evolution.
Results: A total of 6765 patients, mean age 61±12 years, 65% male , were included in the study. A significant burden of cardiovascular risk factors was observed: 58% of patients had hypertension, 23% diabetes, 42% dyslipidemia, 37% were active smokers, and 17% had a family history of cardiovascular disease. In 13.5% of cases, patients had prior history of coronary heart disease. On admission, 49% presented with anterior AMI and 23% with heart failure. Median (interquartile range, IQR) pain-consultation time was 120 minutes (IQR 60 – 285), door-to-needle time 50 minutes (IQR 25 – 110) and door-to-balloon time 100 minutes (IQR 58 – 190)
Overall in-hospital mortality was 8.8%. An exploratory and descriptive analysis was performed to assess the variation in reperfusion and mortality over 8 years, showing no marked changes in mortality despite high reperfusion rates.
Conclusion: In the last 8 years, the mortality recorded in the ARGEN-IAM-ST registry has remained at high values despite the high reperfusion rates reported.

Keywords: Myocardial infarction – ST-segment elevation myocardial infarction – Epidemiology – Balloon angioplasty – Reperfusion

RESUMEN

Introducción: Se presenta el tercer reporte general del registro continuo de infarto ARGEN- IAM-ST
Objetivos: Evaluar los principales marcadores de atención y las complicaciones del infarto agudo de miocardio (IAM) con elevación del segmento ST en el registro continuo de infarto ARGEN-IAM-ST. Conocer la evolución de la terapia de reperfusión y la mortalidad en los últimos 8 años.
Material y métodos: Estudio prospectivo multicéntrico, con alcance nacional. Se incluyeron pacientes con IAM con elevación del segmento ST de hasta 36 horas de evolución.
Resultados: Se incluyeron 6765 pacientes, con una edad media de 61 ± 12 años, 65% de género masculino. Se observó una importante carga de factores de riesgo cardiovascular: hipertensión arterial 58%, diabetes 23%, dislipidemia 42%, tabaquismo activo 37% y antecedentes familiares de enfermedad cardiovascular 17%. El 13,5% presentó antecedente de enfermedad coronaria; al ingreso un 49% presentó IAM de cara anterior y el 23% falla cardíaca. La mediana de tiempo de dolor a la consulta fue de 120 minutos (rango intercuartílico, RIC, 60 – 285), el tiempo puerta-aguja fue de 50 minutos (RIC 25 – 110) y el tiempo puerta balón fue de 100 minutos (RIC 58 – 190).
La mortalidad general intrahospitalaria fue del 8,8%. Se realizó un análisis exploratorio y descriptivo para observar la variación de la reperfusión y mortalidad durante 8 años donde no se muestran cambios acentuados en la mortalidad a pesar de las altas tasas de reperfusión.
Conclusión: En los últimos 8 años la mortalidad registrada en el registro ARGEN IAM-ST se ha mantenido en valores elevados a pesar de las altas tasas de reporte de reperfusión.

Palabras claves: Infarto de miocardio - Infarto de miocardio con elevación del ST -Epidemiología - Angioplastia coronaria con balón – Reperfusión

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INTRODUCTION

Acute myocardial infarction (AMI) is the main cause of death in Argentina, as well as the main reason of clinical cardiovascular disease. Due to the burden it implies for the healthcare system, it is necessary to know the most important indicators of care, as well as the results and complications. (1) The continuous ST-segment elevation acute myocardial infarction (ARGEN-IAM-ST) registry led by the Argentine Society of Cardiology (SAC) and the Argentine Federation of Cardiology (FAC) allows an approach to the reality of care and has generated previous reports alerting on the results together with opportunities for improvement that could impact on usual clinical practice. Moreover, it is well-known that registries of common diseases are very useful tools to control the implementation of policies as the conformation of care networks, promote awareness of early consultation, incorporate new technologies, etc. (2)

In the case of the ARGEN-IAM-ST registry, active since 2015, the participation of centers from different provinces allows knowing the evolution of AMI care throughout time, not only in different regions, but also in different health systems of Argentina. Our objectives were to evaluate the main AMI markers of care and complications in the continuous ARGEN-IAM-ST registry and assess the reperfusion outcome and mortality in the last 8 years.

METHODS

The ARGEN-IAM-ST registry is a national, prospective, multicenter study carried out in collaboration between SAC and FAC, which is active since the end of 2014, and whose protocol has been previously published. (3) The target population were all patients suffering an AMI with ST-segment elevation within 36 hours from the event. Following the end of the first phase in December 2015, all the participating centers were invited to continue with the registry.

The most relevant data collected were coronary risk factors, history of comorbidities, clinical presentation, treatment used (antiplatelet agents, reperfusion, adjuvant therapy) and in-hospital clinical outcome. Data related to delay to achieve effective treatment were one of the mainstays for the registry report.

The following times and delays were considered:

1) Pain-consultation time: time elapsed between the onset of symptoms suggestive of coronary artery ischemia and the first medical contact.
2) Time to reperfusion: time elapsed between arrival to a medical center and onset of reperfusion treatment:
   a) In case of fibrinolytics:
      - Time window: time interval in minutes from symptom onset to start of infusion.
      - Door-to-needle time: time interval in minutes since arrival at the institution and start of infusion.
   b) In case of angioplasty
      - Time window: time interval in minutes from symptom onset to balloon inflation.
      - Door-to-balloon time: time interval in minutes from arrival at the institution to balloon inflation.

Data collection was performed in the REDCap platform.

Statistical analysis

Qualitative variables are presented as frequencies and percentages with their confidence intervals, and quantitative variables are described using mean and standard deviation (SD) or median and interquartile range (IQR), according to their distribution.

Discrete variables were analyzed with contingency tables and continuous variables using Student's t test or the Kruskall Wallis test for unpaired data, or the analysis of variance (ANOVA), as appropriate. Significance was considered for $p<0.05$. The R statistical package was used to perform the analysis.

The protocol was registered in ClinicalTrials.gov under the NCT2458885 number.

Ethical considerations

The ARGEN-IAM-ST registry protocol was approved by the ethics committee of the Argentine Society of Cardiology.

RESULTS

A total of 6765 patients were analyzed, with mean age 61±12 years and 65% male. A significant burden of cardiovascular risk factors was observed: 58% of patients had hypertension, 23% diabetes, 42% dyslipidemia, 37% were active smokers, and 17% had a family history of cardiovascular disease. In 13.5% of cases, patients had prior history of coronary heart disease. On admission, 49% presented with anterior AMI and 77% had Killip and Kimball (KK) A classification (Table 1). Recorded consultation and care times were longer than clinical recommendations, impacting on total ischemic time. Pain-consultation time was 120 minutes (IQR 60-285), door-to-needle time 50 minutes (IQR 25-110) and door-to-balloon time 100 minutes (58-190) (Table 2). Among the main causes of delay physicians reported patient delay in performing the consultation in 61% of cases, followed by ambulance-related delays in 35% and emergency room care in 25% of cases (Table 2 of Supplementary material).

Overall reperfusion rate was 89% and reperfusion strategies used were fibrinolytics in 16.6% and percutaneous coronary intervention (PCI) in 79,3% (89 % primary PCI) (Table 3). The chief cause for non-reperfusion was late presentation of the infarction in 3.5% of cases, according to the survey carried out in the registry (see Table 3 of the Supplementary material). In the case of in-hospital evolution, 12% heart failure (in patients admitted in KK A) and 9.8% atrial fibrillation were the most frequent complications, and 3.5% major bleeding was among other less frequent complications. Overall mortality was 8.8%, and the rest of in-hospital AMI complications are shown in Table 4. An exploratory and descriptive analysis was made to analyze the variation of reperfusion and mortality from 2015 to 2022 (complete annual periods were considered at the time of the report) showing no marked percent changes in mortality despite higher reperfusion rates (Figure 1), with the lowest mortality value recorded in the 2022 period (6%) and the maximum (9.3%) in 2017.

Table 1. Baseline characteristics.

Variable	Data N*	%	95% CI
Age, years, mean ± SD	61± 12		
Male gender	6755	65	64 – 66
Coronary risk factors			
Hypertension	6697	58	57 – 59
Diabetes	6640	23	22 – 24
Dyslipidemia	5125	42	41 – 43
Smoking	6635	37	36 – 38
Family history	6663	17	16 – 17.5
Cardiovascular history			
History of coronary heart disease	5479	13.5	12.5 – 14
Heart failure	6381	2.2	1.9 – 2.6
Stroke	2568	3.7	3 – 4.5
Peripheral vascular disease	2567	1.7	1.1 – 2.1
Atrial fibrillation / Atrial flutter	948	2,2	1.4-3.4
COPD	6386	3,5	3 – 4
Chronic kidney failure	2562	2.2	1.7 – 2.9
Prior aspirin use	6503	22	21 – 23
*Infarct location***	6598		
Anterior		49	48 – 50
Inferior		45	44 – 46
Lateral		5	4 – 5.5
Undefined		1	0.4 – 1.2
*Killip and Kimball on admission***	6598		
I		77	76 – 78
II		15	14 – 16
III		1	0.8 – 1.5
IV		7	7 – 8

* Number of patients from which the data was obtained
** It expresses the proportion of patients in each category
CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; SD: Standard deviation

Table 2. Consultation and reperfusion times (in minutes).

Times	Median	IQR
Pain-consultation	120	60 – 285
Door-to-needle	50	25 – 110
Door-to-needle window	165	90 – 287
Door-to-balloon	100	58 – 190
Door-to-balloon window	310	185 – 595

IQR: Interquartile range

DISCUSSION

This report presents the third general data update of the ARGEN-IAM-ST registry, which allows monitoring the most important parameters involved in the care and outcome of patients treated for infarction in centers of different provinces in Argentina. (3,4)

Despite the core of participating centers has decreased, the registry continues with the incorporation of an annual volume of patients that allows a real-life critical view (see Table 1 of the Supplementary material)

On a first approach, no significant changes in treatment times and overall in-hospital mortality is observed compared with previous registry publications, which continue to be high. In addition, an extensive total ischemic time is recorded, especially in reperfusion times, which are longer than clinical practice guideline recommendations. (5-8) Regardless the heterogeneity of each period, due to the very dissimilar number of participating institutions, as well as their different complexity, which hinder an accurate statistical assessment as a comparative tool, the value of in-hospital overall mortality remains constant in the last 8 years and in percentages that can be improved beyond the comparative instruments.

This promotes the development of effective strategies to reverse this situation, reminding us of successful experiences in Argentina of infarction networks which have been shown to reduce times and

Reperfusion	Data N*	%	95% CI
Reperfused	6757	89	88 – 90
Fibrinolytics	6644	16.6	15.7 – 17.5
Angioplasty in the first 24 hours**	6535	79.3	78 – 80
Type of angioplasty ***	5190		
Primary coronary angioplasty		89.5	88 – 90
Rescue coronary angioplasty		5.5	5 – 6
Pharmacoinvasive therapy		3	3 – 4
Angioplasty for other causes		2	1.5 – 2.2

* Number of patients from which the data was obtained
** It includes primary coronary angioplasty, rescue coronary angioplasty and pharmacoinvasive therapy
*** It expresses the proportion of patients in each category
CI: Confidence interval

Table 3. Reperfusion therapy.

Events	Data N*	%	95% CI
Overall mortality	6752	8.8	8 – 9.5
Postinfarction angina	2969	5	4 – 6
Reinfartion	3030	4	3 – 5
Stroke	2965	2	1.5 – 2.5
Atrial fibrillation	2969	9.8	9 – 11
Heart failure during the evolution	289	12	10 – 13
Mechanical complications	4424		
Septal defect	84	1.9	1.5 – 2.3
Mitral regurgitation	33	0.52	0.3 – 0.8
External cardiac rupture	14	0.32	0.17 – 0.53
Hemorrhage	2458		
Mínimal	69	2.8	2.2 – 3.5
Moderate	49	2	1.5 – 2.7
Major	85	3.5	2.8 – 4.3

CI: confidence interval
* Number of patients from which the data was obtained

Table 4. Events during hospitalization.

