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Continuation of the Revista Mexicana de Cardiología

2023

- Artificial intelligence in cardiology
- EuroSCORE II model for predicting surgery mortality
- Coarctation of the aorta complicated by aortic aneurysm dissection
- Non-ruptured aneurysm of Valsalva sinus with a special shape
- *Streptococcus gordonii* infective endocarditis complicated
- In-flight cardiac arrest
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Editorial

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Artificial intelligence in cardiology: transforming the landscape of cardiovascular healthcare

Inteligencia artificial en cardiología: transformando el panorama de la atención de salud cardiovascular

Guillermo Ceballos,* Nayelli Nájera*

INTRODUCTION

Integrating artificial intelligence (AI) into various fields has revolutionized how we approach complex problems, and cardiology is no exception. In recent years, AI has emerged as a powerful tool in cardiovascular healthcare, offering innovative solutions for early diagnosis, personalized treatment plans, and improved patient outcomes. This essay explores the applications of artificial intelligence in cardiology and its potential to reshape the landscape of cardiovascular medicine.

EARLY DETECTION AND DIAGNOSIS

One of the key areas where AI has shown promise in cardiology is the early detection and diagnosis of cardiovascular diseases. Machine learning algorithms, trained on diverse patient information datasets, can analyze complex patterns and identify subtle abnormalities in medical imaging, such as echocardiograms, magnetic resonance imaging (MRI), and computed tomography (CT) scans. These AI-driven tools enable healthcare professionals to detect cardiovascular conditions at their nascent stages, allowing for timely intervention and prevention of more severe complications.

RISK STRATIFICATION AND PREDICTIVE ANALYTICS

AI algorithms process and analyze large volumes of patient data, including electronic health records, genetic information, and lifestyle factors. By integrating these datasets, AI can assist in risk stratification, providing a more accurate assessment of an individual's likelihood of developing cardiovascular diseases. AI-powered predictive analytics can help identify high-risk patients, allowing healthcare providers to implement preventive measures, lifestyle interventions, and personalized treatment plans tailored to each patient's unique risk profile.

PERSONALIZED TREATMENT PLANS

Artificial intelligence enables the development of personalized treatment plans by considering individual patient characteristics, genetic makeup, and responses to specific interventions. Machine learning algorithms can analyze treatment outcomes from patient data to identify the most effective therapeutic strategies for different cardiovascular conditions. This personalized approach enhances treatment efficacy and minimizes potential side effects by tailoring interventions to each patient's specific needs.

REMOTE MONITORING AND TELEMEDICINE

The advent of AI in cardiology has facilitated the evolution of remote monitoring and telemedicine. Wearable devices equipped with AI algorithms can continuously monitor a patient's cardiovascular parameters, providing real-time data to healthcare providers. This

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remote monitoring allows for early detection of changes in a patient's condition, timely intervention, and the prevention of hospital readmissions. Furthermore, AI-supported telemedicine platforms enable patients to access cardiovascular care from the comfort of their homes, improving accessibility and reducing the burden on healthcare facilities.

CHALLENGES AND ETHICAL CONSIDERATIONS

Despite its numerous advantages, integrating AI in cardiology is not without challenges. Ensuring the security and privacy of patient data, addressing issues of algorithm bias, and maintaining transparent decision-making processes are essential considerations in developing and implementing AI technologies in healthcare. Striking a balance between technological innovation and ethical considerations is crucial to building trust among healthcare professionals and patients.

CONCLUSION

Artificial intelligence has emerged as a transformative force in cardiology, offering unprecedented opportunities to enhance early detection, diagnosis, and treatment of cardiovascular diseases. As AI technologies evolve, their impact on cardiovascular healthcare will likely expand, contributing to more personalized, efficient, and accessible cardiac care. By addressing challenges and ethical considerations, the integration of AI in cardiology holds the potential to usher in a new era of precision medicine, ultimately improving patient outcomes and reducing the global burden of cardiovascular diseases.

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ORIGINAL RESEARCH

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The usefulness of the EuroSCORE II model for predicting surgery mortality in a high specialty hospital in Mexico

Utilidad del modelo EuroSCORE II para predecir la mortalidad quirúrgica en un hospital de alta especialidad de México

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Keywords:
EuroSCORE II, cardiac surgery, heart surgery risk calculator, validation.

Palabras clave:
EuroSCORE II, cirugía cardíaca, índice de riesgo en cirugía cardiaca, validación.