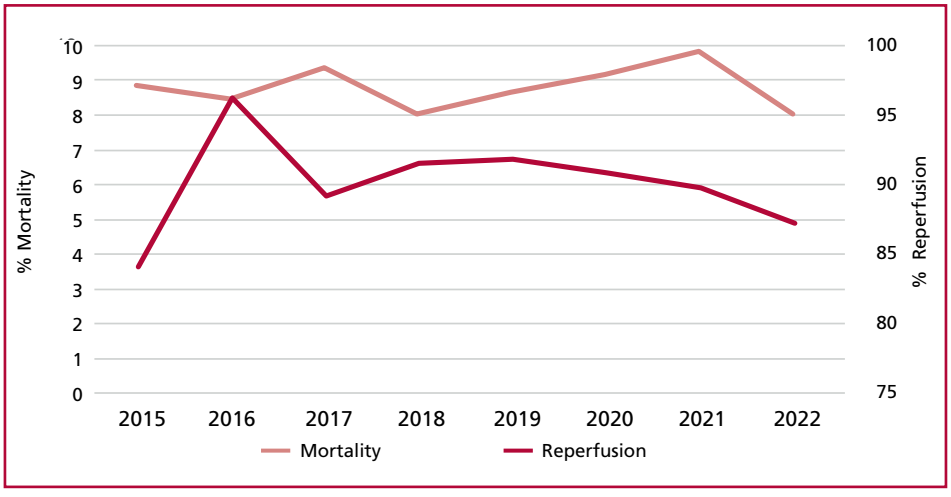

Fig. 1. Time variation of reperfusion therapy and mortality in the ARGEN-IAM-ST registry

improve the mortality rate, in addition to being a reasonable application tool in common clinical practice. (9-12) This type of strategy becomes appropriate considering that physicians reported ambulance and emergency room delays as a second and third factor that impact on total ischemic time, a relevant well-known factor of infarction mortality. (13) Moreover, the centers' heterogeneous complexity also affects results such as in-hospital mortality, indicating that network care could improve the use of resources according to the severity of the clinical condition. (14)

To conclude, it is necessary to highlight that local experiences in infarction care networks have been able to reproduce international results, a great stimulus and incentive for their implementation due to their reproducibility and low cost. (15,16)

Regarding in-hospital mortality, not only high values are observed compared with other registries, but no improvements are perceived throughout 8 years, which raises special concern if we consider the evolution of this marker in other registries over the course of 10 years. An example is the ARIAM registry from Andalucia, which recorded patients with ST-segment elevation and non-ST-segment elevation AMI, and reported 9.2% ST-segment elevation AMI in-hospital mortality in 2011, that decreased to 6.1% in 2021. (17,18)

In another international registry, including European countries, among them Italy, Spain, Denmark, Portugal, Sweden and Hungary, average raw ST-segment elevation AMI in-hospital mortality was 6.8%, and did not exceed 4.4% in 2021. (19,20)

Another behavior observed in the registry deserving attention is the high reperfusion rate in contrast with elevated mortality. A possible interpretation is the high total ischemic time evidenced in this registry and its known close relationship with adverse events, which as reported in previous registries, negatively impacts on survival. (4,13) Finally, although the registry has methodological weaknesses, it is still the only independent instrument open to the scientific community which allows discussing the reality of AMI in Argentina. It should therefore be strengthened to obtain information that will improve the quality of care.

Limitations

The ARGEN-IAM-ST registry is voluntary, without economic stimulus and without case audit in each institution. The contribution of participating investigators and institutions is essential for its support. This registry model can be subject to reporting bias and does not have a sampling strategy.

CONCLUSION

In the last 8 years, mortality recorded in the ARGEN-IAM-ST registry has remained elevated despite the high reperfusion rates reported. The ARGEN-IAM-ST registry shows that notwithstanding the availability of data to monitor the principal markers of AMI care, there have been no advances in strong indicators such as mortality, which is a call for attention indicating that political resolve is required to reverse these undesirable results in Argentina.

Conflicts of interest

None declared.

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

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SUPPLEMENTARY MATERIAL

Acute myocardial infarction. Third ARGEN-IAM-ST registry report and 8-year mortality behavior

Table 1. Participating centers, patients included, reperfusion therapy and in-hospital mortality, discriminated by year

	Reperfusion, n (%)	Mortality, n (%)	Centers
2015, n= 1723	1452 (84.3)	153 (8.8)	172
2016, n= 308	297 (96.4)	26 (8.4)	19
2017, n= 690	617 (89.4)	64 (9.3)	55
2018, n= 911	835 (91.7)	73 (8)	49
2019, n= 1045	961 (92)	90 (8.6)	39
2020, n= 679	617 (91)	62 (9.1)	31
2021, n= 871	788 (90)	85 (9.8)	21
2022, n= 473	417 (87.4)	38 (8)	19

Table 2. Causes of delay (more than one option could be chosen)

Cause of delay	%
Delay in patient consultation	61
Ambulance delay	35
Delay in emergency room care	25
Delay of the hemodynamic team	21

Table 3. Main causes for non-reperfusion

Causes for non-reperfusion	%
Late presentation	3.7
Small infarction	0.4
Older age	0.3
Contraindication for thrombolytic therapy	0.5
Lack of thrombolytic availability	0.3

APPENDIX

Acknowledgements to the participating centers and investigators in this phase of the continuous ARGE-IAM-ST registry.

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- Sanatorio Sagrado Corazón – CABA: Dr. Diego Costa

ORIGINAL ARTICLE

Right-Side Transcatheter Valve Replacement with "Valve-In-Valve" Technique in Congenital Heart Disease: Initial Experience in Argentina

Reemplazo percutáneo de válvulas cardíacas derechas con técnica "válvula en válvula" en cardiopatías congénitas: experiencia inicial en Argentina

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ABSTRACT

Background: Surgical replacement using bioprostheses is a frequently used strategy to treat right-side heart valves dysfunction in congenital heart disease.
Objective: The aim of this study was to present the initial experience in Argentina with right-side bioprosthetic valve ring fracture/remodeling and subsequent transcatheter valve-in-valve replacement in patients with congenital heart disease.
Methods: This was a descriptive and observational study including all patients treated with transcatheter replacement due to bioprosthetic valve dysfunction.
Results: From August 2021 to May 2023, 5 patients (3 female) with right-side bioprosthetic dysfunction underwent transcatheter intervention as an alternative to de novo surgical replacement. Mean age was 21.2±9.20 years and mean weight 56.2±22.2 kg. Five balloon expandable valves were implanted: 3 in pulmonary position and 2 in tricuspid position, in 4 cases with previous fracture of the valve ring. In all cases, valve function was restored without complications. During follow-up, moderate right valve incompetence was observed in one case.
Conclusion: Transcatheter "valve-in-valve" replacement in dysfunctional right-side heart bioprostheses is an attractive and safe strategy in selected cases, which restores competence and eliminates obstructions. This approach is a reasonable option as alternative to *de novo* surgical valve replacement.

Keywords: Heart defects, congenital - Bioprosthesis - Valve dysfunction - Transcatheter replacement - Valve in valve

RESUMEN

Introducción: El reemplazo quirúrgico con colocación de bioprótesis es una estrategia utilizada frecuentemente para tratar valvulopatías del corazón derecho en cardiopatías congénitas.
Objetivo: Presentar la experiencia inicial en Argentina con fractura/remodelación del anillo valvular en bioprótesis valvulares derechas y posterior reemplazo percutáneo "válvula en válvula" en pacientes con cardiopatías congénitas.
Material y métodos: Estudio descriptivo y observacional. Se incluyeron todos los pacientes tratados con reemplazo percutáneo debido a disfunción de prótesis valvular biológica.
Resultados: Desde agosto de 2021 hasta mayo de 2023, 5 pacientes (3 de sexo femenino) con disfunción de bioprótesis derechas recibieron tratamiento percutáneo como alternativa a la realización de un nuevo reemplazo quirúrgico. La edad media fue 21,2 ± 9,2 años , el peso medio fue 56,2 ± 22,2 kg. Fueron implantadas cinco válvulas balón expandibles: 3 en posición pulmonar y 2 en posición tricúspide y en 4 casos, con fractura previa del anillo valvular. En todos los pacientes se restauró la función valvular, sin complicaciones. En el seguimiento, en un sólo paciente se objetivó insuficiencia valvular moderada derecha
Conclusión: El reemplazo percutáneo "válvula en válvula" en bioprótesis disfuncionantes derechas es una estrategia atractiva y segura en casos seleccionados, que restaura la competencia y elimina las obstrucciones. Esta estrategia es una opción razonable como alternativa a la realización de un nuevo recambio valvular quirúrgico.

Palabras clave: Cardiopatías congénitas – Bioprótesis - Disfunción valvular - Reemplazo percutáneo - Válvula en válvula

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INTRODUCTION

Bioprosthetic valves (BPV) with ring are commonly used for right-side surgical valve replacement in congenital heart disease. Satisfactory short and mid-term clinical and hemodynamic outcomes have been shown, though frequently valve dysfunction develops during evolution. Data of BPV durability in tricuspid position are scarce. It is estimated that freedom from reoperation reaches 81% at 10 years post-implantation, though 42% presents echocardiographic valve dysfunction in the same time period. In addition, in patients requiring tricuspid valve implantation before 16 years of age, most bioprostheses are dysfunctional at 5 years post intervention, with valve regurgitation being the main cause in up to 89% of cases. (1) In BPV in pulmonary position, freedom from de novo valve replacement and valve failure/dysfunction at 10 years is estimated at 51.7% and 20.2%, respectively. Young age, diagnosis of pulmonary atresia with ventricular septal defect and valve implantation without stent are among the de novo surgery risk factors.

Transcatheter "valve-in-valve" technique is available for the treatment of valve dysfunction. However, it may reduce even more the internal BPV diameter, especially in prostheses of small caliber, which can potentially lead to functional stenosis or patient-prosthesis mismatch. (3) The intentional fracture or remodeling of the BPV ring in pulmonary and tricuspid position is an attractive technique to achieve a larger internal diameter and better hemodynamic outcome in this strategy, avoiding patient-prosthesis mismatch. Published data on transcatheter "valve-in-valve" replacement (TVVR) in right-side valve bioprostheses for congenital heart disease are very limited.

The objective of the present study was to present the initial experience in Argentina with BPV ring fracture/remodeling and subsequent TVVR in patients with congenital heart disease.

METHODS

This was a descriptive, observational study including all patients treated with TVVR due to BPV dysfunction. The BPV had been previously implanted as part of the initial correction of a congenital heart disease. Valve dysfunction in pulmonary position was defined as peak pressure gradient ≥40 mmHg or the presence of at least moderate valve incompetence demonstrated by color Doppler echocardiography. Tricuspid valve dysfunction was defined as the presence of moderate to severe incompetence, and/or mean gradient ≥9 mmHg.

Color Doppler echocardiograms before, during hospitalization/discharge and during follow-up were performed by a single experimented cardiac physiologist (AC) to standardize the interpretation of the findings.

The valve ring rupture/remodeling strategy and subsequent "valve-in-valve" implantation was performed according to usual standardized techniques. (5) The ultra-high pressure non-compliant balloon selected for the fracture was of the same size or up to 1.5 mm larger than the nominal diameter of the bioprosthesis to be fractured. The rupture pressure applied was as needed to achieve the objective and did not exceed 12 atmospheres (Figures 1 and 2). The diameter of the balloon-expandable valve to be implanted was selected between 0.5 and 2 mm larger than the nominal/commercial BPV diameter. All the patients received aspirin 100 mg/day indefinitely after valve implantation.

Statistical analysis

Data collection and statistical analysis was performed according to guidelines for reporting morbidity and mortality after cardiac valve interventions. (6) Categorical variables are expressed as percentages and continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. The distribution of continuous variables was analyzed using the Kolmogorov-Smirnov test. SPSS 24 software package was used for the statistical analysis.

Ethical considerations

Intentional BPV fracture and subsequent balloon-expandable valve implantation with "valve-in-valve" technique as an alternative to de novo surgical replacement was approved by the institution's ethical committee. All adult patients or their parents/tutors in case of underage patients signed a health information act before the procedure. This study was performed following the Declaration of Helsinki recommendations for observational studies reviewed in 1989.

RESULTS

From August 2021 to May 2023, 5 patients with right-side valve bioprosthetic dysfunction received TVVR as alternative to de novo surgical valve replacement.

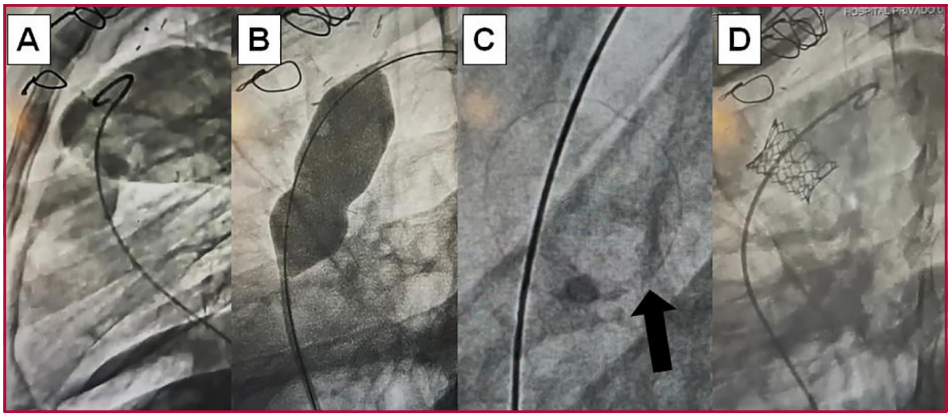

Fig. 1. (**A**) Angiography of Epic Supra™ (St Jude Medical, USA) dysfunctional bioprosthesis in pulmonary position in strict 90 °left lateral oblique projection. (**B**) Ultra-high pressure non-compliant balloon to produce intentional valve ring fracture. (**C**) Fractured valve ring (*arrow*). . (**D**) Angiography in the same initial projection: Myval™ balloon-expandable valve (Meril, India) implanted with "valve-in-valve" technique in pulmonary position.