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ABSTRACT

Introduction: the EuroSCORE model has been used in various countries, including México, to estimate the probability of surgery-associated mortality. Several studies have shown deficiencies in its calibration while retaining good discrimination. The model was updated in 2012 and called EuroSCORE II. **Objective:** to evaluate the calibration and discrimination of the EuroSCORE II model in patients undergoing cardiac surgery in a high specialty hospital in México. **Material and methods:** an observational, cross-sectional, and retrospective study was performed. Patients ≥ 16 years old years who underwent cardiac surgery between the years 2008-2013 were included. The hospital mortality rate was obtained, and the EuroSCORE II was calculated online. Discrimination of the EuroSCORE II model was evaluated with the area under the curve of a receiver operating characteristics curve (AUC-ROC), and the calibration was assessed using χ^2 of Hosmer-Lemeshow (H-L) goodness of fit test and risk-adjusted ratio (RAMR). **Results:** three hundred thirty-eight patients were included. The mean age of participants was 49.8 ± 16.61 years; 162 were women (47.9%), and 176 (52.1%) were men. Surgery types were valvular 108 (31.9%), coronary revascularization 101 (29.8%), congenital 51 (15.08%), and other 78 (23.07%). The average EuroSCORE II was 4.1 (95% CI, 3.53-4.68). Mortality observed was 10.9%. The AUC-ROC was 0.806 (95% CI, 0.739-0.872), consistent with good discrimination. The χ^2 of H-L of 14.2, p = 0.08,

RESUMEN

Introducción: *el modelo EuroSCORE ha sido utilizado en diversas latitudes, incluido México, para estimar la probabilidad de mortalidad operatoria. Varios estudios han mostrado deficiencias en su calibración, conservando buena discriminación. El modelo fue actualizado en el 2012, llamado EuroSCORE II.* ***Objetivo:*** *evaluar la calibración y discriminación del modelo EuroSCORE II en pacientes sometidos a cirugía cardiaca en un hospital de tercer nivel en México.* ***Material y métodos:*** *estudio observacional, transversal y retrospectivo. Se incluyeron pacientes ≥ 16 años operados entre 01/01/2008 y el 31/12/2013. Se registró la mortalidad hospitalaria y se calculó el puntaje de EuroSCORE II en línea. Se valoró la discriminación con el área bajo la curva (ABC) característica operativa del receptor (ROC). La calibración fue evaluada mediante prueba de χ^2 de bondad de ajustes de Hosmer-Lemeshow (H-L) y la razón ajustada al riesgo (RAMR).* ***Resultados:*** *338 pacientes, edad media de los participantes 49.8 ± 16.61 años (16-80), 162 mujeres (47.9%). Tipos de cirugía: valvular 108 (31.9%), revascularización coronaria 101 (29.8%), congénitos 51 (15.08%) y otros 78 (23.07%). El puntaje promedio EuroSCORE II fue 4.1 (IC 95%, 3.53-4.68). Mortalidad observada 10.9%. El ABC ROC fue 0.806 (IC 95%, 0.739-0.872) compatible con buena discriminación. La χ^2 de H-L de 14.2, p = 0.08, compatible de calibración adecuada. La RAMR fue de 2.65, que indica infraestimación del modelo.* ***Conclusión:*** *el modelo EuroSCORE II mostró buena discriminación. La calibración fue adecuada de acuer-*

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compatible with adequate calibration. The RAMR was 2.65, indicating an underestimation of the model. **Conclusion:** the EuroSCORE II model showed good discrimination. The calibration was adequate according to the χ^2 of H-L, but the value of the RAMR suggests that the model underestimates the risk of mortality.

do con la χ^2 de H-L pero el valor de la RAMR sugiere que el modelo infraestima el riesgo de mortalidad.

INTRODUCTION

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a probabilistic model designed in 1999 to estimate the risk of death in patients undergoing major cardiac surgery.[1,2] The model has shown good calibration, with chi-square (χ^2) of Hosmer-Lemeshow (H-L) of 7.5, p2. It was initially published in an additive version and later in a logistic version, both of which have been evaluated in multiple latitudes and countries, showing generally good performance.[3-7]

Nevertheless, in recent years, some authors pointed out that the additive version of the EuroSCORE model overestimated mortality risk in low-risk patients and underestimated it in high-risk patients.[8] On the other hand, several authors have shown that both the additive and logistic versions of the model overestimated risk, especially in high-risk patients.[9-15] As a result of this situation, the Score underwent a redesign and was published in 2012, adopting the name EuroSCORE II.[16]

Some variables of the old model were redefined or modified; for example, renal function was evaluated by creatinine clearance with cut-off points of 85 mL/min, 50-84 mL/min, < 50 mL/min, and on dialysis, replacing the previous one based on serum creatinine levels. The variable neurological dysfunction was replaced by poor mobility due to neurological diseases and musculoskeletal diseases; pulmonary arterial hypertension was redefined as < 30 mm Hg, 30-55 mm Hg, and > 56 mm Hg. In total, 18 variables constitute the EuroSCORE II model. The new model has a predicted mortality of 3.95% and observed mortality of 4.18%, as well as discrimination evaluated through the AUC-ROC of 0.8095 and calibration through the χ^2 of H-L of 15.48 with $p < 0.0505$. The calibration of the model was also assessed using the risk-adjusted risk ratio (RAMR), with a score of 1.058, which shows good calibration of the score.[17,18]

The EuroSCORE II model has been subjected to external validation in different latitudes, with contradictory results.[19-25] It has nevertheless been used to evaluate the risk of mortality in patients undergoing cardiac surgery in our institution without confirmatory studies of its relevance.

Therefore, the present study aimed to evaluate the calibration and discrimination of the EuroSCORE II model in patients undergoing cardiac surgery at the *Hospital Regional de Alta Especialidad del Bajío* (HRAEB).

MATERIAL AND METHODS

Inclusion and exclusion criteria

An observational, cross-sectional, retrospective study was conducted at the *Hospital Regional de Alta Especialidad del Bajío* (HRAEB) in León, Guanajuato, Mexico. The study population consisted of all records (343) of patients who underwent cardiac surgery between 2008 and 2013. The inclusion criteria included having undergone cardiac surgery with and without a heart-lung machine and having all the information requested by the EuroSCORE II model. Four cases were eliminated since they did not contain the information requested by the model, and one case was triplicated, resulting in a total of 338 cases that were included.

Data collection

Four Cardiology and Cardiac Surgery Service physicians collected data from clinical records that met the inclusion criteria. A structured, purpose-built instrument was used to gather the information. The following variables were

Table 1: General characteristics and comorbidities of the study population (N = 338).

Characteristic	n (%)
Age [years], mean ± SD (range)	49.87 ± 16.6 (16-80)
Age groups [years]	
≤ 50	139 (41.12)
51-60	101 (29.88)
61-70	72 (21.30)
≥ 70	26 (7.69)
Gender	
Male	176 (52.07)
Female	162 (47.93)
Weight [kg], mean ± SD	67.21 ± 14.49
Height [cm], mean ± SD	160.06 ± 0.93
Body mass index [kg/m^2], mean ± SD	26.07 ± 5.05
Underweight [< 18.5]	17 (5.03)
Normal weight [18.5-24.9]	135 (39.94)
Overweight [25.0-29.9]	111 (32.84)
Obesity I [30.0-34.9]	61 (18.05)
Obesity II [35.0-39.9]	11 (3.25)
Obesity III [≥ 40.0]	3 (0.89)
Diabetes mellitus type II	91 (26.92)
Insulin-dependent diabetes	42 (12.4)
Non-insulin dependent diabetes	49 (14.49)
Systemic arterial hypertension	153 (45.26)
Hypercholesterolemia	78 (23.08)
Hypertriglyceridemia	105 (31.07)
Smoking	104 (30.77)

SD = standard deviation.

obtained: demographics, comorbidities, unadjusted mortality until hospital discharge, defined as death occurring during the index hospitalization; type of surgery, defined as the procedure or procedures performed during the index surgery whether it was a) valve surgery, b) coronary revascularization surgery, c) surgery to correct congenital malformation(s) and d) surgery of a different type (valve surgery plus coronary revascularization surgery, aortic surgery, closure of postinfarction ventricular septal defect, traumatic heart injury, pericardial resection). In addition, the variables required for the calculation of the EuroSCORE II mortality risk score were collected using the online calculator on the EuroSCORE website: https://www.euroscore.org/index.php?id=1 Data of the participants, obtained from the clinical file, were subjected to an anonymization procedure to dissociate the personal data from the holder, not allowing the participant to be identified due to the structure, content or degree of disaggregation.

Statistical analysis

Quantitative variables are presented as means and standard deviations if normally distributed or as median and interquartile ranges when not normally distributed. Qualitative variables are presented as frequency percentages and compared with χ^2, or Fisher's exact test. Quantitative variables of two groups were compared with Student's t-test when normally distributed and comparison of three or more averages with analysis of variance (ANOVA). A significance level of $p \leq 0.05$ was accepted.

Discrimination is the ability of a mathematical model to identify patients who will survive from those who will die (accuracy), and it was evaluated by the area under the receiver operating characteristic curve (AUC-ROC). Values ≤ 0.5 indicate that the model does not discriminate better than chance, and values of one indicate perfect discrimination. Values greater than 0.75 identify systems with good model discrimination capability.

The calibration compares the expected episodes with the observed ones across the risk range. It was evaluated using the χ^2 of the H-L goodness-of-fit test, which calculates a C-statistic which measures the difference between the model's expected mortality values and the mortality values observed in risk decile groups of the population studied. The lower the value of this statistic and the p-value > 0.05, the better the calibration of the model (expected and observed mortality are close, and there is no statistical difference between them). A p-value greater than 0.05 suggests that the model has a good calibration and consequently predicts the probability of dying for patients across the risk range well.