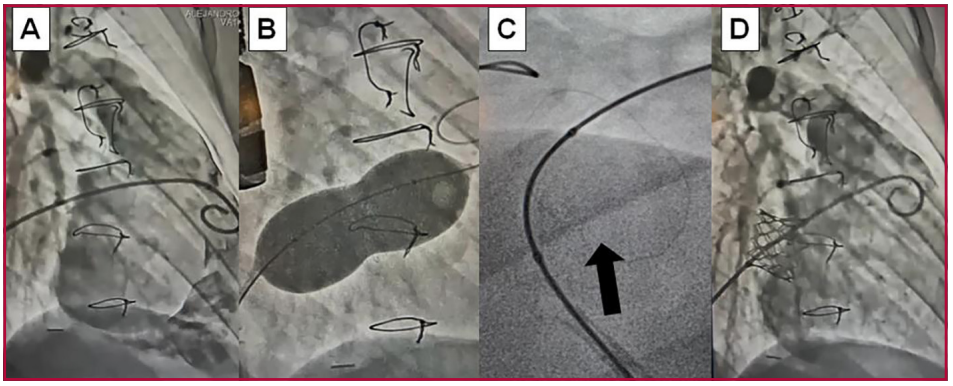

Fig. 2. (**A**) Angiography of Epic Supra™ (St Jude Medical, USA) dysfunctional bioprosthesis in tricuspid position in 45 °right anterior oblique projection. (**B**) Ultra-high pressure non-compliant balloon to produce intentional valve ring fracture. (**C**) Fractured valve ring. (**D**) Angiography in the same initial projection: Myval™ balloon-expandable valve (Meril, India) implanted with "valve-in-valve" technique in tricuspid position.

Mean age was 21±9.20 years, mean weight 56.2±22.2 kg and 60% of patients were female. Two patients had initial diagnosis of tetralogy of Fallot, two of Ebstein's disease and the remaining patient idiopathic dilation of the pulmonary artery trunk with severe valve incompetence. All the patients had functional class (FC) III/IV symptoms of heart failure. In one case, BPV infective endocarditis had been diagnosed in tricuspid position 6 months before the percutaneous intervention.

Regarding valve dysfunction, three patients presented prosthetic dysfunction with predominant pulmonary valve stenosis, one with pure tricuspid stenosis and the remaining patient with double tricuspid anomaly (Table 1). Mean time between the surgical implant and the percutaneous intervention was 6.1±2.6 years.

During TVVR, four patients underwent intentional bioprosthesis ring fracture using ultra-high pressure non-compliant balloons [Atlas Gold ™ or True Balloon™ (Bard, USA)] with diameter equal to or up to 1.5 mm greater than the nominal/commercial size of the ring to be fractured and mean rupture pressure of 9.7±2.6 atmospheres. In all cases rupture was achieved during the first high pressure inflation and then balloon-expandable valves were implanted during the same intervention. In no case was concomitant transient pacemaker stimulation necessary during valve implantation. In the four patients who received intentional ring fracture, the final size of the implanted valve was 1.2 mm larger (0.5-2 mm) than the initial bioprosthesis nominal/commercial diameter. In all cases, the transvalvular gradients were resolved (peak pulmonary gradients decreased from 74 mmHg to 13.6 mmHg and mean tricuspid gradients were reduced from 11.2 mmHg to 3.2 mmHg) with absence of immediate post implant valve incompetence (Table 2). Mean radioscopy time was 19.3±10.3 minutes. Patients remained hospitalized for a median of 24 hours and mean follow-up time was 13.8±6.2 months. No immediate complications or during short or mid-term follow-up were recorded.

Follow-up color Doppler echocardiogram showed mean pulmonary gradient of 16±3.6 mmHg and tricuspid gradient of 6.6±1.2 mmHg. Only one patient developed moderate tricuspid valve incompetence. Clinically, improvement to FC I was observed in four patients and to FC II in the remaining case, and no deaths, valve explants, events of infective endocarditis or need for another reintervention were encountered.

DISCUSSION

Surgical replacement of right-side dysfunctional valves (among them tetralogy of Fallot or Ebstein's disease) with bioprosthesis implantation is a widely used strategy, based on its ample availability, lack of need for posterior anticoagulation and good results compared with mechanical prostheses. (7,8) Most bioprostheses have been used off-label for surgical replacement in these positions since their initial development was for aortic valve replacement. These bioprostheses develop progressive impairment, manifested as stenosis and/or incompetence with pathological changes that include calcification, thickening, pannus formation, thrombosis, tears, and inflammation, potentially related to the occurrence of infective endocarditis. (9) It is generally accepted that BPV remain stable up to 5 years post implantation. However, nearly 80% of patients require a reoperation, or will manifest significant dysfunction at 10 years after bioprosthesis placement. A small pulmonary bioprosthesis and age below 13 years were identified as risk factors for early reintervention. (10) Kwak et al. (11) reported that age under 20 years is associated to greater incidence of dysfunction compared with adult patients, even with larger bioprosthesis diameter.

A de novo surgical valve replacement has been the most accepted conduct following these bioprostheses dysfunction, though this technique is associated with increased morbidity and mortality risk, especially in patients with congenital heart diseases and multiple previous surgeries. (12) The TVVR technique is not new, as there is experience in left bioprosthesis dysfunction, mainly when the prevalent dysfunction is regurgitation. (13) Conversely, in cases of pure valve stenosis, prosthesis dysfunction may coexist with

Table 1. Baseline patient characteristics

	Age (years)	Gender	Weight (Kg)	Disease	Type of prosthetic dysfunction	Transvalvular gradient	Functional class
#1T	17	Male	73	Ebstein	Tricuspid stenosis	11*	III
#2T	16	Female	36	Ebstein	Tricuspid stenosis/ regurgitation	11*	IV
#3P	36	Male	86	Idiopathic pulmonary dilation	Pulmonary stenosis	76**	III
#4P	24	Female	48	Tetralogy of Fallot	Pulmonary stenosis	67**	III
#5P	13	Female	38	Tetralogy of Fallot	Pulmonary stenosis	79**	III

P: Pulmonary; T: Tricuspid; *: Mean tricuspid transvalvular gradient; **: Maximum pulmonary transvalvular gradient
* and ** expressed in mmHg.

Table 2. Transcatheter procedure and outcomes

	Bioprosthesis	Number	High pressure fracture	High pressure balloon	Implanted valve	Number	Residual gradient	Follow-up functional class	Regurgitation
#1T	St Jude Epic	25	Yes	True Balloon 26 mm (12 atm)	Myval	26	1.4*	I	Moderate
#2T	Hancock	25	No	No	Myval	23	6*	II	No
#3P	St Jude Epic	27	Yes	Atlas Gold 26 mm (7 atm)	Myval	27.5	19**	I	No
#4P	St Jude Epic	21	Yes	Atlas Gold 22 mm (12 atm)	Melody	22	11**	I	No
#5P	St Jude Epic	23	Yes	True Ballon 24 mm (8 atm)	Myval	24.5	14**	I	No

atm: atmospheres; P: Pulmonary; T: Tricuspid; *: Mean tricuspid transvalvular gradient; **: Maximum pulmonary transvalvular gradient
* and ** expressed in mm Hg.

patient-prosthesis mismatch, so it is logical to assume that transcatheter valve implantation might reduce even more the ring size and not solve valve narrowing. However, Allen and Johansen (3,14) demonstrated that bioprostheses can be fractured using ultra-high pressure non-compliant balloons with diameter at least 1 mm larger than the nominal/ commercial implanted valve diameter, except with Trifecta (Abbott, USA) and Hancock II (Medtronic, USA) bioprostheses. This strategy allows "valve-in-valve" implantation, decreasing the problem of patient-prosthesis mismatch. The rupture pressure required varied between 8 and 24 atmospheres and the ring fracture was followed by an immediate drop of pressure in the balloon and frequently an audible "crack".

Recently reported results using this technique in BPV in tricuspid and pulmonary position, followed by TVVR, demonstrated a patent clinical improvement, a significant increase in the bioprosthesis internal diameter and better hemodynamic outcomes after transcatheter valve implantation. (15,16)

It is probable that to achieve a successful fracture, other variables beyond the bioprosthesis type and size should be considered in the bioprosthesis rupture/remodeling technique, including tissue remodeling inside and around the valve, as well as the geometry of the implant location. Nonetheless, we followed the recommendation about the use of ultra-high pressure non-compliant balloons, with a size at least 1mm larger than the true internal diameter, and up to 3-5 mm larger than the true inner diameter (3,15) and with this strategy, we were able to intentionally fracture all the rings during the first inflation. The only patient of this cohort with a non-fracturable Hancock II bioprosthesis (Medtronic, USA), presented FC IV, a previous episode of infective endocarditis and small body surface area, which led us to consider that TVVR would not lead to patient- prosthesis-mismatch. It is pertinent to emphasize that the maximum final expansion of a fractured bioprosthesis is not clearly defined, as there are variables inherent to the valve and also to the surrounding tissue that affect the final diameter. (3,17) It is also discussed whether stent implantation prior to TVVR is necessary to avoid fractured valve recoil, though observations suggesting differential forces contributing to this effect have not been clear-

ly established. (18) Therefore, we consider that balloon- expandable valve implantation with adequate radial force is enough to mitigate the possibility of subsequent recoil, thus avoiding the implantation of an additional stent. In parallel, it has also been suggested that the intentional ring fracture could be performed after TVVR, although this strategy presents the hypothetical risk that ultra-high-pressure balloons could damage the valve and/or distort the implanted percutaneous valve skeleton. (19)

Another point to highlight is the occurrence of infective endocarditis in patients with bioprostheses and TVVR. According to Cabalka et al. reports (20) the relative risk is not greater compared with transcatheter valve replacement on a homograft or other types of conduits. However, this association deserves to be studied in depth, especially due to data published in the Society of Thoracic Surgeons registry, in which 12% of adult patients requiring surgical pulmonary valve replacement after percutaneous interventions had a history of infective endocarditis. (21) In the previously mentioned multicenter study (20), the occurrence of infective endocarditis prior to TVVR was not associated with adverse events nor negatively impacted in the results during follow-up.

To conclude, we consider that the collaboration between cardiovascular surgeons and hemodynamic specialists to define the type of bioprosthesis to implant, and the long-term management is essential to achieve the success of this strategy.

Limitations

There are limitations in this study. The data were retrospectively collected from a single center with experience in transcatheter valve implantation, so the results presented might not be of general application. In addition, selection bias could have occurred in the incorporation of high-risk patients with dysfunctional bioprostheses. Finally, this is an initial and preliminary report of a novel procedure with valves approved off-label for use in the right ventricular inflow and outflow tract, with evident need of a longer-term follow-up.

CONCLUSIONS

Right-side valve TVVR in patients with congenital heart diseases is an attractive and safe strategy in selected cases, which restores competence and eliminates obstructions in dysfunctional bioprostheses. Intentional BPV fracture is an effective, technically safe and efficient intervention to increase the diameter of a valve to be implanted and is a reasonable alternative to de novo surgical valve replacement. A larger number of cases and more prolonged follow-up will be necessary to confirm these initial findings.

Conflicts of interest

None declared.

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

Financing

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ORIGINAL ARTICLE

Cardiac Fulcrum, its Relationship with the Atrioventricular Node

Fulcro cardiaco, su relación con el nódulo aurículo-ventricular

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ABSTRACT

Background: The functional anatomy of the helical, continuous myocardium allows envisioning that it initiates and ends at the origin of the great vessels. In our research, we have always considered that it should have a point of attachment to allow its helical rotation to fulfill the fundamental movements of shortening-torsion (systole) and lengthening-detorsion (suction), which once found, was called the cardiac fulcrum.
Objective: The research aims to describe the important aspect of understanding the interrelationship between the cardiac fulcrum and the Aschoff-Tawara atrioventricular node.
Methods: A total of 31 hearts, arising from the morgue and slaughterhouse were used: 17 corresponded to bovids and 14 were human.
Results: Our investigations have shown that the myocardial support termed cardiac fulcrum, located in the trajectory of the aortic annulus septal segment, extending from the left to the right trigone and below the origin of the right coronary artery, is adjacent to the AV node. Another important aspect of this contiguous position is that the fulcrum is surrounded, and even invaded, by a rich nervous plexus interconnected with the node.
Conclusions: This description of the cardiac fulcrum would end the problem of lack of support of the myocardium to fulfill its function of torsion/detorsion. The proximity of the fulcrum to the AV node and the penetration of the nervous plexuses in the support suggest an electromechanical unit, which we have investigated according to the helical anatomy of the heart, establishing an improved cardiac stimulation with a catheter placed in the right ventricular outflow tract.

Key words: Cardiac Anatomy – Myocardium - Cardiac Fulcrum - Myocardial Support - AV node.