We also calculated the RAMR obtained by the coefficient of observed mortality to expected mortality (RAMR = O/E), which has also been proposed to evaluate calibration.[18] A ratio of 1.0 means that the score or test model predicts mortality in a perfect way (the same number

of [observed] patients die as the number of expected [predicted] patients). A RAMR > 1.0 means that the model underestimates mortality, while a RAMR < 1.0 implies that the model overpredicts (overestimates) mortality.[18]

Finally, to obtain final results, a 1000-sample bootstrap procedure was conducted, using robust errors, taking care of any possible errors derived from the distribution of the data and the reduced sample size.

Microsoft Excel spreadsheet was utilized as the database, and descriptive and inferential statistics were performed in Stata version 16.

Table 2: Surgical procedures.

Procedure	n (%)
Valvular	108 (31.95)
Aortic valve replacement	33 (9.76)
Mitral valve replacement + tricuspid repair	23 (6.80)
Mitral valve replacement	20 (5.19)
Mitral and aortic valve replacement	12 (3.55)
Tricuspid valve replacement	7 (2.07)
Mitral valve replacement + coronary revascularization	6 (1.77)
Mitral, aortic, and tricuspid valve replacement	4 (1.18)
Valve conduit + coronary reimplantation	3 (0.88)
Isolated coronary artery bypass grafts	101 (29.88)
Off-pump coronary artery bypass	77 (76.25)
Single-vessel coronary artery bypass	8 (2.36)
Double-vessel coronary artery bypass	43 (12.72)
Triple-vessel coronary artery bypass	46 (13.60)
More than triple-vessel coronary artery bypass	4 (1.18)
Congenital anomalies	51 (15.08)
Atrial septal defect	24 (7.10)
Patent ductus arteriosus	7 (2.07)
Coarctation of the aorta	5 (1.47)
Ventricular septal defect	4 (1.18)
Tetralogy of Fallot	3 (0.88)
Ebstein's anomaly	1 (0.29)
Other congenital anomalies	7 (2.07)
Miscellaneous	78 (23.07)
Pericardial window/resection	34 (10.05)
Thoracic aorta	23 (6.80)
Myxomas	6 (1.77)
Epicardial permanent pacemaker	5 (1.47)
Post-infarction ventricular septal rupture	3 (0.88)
Metastatic tumors	3 (0.88)
Stab wounds	2 (0.59)
Gunshot wounds	1 (0.29)
IV septum rupture + free wall rupture due to MI	1 (0.29)
Aortic clamp time, mean ± SD	88.7 ± 43.4
Extracorporeal circulation time, mean ± SD	118.88 ± 54.4
Patients who died	37/338 (10.95)

RESULTS

The present study was a retrospective review of 338 consecutive patient records of patients who underwent cardiac surgery with or without a heart-lung machine at the HRAEB. The mean age and standard deviation (SD) of the evaluated population were 49.9 ± 16.6 years with a range of 16-80 years. 47.9% were women. The average weight was 67.2 ± 14.4 kg; 32.8% were overweight, and 18% had obesity. 26.9% had diabetes mellitus, a higher figure than that observed in our general population; 45.2% had systemic arterial hypertension, also higher than that observed in our general population, and 30.7% were smokers *(Table 1)*.

The surgical procedures performed were valve surgery 108 (31.95%), coronary artery bypass surgery 101 (29.88%), congenital surgery 51 (15.08%), and miscellaneous surgery 78 (23.07%). The aortic clamping time and extracorporeal circulation time were 88.7 ± 43.4 and 118.88 ± 54.4 minutes, respectively. Thirty-seven patients died during the index hospitalization (10.9%) *(Table 2)*. *Table 3* shows the number and percentage of each of the variables of the EuroSCORE II model found in our study population. *Table 4* compares the variables found in the population from which the EuroSCORE II was obtained and the population evaluated at the HRAEB. The population from which the EuroSCORE II model was derived was almost 15 years older than our study population (64.6 vs 49.9 years). Body weight (77.9 vs 67.2 kg) and height (168.5 vs 160 cm) were also higher. The prevalence of chronic obstructive pulmonary disease (10.7 vs 6.2), the percentage of emergent surgery (4.3 vs 0.9), isolated coronary revascularization (46.7 vs 29.9), and valve surgery (45.5 vs 31.9) were also more frequent in the EuroSCORE II population than in our population.

In contrast, the percentage of women (47.9% vs 30.9%), insulin-dependent diabetes mellitus (12.4% vs 7.6%), poor mobility (7.4% vs 3.2%), infective endocarditis (7.4% vs 2.2%),

Table 3: Distribution, number, and percentage of EuroSCORE II variables in the study.