RESUMEN

Introducción: El estudio de la anatomía funcional del miocardio helicoidal continuo permite visualizar su inicio y fin en el nacimiento de los grandes vasos. En nuestras investigaciones siempre hemos considerado que debía tener un punto de unión que permitiera su rotación helicoidal para cumplir los movimientos fundamentales de acortamiento-torsión (sístole) y alargamiento-destorsión (succión). Una vez encontrado, se le llamó fulcro cardíaco.
Objetivo: Esta investigación tiene como objeto describir y entender la interrelación entre el fulcro cardíaco y el nódulo auriculoventricular de Aschoff-Tawara.
Materiales y métodos: Se utilizaron 31 corazones procedentes de la morgue y del matadero: 17 correspondieron a bóvidos y 14 a seres humanos.
Resultados: En nuestras investigaciones hemos demostrado que el soporte del miocardio, denominado fulcro cardíaco, que se localiza en el trayecto del segmento septal del anillo aórtico y se extiende desde el trígono izquierdo hasta el derecho por debajo del origen de la arteria coronaria derecha, es adyacente al nódulo auriculoventricular (AV). Otro aspecto importante de esta posición contigua es que el fulcro está rodeado, e incluso invadido, por un plexo nervioso interconectado con el nódulo.
Conclusiones: Esta descripción del fulcro cardíaco pondría fin al problema de la falta de apoyo del miocardio para cumplir su función de torsión/destorsión. La proximidad del fulcro al nódulo AV y la penetración de los plexos nerviosos en el apoyo indican la existencia de una unidad electromecánica, que hemos investigado en función de la anatomía helicoidal del corazón. Hemos comprobado una mejor estimulación cardíaca cuando el catéter se coloca en el infundíbulo ventricular derecho.

Palabras clave: Anatomía cardíaca - Miocardio - Fulcro cardíaco - Soporte miocárdico - Nódulo AV

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INTRODUCTION

Previous investigations from our group have shown the presence of a myocardial support which we have named cardiac fulcrum, located in the course of the aortic annulus septal segment, extending from the left to the right trigone (below the origin of the right coronary artery). The origin and end of the myocardium attaches in this site, since as every muscle it needs a support to fulfill its function. (1,2)

When we found the anatomical contiguity of the fulcrum with the Aschoff-Tawara nodule, we set out to analyze the anatomical and histological relationship of the cardiac fulcrum with the atrioventricular node in a group of human and bovids hearts, as well as the possible functionality between both structures.

In human hearts, to demonstrate this relationship, we worked with hearts of fetuses, children and adults.

METHODS

A total of 31 hearts, coming from the morgue and slaughterhouse were used: 17 corresponded to 2-year-old bovids (10 males and 7 females), weighing 800-1000 g and b) 14 were human (8 males and 6 females), two from 16 and 23-week-old fetuses, three from 36-day, 10-week and 27-week-old infants, one from a 4-year-old boy, one from a 10-year-old boy weighing 116 g and seven from adults weighing 300 g.

Anatomical and histological studies were performed. The heart was fixed in 10% buffered formalin. Hematoxylin-eosin, Masson's trichrome staining technique and 4-micron sections were used for the histological study, and 10 % formalin was used as buffer. Immunohistochemistry was also carried out (s100-neurofilaments).(3) Since the material corresponds to morgue and slaughterhouse pieces, no ethical approval was needed.

The single continuous and helical myocardium was deployed according to a previously published technique. (1,4) A fundamental concept at the beginning of deployment must be followed, as any attempt at not respecting in the dissection the axes where the myocardium coils as a helix, elicits the myocardial mass rupture. The concurrence of the cardiac muscle origin and end in the cardiac fulcrum constitutes a meeting point between the right segment and the ascending segment, origin and end of the myocardium (Figure 1). Thus, both ends are situated in the same site, with the origin of the myocardial fibers placed in an anterior plane to those of its end. Samples of the atrioventricular (AV) node and His bundle were obtained in Koch's triangle.

RESULTS

The anatomical investigations have revealed that all the hearts (bovids and humans) have a myocardial support whose histological structure in the analyzed specimens presents with an osseous or chondroid-tendinous character. In this structure are inserted the myocardial fibers at the origin and end of the band, which correspond to the continuous myocardium coiled as a helix (Figure 2).

Location and relationships. The cardiac fulcrum is found in the proximity of the tricuspid valve (right) the aorta (superior) and the pulmonic-tricuspid cord (anterior). In order to localize it, it is necessary to shift the pulmonary artery and the right segment to the left of the observer, stripping the aortic root at the origin of the helical myocardium. This maneuver uncovers the fulcrum below the aorta and inferior and to the left of the right trigone, without any continuity with it, below the origin of the right coronary artery, detached from aortic continuity and located as a complementary element between the aorta and the myocardium.

As it is situated in the atrioventricular junction at

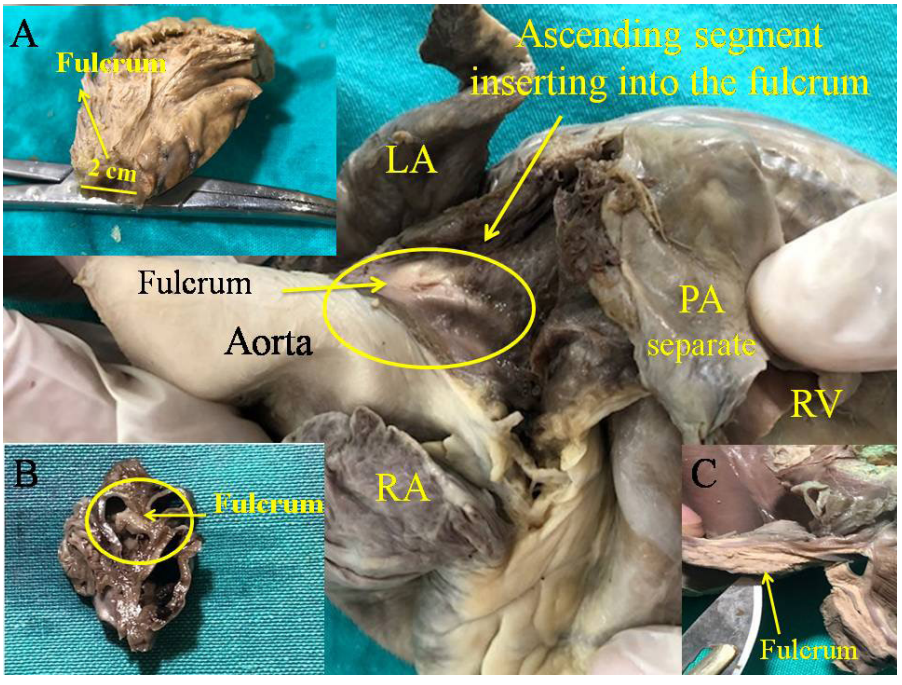

Fig. 1. Adult human heart. The ascending segment is seen inserting into the cardiac fulcrum. LA: left atrium; RA: right atrium; PA: pulmonary artery; RV: right ventricle. A: Cardiac fulcrum in a ten-year-old human heart. B: Cardiac fulcrum in the heart of a human embryo (23 weeks of gestation). C: Fulcrum resected from an adult human heart.

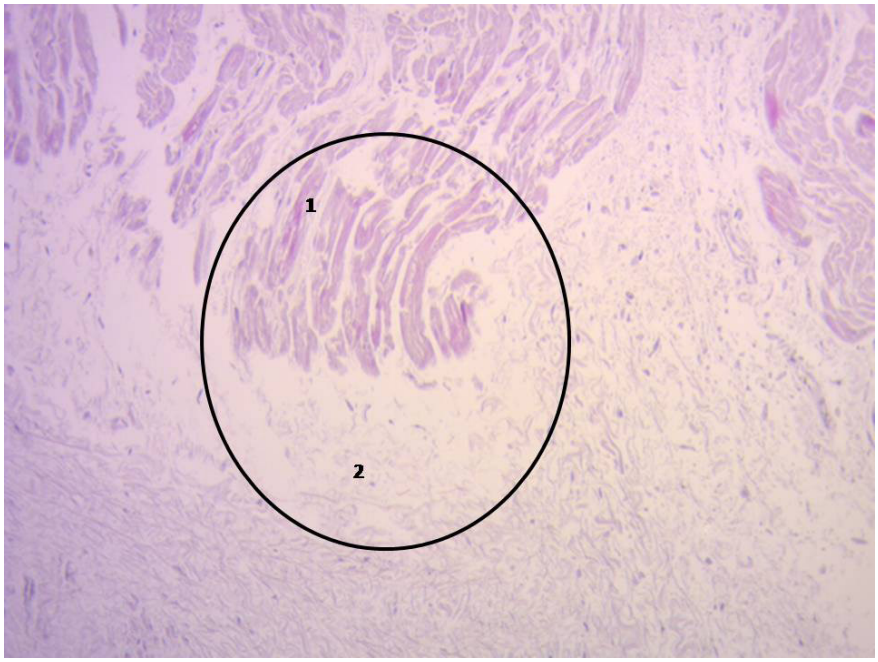

Fig. 2. Cardiomyocytes penetrating the fibrocollagen tissue of the cardiac fulcrum. 1. Cardiomyocytes; 2. Fibrocollagenous matrix (adult human heart). Insertion site is detailed in a circle. Hematoxylin-eosin technique (15x).

the insertion of the interventricular septum, below the aorta and the pulmonary artery, it is adjacent to the AV node, which is positioned at its right (Figure 3). The AV node is in the atrioventricular junction, at the base of the muscular septum, below the origin of the great vessels. It is adjacent to the cardiac fulcrum, placed between this and the implantation of the tricuspid septal leaflet. It constitutes a cluster of cells (specialized myocytes) that Rushmer defines as a spherical or bulbous end consisting of bundles of fibers (5) that send the electrical impulses to the myocardial mass. In its continuity it is slowly transformed into the His bundle, whose course is short, and sometimes, even inexistent.

Histology. In bovids, the fulcrum is triangular. Its size, corroborated by dissection and imaging techniques, has an average of 37 mm in length, 45 mm in width and 15 mm in thickness. (2) The microscopic analysis of the bovid cardiac fulcrum shows the presence of osseous trabeculae as a result of endochondral ossification. Its general structure resembles the metaphyseal growth of long bones. It is possible to observe osseous trabeculae with osteoblasts and segmental lines secondary to osseous apposition. The same histological findings have been encountered in the rest of the mammals. (6)

In the 10-year-old human heart, the description of the cardiac fulcrum is related with this early age, as it shows evidence of a central area of the fulcrum formed by chondroid tissue. Given the age, it is logical that its size is smaller. This finding was repeated in the 23-week-old human fetus with the characteristic prechondroid bluish areas in a myxoid stroma and in the heart of the 36-day newborn.

The histological analysis of the adult human heart fulcrum (average size of 25 mm in length and 15 mm in width) revealed a chondroid-tendinous matrix. In principle, similar evidence of detection, localization and morphology of the fulcrum has been found in all the analyzed hearts, both human and bovid. They present myocardial insertion in the rigid fulcrum structure, forming a cardiomyocytic matrix unit, independently of their osseous, cartilaginous, or tendinous nature in the different specimens studied. This point of attachment implies exerting as in any muscle the supporting function of muscular lever and also to act as bearing or pad, preventing that the ventricular rotation force, either by torque or torsion effort is transferred to the aorta. Thus, it dissipates the energy produced by the helical muscle movement and avoids the strangulation or bending of the artery during the systolic ejective period.

Insertion. The histology of the fulcrum, of collagen-cartilaginous nature, determines the need of an additional analysis to understand its function. In every heart and in all the histological analyses we have verified the insertion of the myocardium in the fulcrum, a finding that becomes a strong point of reasoning to understand the function of the cardiac fulcrum in its biomechanical action of torsion-detorsion. In all the hearts analyzed we found this attachment of the myocardium in the rigid structure of the fulcrum according to the studies carried out during this investigation.