Characteristic	n (%)
Patient-related factors	
Age [years], mean ± SD	49.87 ± 16.61
Women	162 (47.93)
Extracardiac arteriopathy	19 (5.62)
Creatinine clearance (Cockcroft-Gault) [mL/min]	
85	201 (59.46)
50-85	101 (29.88)
< 50	16 (4.73)
On dialysis	20 (5.91)
Poor mobility	25 (7.39)
Previous cardiac surgery	47 (13.90)
Chronic obstructive pulmonary disease	21 (6.21)
Active endocarditis	24 (7.10)
Critical preoperative condition	49 (14.49)
Diabetes under insulin control	42 (12.42)
Cardiac-related factors	
NYHA functional class	
Class I	46 (13.6)
Class II	172 (50.9)
Class III	95 (28.1)
Class IV	25 (7.4)
SCC class IV angina	39 (11.5)
Left ventricular ejection fraction	
More than 50%	223 (65.97)
31-50	113 (33.43)
21-30	2 (0.59)
≤ 20	0 (0.00)
Recent myocardial infarction	46 (13.64)
Pulmonary artery systolic pressure [mmHg]	
No	115 (30.02)
Moderate [31-54]	171 (50.59)
Severe [≥ 55]	53 (15.68)
Surgery-related factors	
Type of surgery	
Elective	179 (53.0)
Urgent	155 (45.9)
Emergency	3 (0.9)
Salvage	1 (0.3)
Extent of surgery	
Isolated CABG	90 (26.6)
One non-CABG procedure	189 (55.9)
Two procedures	38 (11.2)
Three procedures	21 (6.2)
Surgery on the thoracic aorta	23 (6.8)

NYHA = New York Heart Association. SCC = Canadian Society of Cardiology. CABG = coronary artery bypass grafts.

and critical preoperative status (14.5% vs 1.7%) were higher in the present series. The predicted risk in the EuroSCORE II model was 3.95%, and in this study group, it was 4.10%.

The EuroSCORE II model in the present study had an AUC-ROC of 0.806 (95% CI, 0.739-0.872), consistent with good discrimination *(Figure 1)*. The χ^2 of H-L was 14.2, with $p = 0.08$, which is compatible with good calibration. However, the other tool proposed to evaluate calibration, the RAMR,[18] was 2.65, consistent with the EuroSCORE II model, generally underestimating perioperative mortality in our series *(Figure 2)*.

DISCUSSION

Implementing a mathematical model to predict operative mortality in cardiac surgery requires evaluating its performance in the hospital where it is to be used. The present study included a retrospective series of 338 adult patients who underwent cardiac surgery and aimed to evaluate the discrimination and calibration of the EuroSCORE II model in the HRAEB.

The EuroSCORE model for predicting perioperative mortality in general cardiac surgery in adult patients was widely used in the first decade and part of the second decade of the present century in various latitudes, showing generally good predictive performance. Nevertheless, it has shown deficiencies in its calibration while retaining good discrimination in recent years. For this reason, the model was updated in 2012 and called EuroSCORE II.

The new model improved its discrimination: AUC-ROC 0.8095 (95% CI, 0.7820-0.8360) and its calibration, χ^2 of H-L of 15.48, with $p < 0.0505$.[16] In addition to being evaluated by the classical χ^2 method of H-L goodness-of-fit, the calibration was also assessed by the RAMR, which was 1.058.

Like the EuroSCORE II, our study included patients who underwent general cardiac surgery (ischaemic, valvular, congenital, and mixed) with and without a heart-lung machine. Compared to the population used by Nashef et al., from which the EuroSCORE II model was derived,[16] our population appears to have advantages concerning risk: younger

population, lower prevalence of chronic obstructive pulmonary disease, and emerging surgeries. However, it was more prevalent in other relevant prognostic variables: more women, insulin-dependent diabetes mellitus, poor mobility, infective endocarditis, and preoperative critical condition *(Table 4)*. Therefore, it is unsurprising that the EuroSCORE II in our population was higher but only slightly compared to the original EuroSCORE II model population, 4.10% vs 3.95%.

On the other hand, several studies have evaluated the discrimination and calibration of the EuroSCORE II model with contradictory results. Some studies corroborate good to very good discrimination and good calibration, while other studies, although corroborating good discrimination, question its calibration. Di Dedda et al., in a retrospective series of 1,090 patients, report discrimination, with AUC-ROC of 0.81 (95% CI, 0.78-0.83) and good calibration, with an observed mortality of 3.75%, expected of 3.10 and conclude that «the EuroSCORE II represents a useful update of the previous version of the EuroSCORE, with much better clinical performance and the same good level of accuracy».[26] Barili et al., in a retrospective validation study of the new model involving 12,325 general cardiac surgery patients report an AUC-ROC of 0.82 (95% CI, 0.80-0.85) consistent with good discrimination and «optimal calibration but only up to 30% of predicted mortality».[23] Gao et al., in a series of 1,628 Chinese patients, reported good discrimination with AUC-ROC of 0.90 and good calibration, with the χ^2 of H-L of 0.071 ($p > 0.05$). However, discrimination and calibration decreased efficiency up to five years after patient follow-up.[27] Borracci et al., in a prospective series of 2,000 Argentinean

Table 4: Variables from the present study and the EuroSCORE cohort.