To establish the identity of the cardiac fulcrum, a histological analysis was also performed on the trigones, trying to find cardiomyocytes in their composition as a possible insertion of the cardiac muscle in

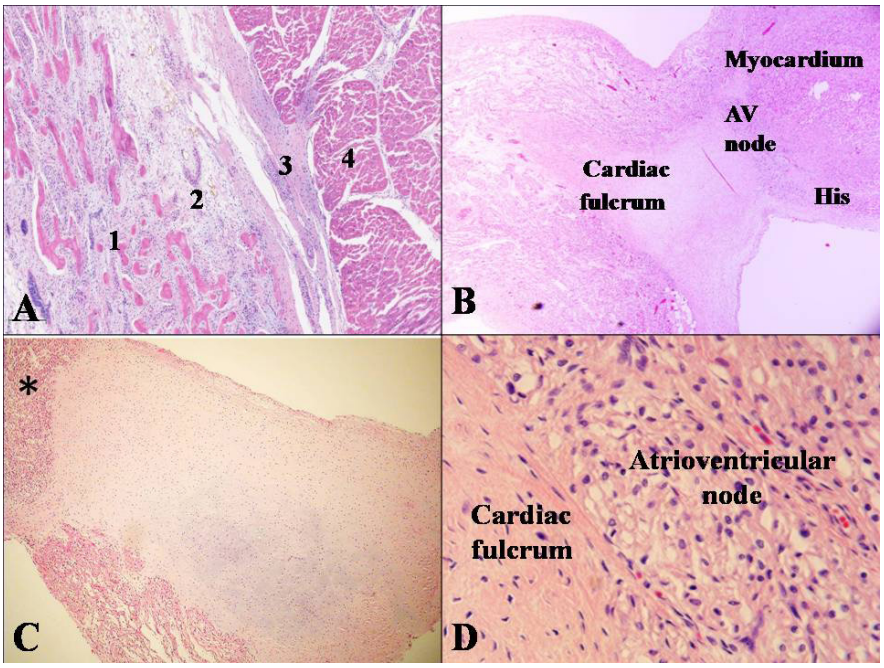

Fig. 3. A: Bovid heart, HEx25. Plexuses associated with fibrochondroid trabeculae and myocardium are observed. 1: bony trabeculae. 2: plexuses. 3: fibroconnective tissue. 4: myocardium. **B:** 36-day-old newborn human heart, 20x magnification. The cardiac fulcrum of cartilaginous matrix is observed with the myocardium and with the adjacent AV node. AV: Aschoff-Tawara atrioventricular node. **C:** 10-week infant heart. Cartilaginous cardiac fulcrum adjacent to the atrio-ventricular region (the asterisk indicates the AV node). H&E x100. **D:** Human heart. Fulcrum and Aschoff-Tawara AV node are seen in contiguity

these structures. Our research only showed collagenous tissue without cardiomyocytes in the trigones, confirming that the fulcrum is the support of the myocardium, both at its origin and end.

Relationship of the cardiac fulcrum with the AV node. This investigation reveals, both in human and bovid hearts, an important topic for cardiac stimulation therapeutics. In the histological study the fulcrum was found adjacent to the AV node, forming a rich cellular accumulation of plexuses with neurofilaments. This contiguity between both structures was obtained in all the specimens studied, both in bovid and human hearts. The essential point for the analysis is that the neurofilaments (Figure 4) are also found inside the cardiac fulcrum.

DISCUSSION

Myocardial fibers constitute a single and continuous muscle that describes a double helix to form the walls of both ventricles. (4,7,8) In order to fulfill its torsion-detorsion muscular function, it needs a point of support that we have found and called the cardiac fulcrum, to which itis attached at its origin and end, similarly to any other muscle. At this point there is an analogy between the skeletal muscle and the myocardium. The former performs its contraction between a fixed and a mobile point of support. This situation is found in the continuous myocardium, as there is greater solidity in the insertion between the fulcrum and the ascending segment in relation to the initial attachment of the right segment in that support.

From this experience, fundamental questions arise: why have we found that in fetus, infant, child, and adult human hearts, the cardiac fulcrum has cartilaginous characteristics, beyond that it fulfills the same function of attaching the helical myocardium that other species have? Let us bear in mind that the cartilage is the substrate for endochondral ossification, and although it does not always ossify, it is necessary to that end. Our interpretation is that perhaps the cardiac fulcrum with an osseous characteristic -as observed in bovids- is a vestigial organ typical of the evolution of mammals. A vestigial structure must be understood as the preservation during the "evolutionary" process of genetically established attributes which have lost all or part of their ancestral function in certain species. In this case, the osteo-cartilaginous histology identified in bovids refers to a cartilage-tendinous matrix which is sufficient to achieve myocardial insertion and attain a muscle power that is much lower than that of larger mammals. Let us recall that in in this investigation the bovid fulcrum is of osseus nature. (2)

The important fact that establishes the attachment of myocardial fibers to the cardiac fulcrum stems from both macroscopic and microscopic observation. Its conformation was confirmed by histology. We have called this structure, origin and end of the helical continuous myocardium, cardiac fulcrum, as a parallelism and tribute to the definition of the point of support acting as a lever expressed by Archimedes of Syracuse. It should be noted that in order to visualize the cardiac fulcrum it is essential to deploy the helical myocardium.

In 1669, Richard Lower considered that the myocardium was subjected to a torsional movement asso-

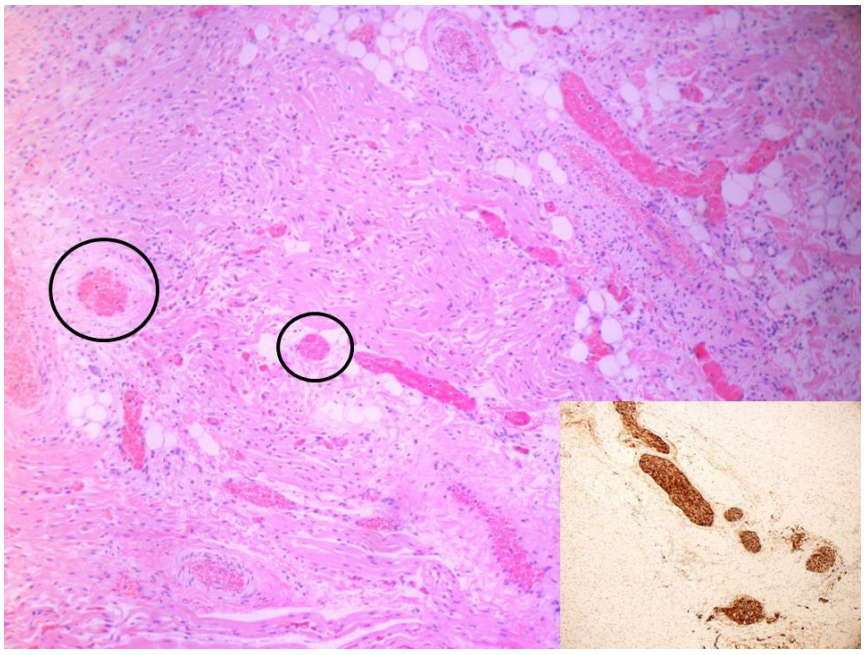

Fig. 4. Heart of a 27-week infant. Nerve trunk hypertrophy is seen in the cardiac fulcrum (black circles) adjacent to the AV node. HEx200. The inset shows a large-diameter nerve trunk in the cardiac fulcrum confirmed with immunohistochemistry for S-100.

ciated with the helical arrangement of its fibers. He expressed that the heart exerted a movement similar to "wringing a towel." Later, Henson (9) studied and verified this concept in mice. (1) The heart achieves the ejection of its content through the torsion of its walls and initiates its filling by generating a negative pressure through detorsion. The synchronous torsional movement with longitudinal ventricular shortening can be explained by the helical arrangement and continuity of the cardiac muscle. (10-13)

The spatial arrangement of the continuous helical myocardium clearly indicates that the propulsion is given by its walls in the ventricular cavities that delimit these structures. Formed by the basal loops (right and left segments) and the apical loop (descending and ascending segments), the muscular unit they form are the walls of the ventricles, to which it provides propulsion power. (14-17)

Muscle homogenization masks the real spiral continuity of the fibers by the overlapping of its segments. Even the transverse interconnections between the tracts do not invalidate the concept of continuous myocardium, understanding that this compact arrangement is the result of the evolutionary development to obtain solidity in its structure in a strict relationship to its function. This implies considering that its structural strength is required in birds and mammals to ensure that blood is ejected at a high speed during a limited time, by an organ that must supply two circulations (systemic and pulmonary). The anatomical investigation of the heart through an adequate dissection (1), histological examination (2), imaging analysis of radiological and echocardiographic studies, (18-20) electrophysiological studies carried out with three-dimensional electroanatomical mapping (8,21) and diffusion tensor cardiac magnetic resonance imaging (14,15) show the continuous muscular course that circumscribes the two ventricles.

The spatial helical arrangement of the myocardium forces the muscle to overlap segments. This anatomical situation has a profound correspondence with myocardial movements and with the stimulation that runs through its segments (21-23), according to the electrophysiological studies that we have previously carried out. (21,22) The interpretation of the anatomical relationship between the cardiac fulcrum and the AV node implies the complementarity of the anatomy with the physiology of the continuous helical myocardium, since the contiguity that they show is found in the point where the stimulation starts and ends, with the development of the mechanical action of torsion and detorsion in the ventricular systolic and suction phases.

The cardiac fulcrum, support and insertion of the myocardium to perform the lever function in its movements, is located adjacent to the Aschoff-Tawara AV node. Thus, an electromechanical unit located at the origin and end of the single helical myocardium is constituted. This anatomical and functional disposition of the myocardium is supported by a rich plexus of specialized filaments that interact with the mechanically working cardiomyocytes.

The interpretation of the findings in this research carried out in human and bovid hearts inevitably leads to therapeutic action. What is the explanation, according to our experience, why a better synchro-

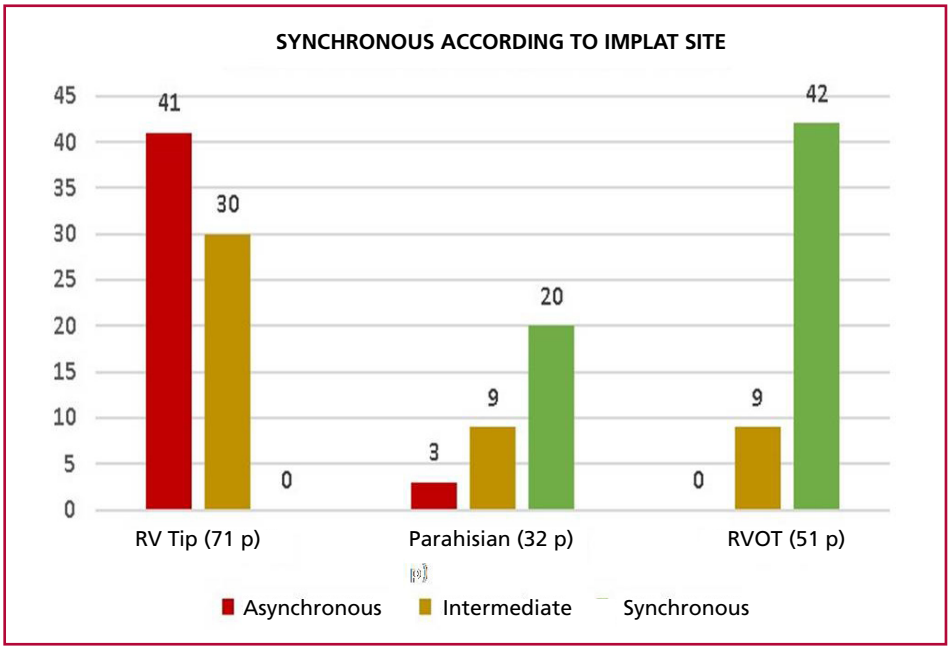

Fig. 5. Comparison of pacemakers implanted in different points of the right ventricle (RV): tip, parahisian, right ventricular outflow tract (RVOT). p: patients.

ny of pacemakers was evidenced with the catheter placed close to this electromechanical unit? The AV node is situated over the base of the muscular septum at the base of the tricuspid valve septal leaflet implantation, at the site of insertion of the interventricular septum with the aorta and the pulmonary artery. In this regard, the adjacency between the cardiac fulcrum and the origin of the continuous myocardium in its helical course in relation to the AV node, demonstrated that stimulation in the right ventricular outflow tract was more effective. In this experience with pacemakers implanted in different points of the right ventricle (tip, parahisian, outflow tract), using active standard fixation catheters, the right ventricular outflow tract achieved better electrical synchrony in the left ventricle (Figure 5). (24) The ideal region for the location of the pacemaker stimulation catheter would be high in the outflow tract, below the pulmonary valve, and preferably on the septum, but not on the free wall.

Function leads the myocardium to have a point of support as any skeletal muscle, both at its origin and end. If the myocardium did not have this helical spatial anatomical conformation, with an insertion at both ends in the cardiac base remaining free at the apex, that is, as a pendulum in the thorax; and if it did not present a stimulation allowing torsion and detorsion, it would be unable to fulfill its extraordinary muscular power.

Having found an osseous structure in the bovid cardiac fulcrum and its relationship with the myxoid-chondroid texture in human hearts, even in embryos, is consistent with the analysis of its interpretation. This disparity is associated with the different age evolution from chondroid to osseous material and with the greater power developed by bovid hearts, requiring a more rigid point of support.

Beyond its mere mention, until our investigations, no function or meaning of its presence had ever been assigned, as well as its lack of description in human beings.

The adjacency of the cardiac fulcrum to the AV node, surrounded and even invaded by a rich plexus of neurofilaments leads us to the anatomical consideration of an electromechanical unit in which stimulation energy and muscle mechanics participate. The effectiveness achieved with the placement of the pacing catheter in the vicinity of the right ventricular outflow tract confirms the findings of this investigation.

Limitations

The most relevant limitation is the number of specimens studied, so this experience should be expanded. Future electrophysiological experiments and clinical investigations are necessary to explore this topic, since this research can be classified as initial.