Variable	HRAEB	EuroSCORE II
Number, n	338	22,381
Age [years], mean	49.9	64.6
Women, %	47.9	30.9
Weight (kg), mean	67.2	77.9
Height (cm), mean	160	168.5
Diabetes mellitus (total), %	26.9	25.0
Insulin-dependent diabetes, %	12.4	7.6
Chronic obstructive pulmonary disease, %	6.2	10.7
Poor mobility, %	7.4	3.2
Extracardiac arteriopathy, %	5.6	
Infective endocarditis, %	7.4	2.2
Serum creatinine [mg/dL]	1.2	1.3
Ejection fraction, %		
> 50	65.9	
31-50	33.4	
21-30	0.6	
< 20	0.0	
Critical preoperative status, %	14.5	1.7
Emergency surgery, %	0.9	4.3
Isolated CABG, %	29.9	46.7
Valve surgery, %	31.9	45.5
EuroSCORE II, %	4.1	3.9

HRAEB = *Hospital Regional de Alta Especialidad del Bajío*. CABG = coronary artery bypass grafts.

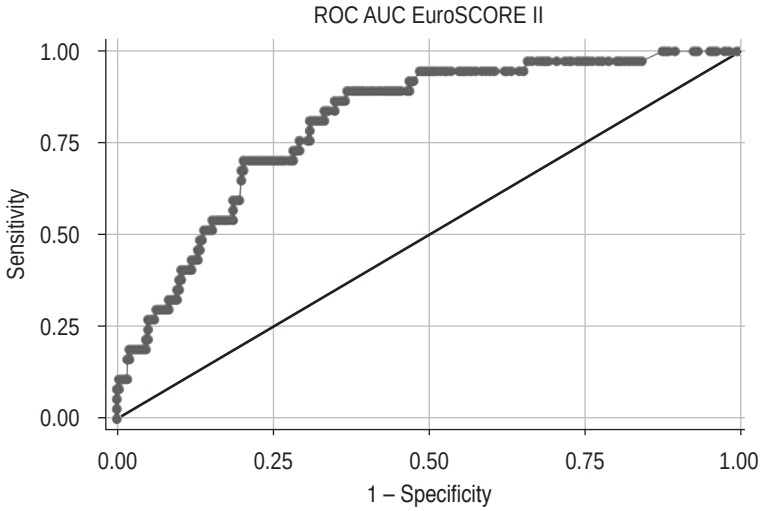

Figure 1: Area under ROC curve = 0.8057 (95% CI, 0.738-0.873).

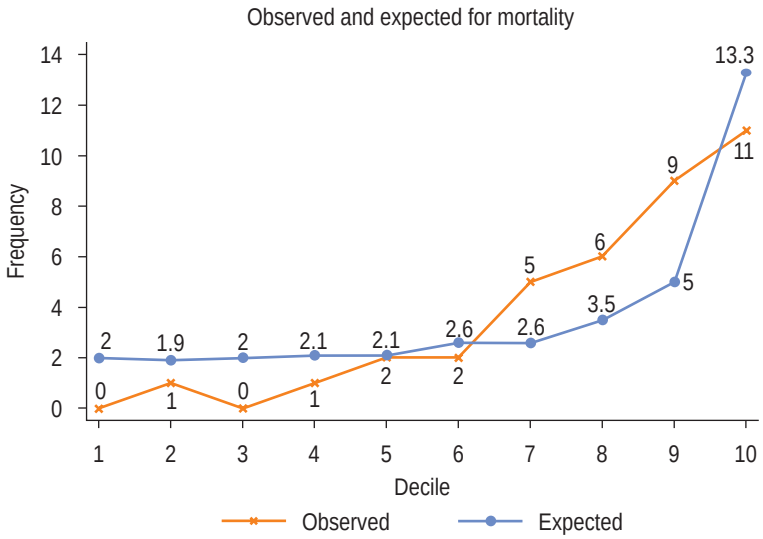

Figure 2: Expected mortality vs observed mortality.

patients undergoing general cardiac surgery, reported an AUC-ROC of 0.80 (95% CI, 0.75-0.85), compatible with good discrimination and χ^2 of H-L values of 11.4 (p = 0.178), consistent with good calibration.[28] Kinkel et al., in a retrospective series of 704 adult patients undergoing general cardiac surgery, found an AUC-ROC of 0.821 (95% CI, 0.772-0.871) and a χ^2 of H-L = 17.7, p = 0.64, consistent with good discrimination and calibration. In the present retrospective study of 338 patients who underwent general cardiac surgery, we found AUC-ROC of 0.806 (95% CI, 0.739-0.872) compatible with good discrimination and a χ^2 of H-L of 14.2, p = 0.08, suggestive of adequate calibration.[24]