CONCLUSIONS

The muscular segments that in continuity make up the ventricular chambers must carry out their movements on a point of support, which we have investigated and termed cardiac fulcrum, same as a skeletal muscle does in a firm insertion.

Its presence is constant in all the hearts studied, both bovid and human, but its structural characteristic is different. And this difference in the intimate analysis of the cardiac fulcrum is undoubtedly related to the resistance that it must oppose to the energetic action of the myocardium in hearts of different sizes.

The adjacency of the cardiac fulcrum to the AV node is important to explain the electromechanical unit of the heart.

Conflicts of interest

None declared.

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

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Myocardial Infarction as Debut of Catastrophic Antiphospholipid Syndrome in an Adolescent

The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by thrombosis (venous, arterial, and/or microvascular events), and obstetric morbidity. It appears in the presence of one or more of these antiphospholipid antibodies: lupus anticoagulant, anticardiolipin antibodies (immunoglobulin G or immunoglobulin M), anti-β2-glycoprotein 1 antibodies (immunoglobulin G or immunoglobulin M). The APS may occur on its own (primary APS) or together with other both autoimmune and infectious diseases (secondary APS). (1)

Sixty to 80% of APS patients are female. While the pathophysiology is still unclear, it might be due to the presence of antibodies targeted against vascular endothelial cell surface proteins or platelets, which could be associated with the thrombotic events resulting from this syndrome. (1)

Catastrophic APS is a severe form of this disorder characterized by rapid involvement of 3 or more organs and associated with high mortality rates. (2) The most commonly affected organs are the kidneys, followed by the lungs and the brain. Fewer patients experience cardiac consequences.

According to Euro-Phospholipid, (3) catastrophic APS represented just 0.8% of the entire cohort. In terms of cardiac occurrences, the most common was valve dysfunction (11%), followed by acute myocardial infarction in 5.5% of patients, although the latter was the initial outcome in just 2.8% of cases.

Our clinical case involved a young female patient diagnosed with catastrophic APS, with ST-elevation acute coronary syndrome as the form of presentation.

This 17-year-old female patient, with no risk factors or cardiovascular history, came to the Emergency Department with sharp precordial pain lasting an hour, in association with a syncope with *restitutio ad integrum*. She had recently started oral contraception with drospirenone and ethynyl estradiol. Upon admission, she had precordial pain, normal blood pressure, tachycardia (120 beats/minute),, and generalized paleness. Lab tests upon admission showed serious anemia and thrombocytopenia, 17% hematocrit, 5.9 g/dL hemoglobin, and 14,100/mm^3 platelet count. She had impaired renal function, with serum creatinine 1.45 mg/dL (normal value: 0.5-1.2 mg/dL) associated with proteinuria and granular hyaline casts. The high-sensitivity troponin dosage was 227.7 pg/mL (normal value: up to 14 pg/mL). The electrocardiogram showed sinus tachycardia with ST-segment elevation on the inferolateral dorsal leads, associated with ST-segment specular depression in anterior leads (Figures 1A and 1B). A Doppler transthoracic echocardiogram was performed which showed akinesia of all lower segments and moderate mitral regurgitation, with eccentric regurgitant jet to the posterior leaflet, secondary to retraction of the posterolateral papillary muscle. The left ventricular ejection fraction was estimated at 40%.

Due to the complexity of the condition and serious blood count results, there was an emergency referral to Hematology and Rheumatology Departments. A peripheral blood smear showed anisocytosis, microcytosis, and hypochromia, with a 1% schistocytes count associated with thrombocytopenia. The emergency immune and hematological study reported autoimmune hemolytic anemia mediated by warm and cold antibodies, immunoglobulin G (IgG), and complement. As a result of severe bicytopenia and a history of syncope leading to traumatic brain injury, a brain, chest, and abdomen computerized tomography (CT) was performed to rule out brain bleeding. The CT showed multiple acute splenic infarctions.

Transient complete AV block occurred intercurrently during her stay at the Emergency Department; therefore, an emergency coronary cineangiography was requested. It showed occlusion of the atrioventricular branch of the dominant circumflex artery, with an angiographic image consistent with abundant endoluminal thrombotic material (Figure 2A). The attempts of mechanical thrombectomy with balloon, manual endoluminal thrombus aspiration, aspiration through guide catheter extension and Sophia catheter failed. Then, atrioventricular branch occlusion was observed consistent with coronary artery dissection. As a result, a drug-eluting stent was placed in this vessel with good angiographic results (Figure 2B). A temporary transjugular pacemaker was implanted during the same procedure with semi-permanent vascular access. In addition, 1 g methylprednisolone was administered intravenously as initial immunosuppressive therapy.

Within 24 hours after admission, the laboratory tests showed positive lupus anticoagulant (LAC), and high anticardiolipin and anti-β2-glycoprotein 1 antibodies levels, so the condition was considered to be a catastrophic APS with coronary, splenic, and microvascular renal involvement. Anticoagulation with heparin was administered by continuous infusion

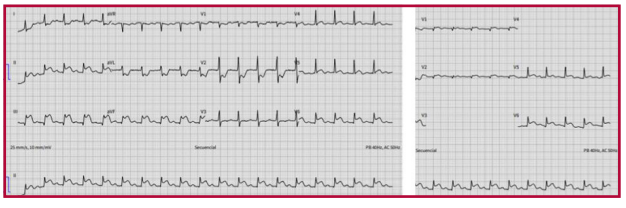

Fig. 1. A) 12-lead ECG showing sinus tachycardia with ST-elevation on the inferior and lower lateral wall (DII, DIII, aVF; V5 and V6 leads) **B)** Right and posterior leads ECG showing ST-elevation both in right and posterior leads (V3R, V4R; V7 and V8)

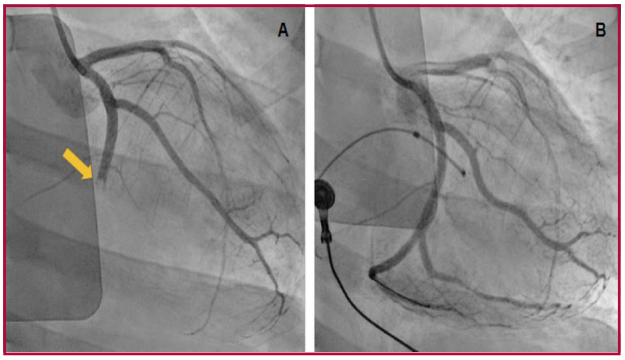

Fig. 1. Coronary cineangiography images. **A)** Right caudal oblique view. The yellow arrow shows the site of occlusion of the AV branch of the circumflex artery, with angiography images consistent with abundant endoluminal thrombotic material. **B)** The same view shows the final angiography result after placement of a drug-eluting stent in the AV branch of the circumflex artery. There is also embolization of thrombotic material in the distal part of the posterior descending branch.

pump. Intravenous methylprednisolone pulses, 3 plasmapheresis cycles, and 1 g rituximab were also prescribed. The patient showed favorable clinical progress and was discharged after 8 days of hospitalization under oral corticosteroids. A triple antithrombotic therapy was selected, including one-month anticoagulation with warfarin and dual antiplatelet therapy with aspirin and clopidogrel, followed by warfarin and clopidogrel. Subsequent cardiology follow-up included cardiac magnetic resonance imaging (MRI) to assess the ventricular function, showing a 49% left ventricular ejection fraction with moderate mitral regurgitation and extensive late enhancement, as well as evidence of extensive necrosis in the inferior and inferolateral segments.

While the incidence of catastrophic APS is low according to literature, this case shows the importance of considering this condition due to the severity and systemic consequences involved.

In our patient, the main target organ was the heart, with ST-elevation acute coronary syndrome (STEACS) secondary to acute occlusion of the circumflex artery. As described above, cardiac occurrences are not the most common, with acute coronary syndrome representing a minority of cases.

This case reflects the importance of considering this diagnosis in young patients with STEACS, together with blood count variations. In addition, the difficulty of interdisciplinary management and rapid decision-making is highlighted. Although thrombus aspiration failed, this strategy might be the most suitable to treat coronary occlusion by limiting the use of antiplatelet agents, and thus, reducing the risk of bleeding.

Besides, a long-term antithrombotic scheme is controversial. While clinical practice guidelines (4,5) recommend only one week of triple therapy for patients with a high risk of bleeding, in this case, the high risk of thrombus led to one-month triple therapy. Warfarin was selected as the anticoagulant, since current literature shows that vitamin K antagonists continue to be better than new oral anticoagulants. (6) Finally, and most importantly, this case proves the relevance of a multidisciplinary and early approach by all the departments involved (Cardiology, Interventionist Cardiology, Emergency, Nephrology, Rheumatology, and Hematology) for the decision-making process in a condition entailing both diagnostic and therapeutic challenges.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web)

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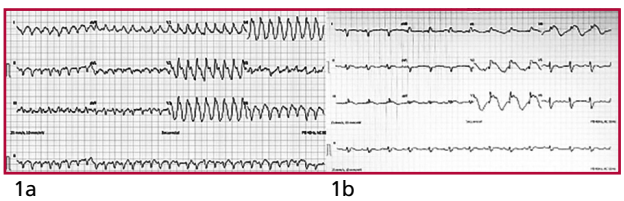
Brugada Syndrome in Children. The Tip of an Uncommon and Fatal Iceberg. First Unusual Case Report in a Child and Her Family Members in Argentina

A 9-month female baby was referred to our hospital following admission in another institution with poor general condition, tachycardia, and fever resulting from the usual immunization schedule. Upon admission, she was under mechanical ventilation, with signs of hemodynamic instability. The ECG showed regular monomorphic ventricular tachycardia (VT), heart rate (HR) >200 bpm, and wide QRS with complete right bundle branch block (CRBBB) (Figure 1a). She was under regular doses of intravenous (IV) amiodarone and propranolol. The patient was unresponsive to adenosine and electrical cardioversion (ECV), and after confirming severe left ventricular systolic function (LVSF) impairment, she received peripheral extracorporeal membrane oxygenation (ECMO) and IV milrinone. After a few hours, the ECG showed sinus rhythm, HR 80 bpm, AV conduction 1:1, PR interval 220 msec, CRBBB, QRS 240 msec, with probable late potentials after the QRS complex, particularly in right precordial leads (Figure 1b). The color Doppler imaging showed absence of structural heart disease, normal coronary arteries at their origin, normal LV diameters with improved LVSF, and moderate dilatation in the right chambers.

Our differential diagnosis was Brugada syndrome (BrS), a sodium channelopathy that might lead to arrhythmia and myocardial involvement, vs giant cell myocarditis, vs arrhythmogenic cardiomyopathy. As a result, a gadolinium enhanced nuclear magnetic resonance was required, which was normal, and allowed us to rule out myocarditis (1) and any mediastinal tumors (2) that may appear with a "Brugada-like pattern" on the ECG. The laboratory infection and toxicology screens were negative. A thorough interview with the parents revealed that the baby was the first child of non-consanguineous parents, the pregnancy was spontaneous and uncomplicated and the delivery was natural. According to the parents, when the child was 6 months old, she had generalized paroxysmal events of tonic-clonic type due to post-immunization fever, which were considered unsignificant by her pediatrician. Her 34-year-old mother claimed to have experienced two syncope events 15 years before, which were preceded by palpitations during physical exercise. Her maternal grandfather experienced sudden death at 22, as well as some of his siblings (Figure 2a). The mother's ECG showed a spontaneous type 1 Brugada pattern (Figure 2b). The Holter showed symptomatic atrial tachycardia (AT) events (Figure 2c) that improved under oral ivabradine.

A genetic test (GT) was requested considering our patient as an index case and using a next-generation sequencing (NGS) panel in accordance with present guidelines. (3) Amiodarone was discontinued, and oral quinidine was administered; the adult dose was adjusted based on the patient's weight and body surface. The patient was stabilized and discharged under home monitor and automated external defibrillator. However, she was readmitted only 12 hours later with HR 270 bpm, wide QRS and CRBBB, but this time responsive to ECV. Atrial tachycardia was assumed, and therapy with oral ivabradine and cilostazol was added; however, she showed torpid evolution with subintrant tachycardias that resulted in readmission and peripheral ECMO. As it became difficult to control her high HR, IV esmolol was given with good response; quinidine and cilostazol were discontinued, and milrinone and sotalol were administered. While the patient was under ECMO we performed an electrophysiology test. No arrhythmia could be induced; thus, an AV node ablation procedure was conducted with placement of a dual chamber epicardial implantable cardioverter-defibrillator (ICD), which revealed failure to capture and high epicardial thresholds in both ventricles. Consequently, the defibrillator lead was replaced in the endocardial right ventricle by a transatrial approach and was programmed to operate in DDD mode. When the patient was no longer under ECMO, she experienced constant VT with a HR 170 bpm, both properly censored and reverted using antitachycardia therapy, reinduction after a few minutes,



1a 1b

Fig. 1.

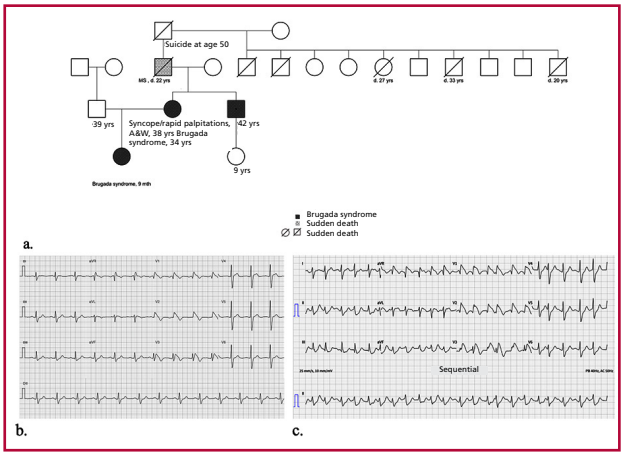


Fig. 2. a) Family history; b) Maternal ECG; c) Maternal ECG, atrial tachycardia

and appropriate shock. As VT became more frequent in DDD and/or VVI mode with HR 90 bpm, we decided to reset the ICD to VVI 60 bpm and managed to fully control tachycardia.

The GT revealed a heterozygous pathogenic variant in SCN5A gene c.535C>T (p.Arg179*). We know that this genetic change leads to early protein truncation, resulting in absent or abnormal protein, and subsequent loss of cardiac sodium channel function, a genetic mechanism considered to be the cause of BrS. The patient's mother and mother's brother (i.e., the patient's uncle) are both carriers of the same pathogenic variant in SCN5A gene. Fortunately, her uncle's daughter is negative, i.e., she has not inherited her father's pathogenic variant (Figure 2 a). As with other genetic disorders with an autosomal dominant inheritance pattern, although our patient inherited her mother's mutation, and her mother, in turn, inherited the variant from her own father, there is still no explanation why the patient had such a severe phenotype, while her mother barely experienced any symptoms and her uncle had none (and even had a normal ECG). Cascade testing was performed for the rest of the family, those with negative results were exempted from longitudinal follow-up, and prevention and monitoring actions were taken in those with a positive GT.

In addition, epilepsy was confirmed in the baby, and she was prescribed levetiracetam with optimal response. The pathophysiology shared by idiopathic epilepsy and BrS is an impaired transmembrane ion current caused by mutations in genes that encode the subunits of several ion channels. Sodium channel dysfunction is a common pathogenic route for these two clinical conditions, suggesting that it might be the cause of heart and brain manifestations in this group of patients. (4)

In 1987 doctors Brugada treated a 3-year-old patient who recovered from cardiac arrests and had a structurally normal heart, whose sister experienced sudden death at the same age. Both children had a distinct ECG pattern that is now known as BrS. (5) Research then focused on young adults with no evident heart disease, recognized as a major cause of sudden death (SD). While several studies estimate that BrS represents up to 20% of SD cases in infants and young individuals, little is known about the prevalence, diagnostic criteria, natural course, and treatment of this disease in pediatric patients. (6)

This very young patient with BrS first experienced monomorphic ventricular arrhythmias with CRBBB from the left ventricle, and severe atrial arrhythmias requiring exceptional therapy, and finally received a drug treatment uncommon for patients with BrS. In this case, arrhythmias were later controlled using betablockers and maintaining a very low HR for her age.

The SCN5A mutation results in absence of a protein, which is associated with severe phenotypes. Her mother and other family members were diagnosed after the child's diagnosis, and both follow-up and counseling was arranged for family planning. The latter highlights the importance of careful symptom assessment, detailed family history, and thorough ECG review.

This case is intended to raise awareness on the importance of BrS identification in pediatric patients, in an attempt to understand the pathophysiology of this complex, heterogeneous and life-threatening condition. We also emphasize the need for further studies and exchanges in order to build consensus in terms of Brugada syndrome management both in children and adults.

Conflicts of interest

None declared.

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

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Harlequin Syndrome as an Unusual Presentation of Carotid Artery Dissection

This is the case of a 40-year-old male patient with no relevant medical history.

In February 2022, the patient presented to the Emergency Department, with headache and acute right palpebral ptosis after playing football. A magnetic resonance angiography (MRA) of the neck and intracranial vessels was performed, which resulted in right internal carotid artery dissection (ICAD) diagnosis (Figure 1 A & C).

The patient was treated with low molecular weight heparin and then aspirin.

He progressed with improvement of his Horner syndrome (palpebral ptosis, miosis), so he was discharged 4 days later.

The MRA was repeated after 30 days, and it revealed, as the previous imaging test though to a lesser extent, a reduction in the diameter size and irregularity of the right internal carotid artery from the visible extracranial area to the bifurcation, with no apparent involvement of the ipsilateral middle cerebral artery. It also revealed a larger luminal diameter of the postbulbar segment of the right internal carotid artery compared to the previous imaging test (Figure 1 B & D).

The patient continued with milder palpebral ptosis. Anisocoria improved as well.

Three months later, while monitoring his condition, the patient claimed to notice flushing and sweating on the left side of the face during strenuous physical activity, with the right side remaining pale and non-sweaty (Figure 2).

These symptoms remitted after a few minutes of rest.

ICAD clinical findings may include local signs and symptoms such as unilateral headache (periorbital and frontotemporal pain in the face or anterior part of the neck), Horner syndrome (miosis, ptosis, and anhidrosis), and cranial nerve paralysis. Horner and Harlequin syndromes result from compression, stretching, or hypoperfusion of the sympathetic nerve fibers (vasomotor and sudomotor fibers) within the carotid wall. (1)

Acute onset painful Horner syndrome is almost a pathognomonic sign of ICAD. Asymmetrical flushing (Harlequin syndrome) is an uncommon finding in ICAD, as both vasomotor and sudomotor fibers innervating the face are mostly adjacent to the external carotid artery wall. (2)

The MRA is currently the preferred technique to confirm ICAD diagnosis.

Awareness of this cosmetically striking syndrome following ICAD is useful to avoid unnecessary additional tests, as it spontaneously disappears over time. (3)

Conflicts of interest

None declared.

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

Ethical considerations

The patient signed informed consent form for the publication of his photograph.

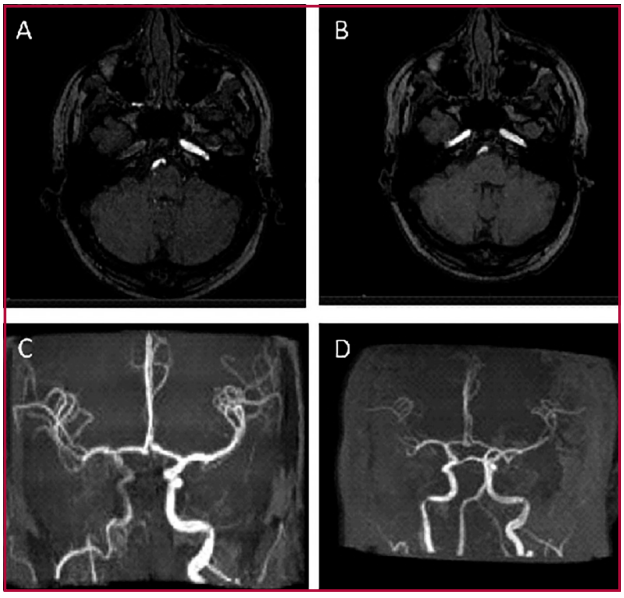

Fig. 2. A & C. Magnetic resonance angiography of neck vessels upon admission **B & D.** Magnetic resonance angiography after 30 days

Fig. 1. Paleness and anhidrosis on the right side of the face after strenuous physical activity. Ipsilateral palpebral ptosis is also observed.

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WILLIAM HARVEY (II) "DE MOTU CORDIS". ANALYSIS (first part)

William Harvey (II)
"De Motu Cordis". Análisis (primera parte)

JORGE C. TRAININI[MTSAC]

Harvey's exceptional book is titled *Exercitatio anatomica de motu cordis et sanguinis in animalibus*. It was written in Latin and published in Frankfurt am Main. On its cover it reads: William Harvey, English, Royal Physician and Professor of Anatomy at the London Medical College, Frankfurt, William Fitzeri, 1628.

To reach a full knowledge of blood circulation required innumerable steps, which like fragments, sometimes staggered, sometimes superimposed, took place to achieve a total understanding of the system through Harvey´s work.

The scholars who contributed to the effort of observation and investigation, sometimes even with tragic events such as the death of the Spaniard Miguel Servetus, constituted a prestigious group. We have seen in the development of the previous articles, that, from the earliest ancient times, blood and its movement generated a deep debate that lasted until the 17th century, when Harvey and Malpighi demonstrated the reality of such movement through its anatomical steps.

Not a few authors have seen in this historical development of knowledge, the intention to glimpse the understanding of the major blood circulation, in times prior to the appearance of *De Motu Cordis*. Thus Galen, de la Reyna and Cesalpino were catapulted to this an honor, aspiring to find in them such a discovery.

In fact, an abbreviated course of events tells us that Ibn an-Nafís, despite being the first to demonstrate minor circulation, suffered the misfortune of oblivion until the distant 1924. The Spanish Miguel Servetus was the author of the first print in which pulmonary circulation (1553) was demonstrated, on a manuscript that he had sent to Calvin in 1546. Due to the Inquisition, his work remained "secret" until another Spaniard, Juan Valverde in 1556, and the famous professor of Padua, Realdo Colombo in 1559, correctly exposed the minor circulation.

In 1546, Francisco de la Reyna, a veterinarian by profession, was the author of a paragraph in his work the Book of Albeytería, where some saw erroneously described the major circulation, by stating that in the limbs blood passes from the arteries to the veins. For his part, Andrea Cesalpino exhibits in his text *Quaestionum peripateticarum* (1593) an interesting knowledge about circulation. He shows that blood can be moved centripetally in the peripheral veins, dethroning the liver of Galen as the center of blood and placing Aristotle's heart in its place.

By using the word "*circulatio*", it was thought that Cesalpino had found the real circulatory physiology, but his belief in the continuous peripheral consumption of blood, cancels such a concept. He foresaw the function of heart valves, which in his concept prevented the return of blood from the heart towards the vena cava. He also mentioned the arteriovenous anastomoses. In short, the "*continuus motus*" described by him would displace the blood from the vena cava to the right heart, then part of its amount would pass through the lung to the left ventricle and from there to the parts of the organism, with acceptance of the pores of the septum. He spoke of the "*in capillamento resolvuntur*", which represented the thin venous and arterial terminal ducts.

Using all this background, even of details such as the true function of venous valves, Harvey applied not only observation but also experimentation to definitively dismantle the theory that had prevailed during fourteen centuries. In a patient methodological work, based on reasoned explanation and research on different animals he was able to distort the concepts that opposed the correct movement of blood. The appearance of the microscope would enable Marcelo Malpighi in 1661, to close the gap between the arteries and the veins by discovering the capillaries.

Dedications

From the first page Harvey seeks to have no weaknesses in his work, not even at the level of dedications. Thus, the first of them is addressed to the "Most serene and undefeated" Charles I, king of Great Britain, France and Ireland, and defender of the faith, comparing him with the "main engine" of the heart and to whom he reports the "news about the heart."

The second dedication is to the president of the London College of Physicians, Dr. Argent. In it he speaks of a work "of nine years or more" on the sub-

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ject, since in 1616 the manuscripts prepared for the *Praelectium anatomiae* referred to the circulation. In these first pages he shows great respect for his colleagues by treating them as "most learned and most expert", and then categorically sustains "the blood runs and returns along the same path."

The search for support in the College of Physicians is evidenced when he denotes extreme prudence in his work: "whatever we know, is only a small part of what we ignore." There is a clear concept of a Renaissance experimenter when expressing: "philosophers...cannot bear to be enslaved or lose their freedom to the point of believing their own eyes", and later "...I am not pursuing anything else but the truth".

Proem

Harvey mentions the need to use prior knowledge, but modifying it in relation to experience, dissection and observation. He promptly establishes a separation between the function of pulse and respiration, pointing out that the structure and movement of the heart are different from those of the lung. He contrasts his idea to that of Galen and of Fabrizio d' Acquapendente, who in his work *De respiratione et eius instrumentis libellos duos* (Venice, 1615) stated that the lungs surrounded the heart to cool it, since the arteries were not enough to ventilate it.

In the proem, through successive questions he dismisses the prevailing Galenic physiology. He emphasizes that the arteries carry heat rather than ventilation and refrigeration to the parts.

"How can diastole simultaneously attract spirits of the heart to heat the parts and air from outside to cool them?" According to Harvey there are mixed opinions among the precursors. Against Erasistratus and in favor of Galen he states that arteries contain only blood. To demonstrate this, he mentions Galen's experiment: "If, having placed ligatures in two places of an artery, the segment that remains between them is longitudinally cut, it is found that it only contains blood." Later he declares "spirits and blood are intrinsically linked" whereby we can glimpse a certain approximation to the blood oxygenation process.