García-Valentín et al. report the results of a prospective study conducted in Spain to validate the EuroSCORE II in which 20 Spanish hospitals participated, recruiting 4,034 adult patients who underwent general cardiac surgery. The AUC-ROC was 0.78 (95% CI, 0.76-0.82), compatible with good discrimination, and χ^2 of H-L of 38.98 (p < 0.001), consistent with poor calibration.[29] In the same sense, Kunt et al., in a retrospective series of 428 adult patients from Turkey who underwent coronary artery bypass surgery, found an AUC-ROC of 0.72 (95% CI, 0.62-0.81), compatible with acceptable discrimination. The observed mortality was 7.9%, the predicted mortality by EuroSCORE II was 1.7%, and they concluded that while the model showed good discrimination, it significantly underestimated the risk of perioperative death.[22]

The RAMR has yet to be used in most studies evaluating the calibration of the EuroSCORE II model, with some exceptions. For example, Alvarez-Cabo, in an ambispective series of 206 adult Spanish patients undergoing coronary revascularization surgery, in addition to the χ^2 of H-L to evaluate calibration, also used the RAMR, with a point value of 0.83, suggesting a slight overestimation of the model, supported by the 95% confidence interval of the point value of the RAMR reported.[29] Similarly, Borracci et al., in their prospective series of 2,000 Argentinean adult patients undergoing general cardiac surgery, used in their calibration evaluation in addition to the χ^2 of H-L the RAMR, whose point value was 1.4 suggestive of slight underestimation of risk; «the clinical validation of the model, based on the ratio of observed/expected mortality, showed that the system performed better in the lowest and highest risk groups while underestimating the risk in the intermediate groups.»[28]

We used the present work's H-L χ^2 and the RAMR to evaluate the calibration. According to χ^2 of H-L, the model has an adequate calibration. Nevertheless, according to the RAMR (point value 2.65), the model, in general, underestimates the risk of death in our study

population; in graph 2, we can see how, in the first deciles, the model overestimates the risk, but in the high-risk deciles, underestimation of the risk predominates.

In this study, the observed mortality of 10.9% stands out, higher than that reported in the EuroSCORE II and multiple validation studies in European and Anglo-Saxon populations, but similar to that reported in our country: 9.68% in the Rodriguez-Chávez series of 1,188 valve surgery patients to validate the EuroSCORE[30] and 12.5% at 30 days reported in the Kinkel series of 704 patients undergoing general cardiac surgery.[24] The explanation for this high mortality is given by factors related to the patient: biological status, socioeconomic status, and low health education that leads to seeking medical attention late, when the condition has already produced advanced structural and functional cardiac and extracardiac damage,[30] as well as factors related to health care centers: resources, infrastructure, experience, previous results, among others.[31]

In summary, the performance of the updated EuroSCORE II model evaluated in our population showed good discrimination. As assessed by χ^2 of H and L, the calibration suggests adequate calibration. However, when calibration was evaluated using the RAMR, the result was consistent with underestimating the risk of death, in line with the observed mortality.

Limitations

The study's period and the presentation of the results are long. However, the model has retained relevance and contributes to re-evaluating the EuroSCORE II calibration measure. Future studies should include patients who intervened during recent years and increase the sample size or design a prospective study with an adequate sample size to have a fairer evaluation of the performance of the EuroSCORE II model in the Mexican context.

CONCLUSIONS

In the present study, the EuroSCORE II model showed good discrimination and adequate calibration based on the χ^2 data of Hosmer and Lemeshow. However, the data obtained from the RAMR indicates that the model underestimates the risk of death in the medium- and high-risk groups of patients. Considering the limitations mentioned above, we considered continuing the EuroSCORE II instrument in the hospital where the study was conducted. Ultimately, it is necessary to design a model to measure the risk of operative mortality in cardiac surgery in Mexico that includes characteristics and variables specific to the Mexican population, not contemplated so far by traditional international instruments.

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Clinical case

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Coarctation of the aorta associated with bicuspid aortic valve complicated by aortic aneurysm dissection

Coartación aórtica asociada a válvula aórtica bicúspide complicada con aneurisma aórtico postdisección

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Keywords:
coarctation of the aorta, chronic aortic dissection, ascending aortic aneurysms, bicuspid aortic valve.

Palabras clave:
coartación aórtica, disección aórtica crónica, aneurisma aorta ascendente, válvula aórtica bicúspide.

ABSTRACT

Coarctation of the aorta is a congenital disorder that affects not only the aorta but also might be associated with bicuspid aortic valve disease and predisposes to aortic syndromes. We report the case of a 28-year-old patient with secondary hypertension due to post-ductal aortic coarctation associated with a complicated bicuspid aortic valve and chronic dissection of the ascending aorta. The coexistence of aortic valve disease, as well as multiple aortic conditions is a rare situation that requires highly specialized evaluation to ensure a favorable outcome. Treatment was established in two phases: aortoplasty with stent placement and then aortic and valvular replacement surgery, with a favorable recovery.