He denies Galen's "pulsific" jump originating in the heart, claiming "that blood pulse distends the arteries." In his controversy with Jean Riolano, after the release of *De Motu Cordis*, he incorporates a clinical case referring to this topic, which implies the use of pathology to explain circulatory physiology. So, in the "Second Epistle" (1649) he literally replies to Riolano, who was firmly against the circulatory theory, with the following experience in a patient he treated: "the descending aorta had turned into a bone tube, but nonetheless, the arterial blood reached the lower extremities and made their arteries pulse... Where it was changed into bone it could not expand or contract like a bellows; nor transmit the pulsating power from the heart to the lower vessels; nor propagate a force that was incapable of receiving through the solid matter of the bone. However, I frequently noticed the pulse in the legs and feet of this patient, while he lived, since I was his most caring doctor and his very special friend." Let us remember that, in opposition to Harvey, Riolano wrote first his text *Encheiridium anatomicum* (1648) and later his *Opuscula anatomica nova* (1649).

Another question he poses to himself corresponds to the analogous constitution of both ventricles: "how could it be claimed that the function of this [the left ventricle] is to draw out and prevent the return of the spirits and that of the right ventricle is to draw out and prevent the return of blood?", if both are similar in their constitution. The same requirement corresponds to the "*vena arteriosa*" in relation to the "*arteria venosa*", wondering why they have the same size for different functions.

There is also concern in this reasoning: "How can we assume that so much blood is necessary for the nutrition of the lung?", if the "*vena arteriosa*" is larger than the vena cava. When studying the right ventricle, Harvey wonders why would this cavity, so close to the lung, have a nutritional function for the latter only, when expressing: "to nourish the lung,...add another ventricle to the heart?"

The next question refers to the left ventricle and the "*arteria venalis*". Why do they have two functions? a) to remove fuliginous matter towards the lung and b) to transmit spirits to the aorta, shrewdly expressing "what... prevents the spirits from mixing and confusing with the fuliginous matter?" Furthermore, in a series of questions on the capacity that the atrioventricular valves would have to prevent the exit of air, and to allow the fuliginous matter to pass, he exposes the most fragile structure of the Galenic system. With the same reasoning he investigates the possible mechanism for the semilunar valves to prevent the "spirit" from returning to the left ventricle. Faced with the topic of various uses for the "*arteria venalis*" -he answers- "nature does not manufacture a single vessel for opposite functions."

He confirms that there is no air in the "*arteria venalis*", but blood. If there were air, its constitution would not be that of a vein, but "the path...should be ringed as that of the bronchi, in order to remain always open without collapsing." He denies the porosity of the interventricular septum, a concept that, as we know, was previously expressed by Servetus, Vesalius, Valverde and Colombo, of whom he does not make direct reference. When expressing that in the fetus blood passes through the foramen ovale, he assumes that it could not do so easily through the septum of the adult, if it is understood that it is of a denser composition.

Harvey concludes his excellent proem, pointing out with methodological success that the paths to reach the truth are vivisection and "*ob oculo*" observations.

BRUNO BUCHHOLZ

Cardioneuroablation and the Downside of Parasympathetic Denervation of the Heart

Chung W, Masuyama K, Challita R, Hayase J, Mori S, Cha S, et al. Ischemia-induced ventricular proarrhythmia and cardiovascular autonomic dysreflexia after cardioneuroablation. **Heart Rhythm. 2023;20:1534-45. http://dx.doi.org 10.1016/j.hrthm.2023.08.001.**

The autonomic nervous system is strongly involved in the pathophysiology of some diseases that often represent a great challenge for clinical management. Such are the cases of the vasovagal syncope, the syncope caused by carotid sinus hypersensitivity, the functional bradycardias with autonomic components, and the atrioventricular block, among others.

Although vasovagal syncope is a benign entity, it is frequent and, in many cases, produces severe episodes associated with trauma and general risks from loss of consciousness. The causal mechanism of vasovagal syncope is not yet completely understood, but it is known that hemodynamic, neurohormonal and autonomic components are involved; hyperreactivity of cardioinhibitory and vasodepressor mechanoreflexes is the most accepted mechanism. In this context, cardioneuroablation has emerged as a promising treatment for the most severe cases, especially those with a strong bradyarrhythmia component due to parasympathetic hyperactivity. Despite some technical and anatomical localization differences, as is the case of ablation for some atrial fibrillations, cardioneuroablation consists of radiofrequency ablation of some epicardial ganglionated plexuses of the intrinsic cardiac nervous system. Several clinical studies have shown improvement in these patients. However, many important aspects of this procedure have not been fully studied, such as the correct identification of the ganglionated plexus to be ablated, the optimal approach for ablation, the histological effects, and the long-term consequences of disrupting the delicate autonomic balance that controls cardiovascular function.

Wei-Hsin Chung et al. performed an interesting and well-conducted study in an experimental model of percutaneous cardioneuroablation in pigs to demonstrate the histological and functional effects in the acute and mid-term stage. Incomplete disruption of the ganglia that comprise the left superior ganglionic plexus and the right atrial ganglionated plexus was enough to block the effects of right vagal stimulation on heart rate reduction and the effects of left vagal stimulation on PR interval prolongation. These effects persisted six weeks after the procedure. Importantly, vagal stimulation in denervated animals activated compensatory sympathetic mechanisms which led to an increase in heart rate, left ventricular systolic pressure and dP/dt (change in pressure during isovolumetric contraction). An altered reflex response in ablated pigs was also observed with sympathetic stimulation. The paradoxical autonomic response after cardioablation demonstrates that the effect may extend beyond autonomic control of the conduction system nodes and, furthermore, that the persistence of this dysautonomia may have a long-term impact on overall cardiovascular health. They also observed a significant increase in the incidence of ventricular arrhythmias induced by myocardial ischaemia due to occlusion of the left anterior descending artery at six weeks in the ablation group compared to the control group. The increased susceptibility to severe arrhythmias occurred in the context of impaired repolarization and dispersion of ventricular repolarization. A combined effect of local denervation, cardiac dysreflexia and altered repolarization dynamics may be responsible for the arrhythmias.

The intrinsic cardiac nervous system consists of a complex system of highly interconnected nerve fibres and ganglia, which form a subepicardial neural network and another subendocardial (purely fibrillar) one which finely regulate regional cardiodynamic functions. The epicardial plexus is divided into subplexuses based on their anatomy and function, although much is yet to be known. Intracardiac sympathetic, parasympathetic, afferent and interconnecting neurons, in turn, have a functional relationship in an ascending hierarchical stochastic system to the higher centres. The recruitment of each neural level takes place through a delicate balance that determines the autonomic tone and conditions the normal functioning of each cardiac activity. Moreover, it extends far beyond the boundaries of the heart to regulate the entire cardiovascular tree and the kidney function as well as to condition our behaviours and emotions. The degree of dysautonomia may determine the course of many cardiovascular diseases and condition the patients' prognosis. In this regard, the presence of paradoxical reflexes and autonomic imbalances following cardioneuroablation in this experimental model should at least be a warning sign.

In addition, the increased incidence of arrhythmias caused by a very brief ischemia is a reminder of the important role of the autonomic nervous system in the regulation of heart rate and electrical stability of the myocardial syncytium. It also reminds us of the protective role of the parasympathetic system, which activates cell survival pathways, reduces inflammatory and oxidative stress, and is anti-fibrotic and pro-angiogenic, among other effects. Undoubtedly, a large group of people suffering from syncope with severe manifestations require a response, and cardioneuroablation has emerged as a very interesting proposal with promising symptomatic results. However, more studies are needed not only to delve more deeply into the long-term local and systemic effects but also to better understand the pathophysiology of syncope with significant involvement of the autonomic nervous system to find more selective solutions..

Closing Speech of the 2023 SAC Academic Ceremony

Discurso de cierre del acto académico 2023

Authorities of the Argentine Society of Cardiology and international societies, ladies, gentlemen, colleagues, family, and friends.

This is a great opportunity to recall a verse from a famous song by Vox Dei that many of you will remember, perhaps the younger ones will not, titled "Present". The verse goes: "Everything comes to an end, nothing can escape, everything has an end, everything ends...".

However, I must say that when we started managing the SAC three years ago, it seemed endless and never-ending.

The workload increased in 2023 when I took over as president. The goals we set required hard work, which can only be achieved through joint effort, in agreement with the full Executive Board, the Advisory Council, and all the leaders of the different councils, areas, and staff of the Society. Our shared love for the Society aligns us in this endeavor.

We restructured the SAC by dismissing the General Manager and Administrative Manager on April 21, 2023, as well as the legal advisor. We also incorporated a new law firm, WNS & Asociados, with whom we negotiated an agreement with Alejandro Delle Sedie. As a result, we outsourced the SAC.23 Congress to Plan A, a company owned by Andrea Juncos. During this period, we have also designated the new manager, Dr. Analía Llanos. The administration underwent restructuring, which involved adjusting existing resources and incorporating new ones, without increasing the number of employees.

New guidelines have been issued regarding the inclusion of young people and individuals from different districts. The Communication Area has shared guidelines for disseminating information through networks, and two new areas of the SAC have been created: Design Area and Website Area. Regarding SAC's image, a new website is being designed and created by a company. The website will be managed by the web development and Design Area of the SAC. Additionally, a company is developing the SAC's Trademark Manual. Despite the country's economic crisis and inflation rate of over 145%, the cost of SAC increased by only 30%.

The RAC has a new website in HTML format, which is a requirement for being indexed. We have implemented on-demand courses and developed a cardiology course for non-cardiologists. There have been more than 46 courses this year.

Two new fellows were incorporated to the Research Area, and we launched a SAC fellowship, which was awarded to six winners receiving funding of one million pesos each. This year, the Rosenbaum Award for the Best Scientific Paper published in the RAC between July 2022 and August 2023 was granted $1 000 000 to the winner. We hope to be able to offer a monetary award in future years.

We have introduced new benefits for our members, including a 30% discount for retired physicians and a 12-installment payment plan for technicians. We encouraged young people to become members of SAC councils and areas at the end of the two-year course. We coordinated activities between SAC Young Community, Districts and CONAREC.

In October, we organized the SAC.23 Congress in collaboration with CARDIOSUR, a successful event with 12 087 attendees and 14 423 registered participants. The Imaging Congress, held once again onsite, was attended by 1200 registered participants.

The Heart and Women's Area presented a bill in the Chamber of Deputies to establish October 9 as Cardiovascular Disease (CVD) in Women Awareness Day.

As an institution, the SAC requested a hearing from the National Ministry of Health regarding Law No 27177, which establishes the creation of the National Institute for the Prevention, Diagnosis, Treatment and Research of CVD.

The accreditation of the SAC as scientific certifying board for specialty certification was renewed for 5 years until 2028.

We have released a joint statement with other scientific societies regarding the issue of medical fees and supply shortages. The statement received significant support and attention.

We invited CONAREC to participate in the areas of the SAC.

We renewed the agreement with the UCA (Catholic University of Argentina) for the Diploma Course in Hypertension, Dyslipidemia and Cardiometabolism. We will sign an agreement with USAL (Universidad del Salvador) for the planning and development of academic cooperation activities. We are still working on our University Institute project.

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We bought a CPR manikin for the Argentine Foundation of Cardiology.

Our districts organized 10 regional conferences, 8 workshops and webinars.

We conducted the third edition of the Sonqo Calchaquí Program in the indigenous peoples of Cachi in Salta, Colalao del Valle in Tucumán, and Fuerte Quemado in Catamarca.

At the international level, we were invited to participate in various activities organized by the American College (Congress in New Orleans). We also participated in the European Congress of Cardiology in Amsterdam, in an official joint session and in the presentation of the Daily Highlights. We were also invited to Latin American meetings in Costa Rica, the Dominican Republic, Paraguay, Chile, Brazil and Uruguay.

We actively participated in the Congress of the Russian Society of Cardiology, as well as in India and Africa (Morocco). We participated in a joint virtual session at the GWICC (Great Wall International Congress of Cardiology of China).

For the second year running, through an agreement with the New York Chapter of the ACC, we awarded a scholarship to a resident for an internship in a hospital in New York, and a scholarship to attend the 2023 ACC Global Leadership Institute (scholarship for the Argentina Chapter of the ACC for leadership training in Washington).

We have completed numerous activities thanks to our exceptional team of colleagues. I would like to express my gratitude to Executive Board, Board of Directors, and the Advisory Council for their support during my tenure as President.

I am also grateful to Marina and Analía Llanos for their support and dedication, as well as to the entire staff for their excellent work, and to Pablo, Gabriel, Silvia, Diego and Belén from the Executive Board.

Special mention goes to two people with whom we worked hard: Víctor Mauro and Hugo Silva. We spent hours at the Society planning the changes, working side by side. At night, we continued at the bar.

Things go well because of the commitment we agreed to work from all areas and councils, I really would not finish this speech, but I thank them all. I also want to tell you that I will miss all of you in this board, and as I said in my opening speech, one makes many friends.

I am grateful to the pharmaceutical companies for their constant support for our courses and congresses.

Thank you very much.

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