RESUMEN

La coartación aórtica es un trastorno congénito que afecta no solamente a la aorta, sino que también puede asociarse a válvula aórtica bicúspide y predispone a síndromes aórticos. Se reporta el caso de un paciente de 28 años de edad con hipertensión secundaria debido a coartación aórtica postductal asociada a válvula aórtica bicúspide que a su vez presentó disección crónica de la aorta ascendente. La coexistencia de enfermedad valvular aórtica, así como múltiples condiciones aórticas, es una situación rara que requiere una evaluación altamente especializada para garantizar un resultado favorable. El tratamiento se estableció en dos fases: aortoplastia con colocación de stent y luego cirugía de reemplazo aórtico y valvular, con una recuperación favorable.

INTRODUCTION

Coarctation of the Aorta (CoA) is a congenital disease that affects the aorta, aortic and mitral valves together with intracerebral arteries.[1] Once clinical suspicion has arisen, various paraclinical tests should be done in order to confirm and evaluate disease extension and possible complications. Besides, systemic hypertension is part of the natural history of disease and consistently leads to deleterious consequences;[2] adequate treatment, therefore, is imperative. Stenotic correction is the treatment of choice, stenting angioplasty over surgical technique, depending on the presence or absence of cardiovascular comorbidities, age, and other aortic segments compromise, particularly if aortic disease is present,[3] such as aortic dissection (AD) which constitutes alone a life-threatening cardiovascular condition with a high mortality risk at presentation; however, uncommonly some patients might have a subclinical course leading to a delayed diagnosis.

CASE PRESENTATION

A 28-year-old patient was diagnosed with systemic arterial hypertension six years ago, receiving a medical prescription and no

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further evaluation until he presented to an emergency department after suffering sudden left hemiparesis and dysarthria. The immediate evaluation revealed systemic blood pressure of 220/110 mmHg, and subsequent non-contrast cranial tomography displayed right basal ganglia hemorrhage. The patient refused medical admission, alleging personal reasons; henceforth, home rest and effective hypertensive treatment consistent with enalapril and amlodipine were prescribed, besides the appropriate diagnostic approach. Two months later, a first thorough evaluation at a consulting room found a harsh, holosystolic murmur along the left parasternal border irradiated to the ipsilateral dorsum. Blood pressure in both arms differed by more than 30 mmHg compared to lower extremities (220/120 versus 140/90 mmHg) and the absence of femoral and distal pedal pulses. Twelve leads electrocardiogram showed only diastolic overload and a chest radiograph revealed inferior costal notching *(Figure 1*, black arrows) and the inverted number three sign *(Figure 1*, white arrow), ascending aorta (AscAo) dilation and discrete cardiomegaly; blood tests were unremarkable. Secondary systemic hypertension due to CoA was suspected. Therefore, he was admitted to a tertiary care center. A Transthoracic echocardiogram confirmed left ventricle hypertrophy and also revealed sinus of Valsalva dilation (50 mm, 27.7 mm/m^2) extended to AscAo along a presumptive dissection anterior flap *(Figure 2A)* bicuspid aortic valve (BAV) *(Figure 2B)* with no significant aortic insufficiency (AI). Surprisingly, the patient did not recall any previous chest pain episodes.

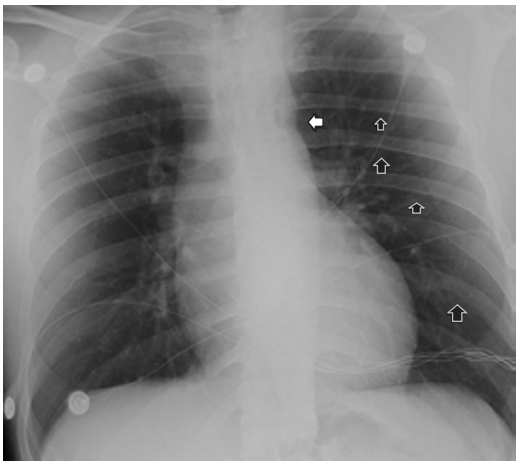

Figure 1: Bilateral inferior costal notching is seen (black arrows) due to collateral vessel formation, and also, the inverted three sign is seen (white arrow), characteristic of coarctation of the aorta.

Nevertheless, expediting both lowering blood pressure and heart rate treatment was instated. A computed aortic tomography (CTA) confirmed CoA, the narrowest site up to 4 millimeters, post-stenotic dilation up to 34 mm *(Figure 3)* and aortic aneurysm (AA) and AD secondary to a dissection flap just above right coronary ostia extending just before the aortic arch, with a maximal diameter at the sinus of Valsalva level up to 56 mm *(Figures 4*

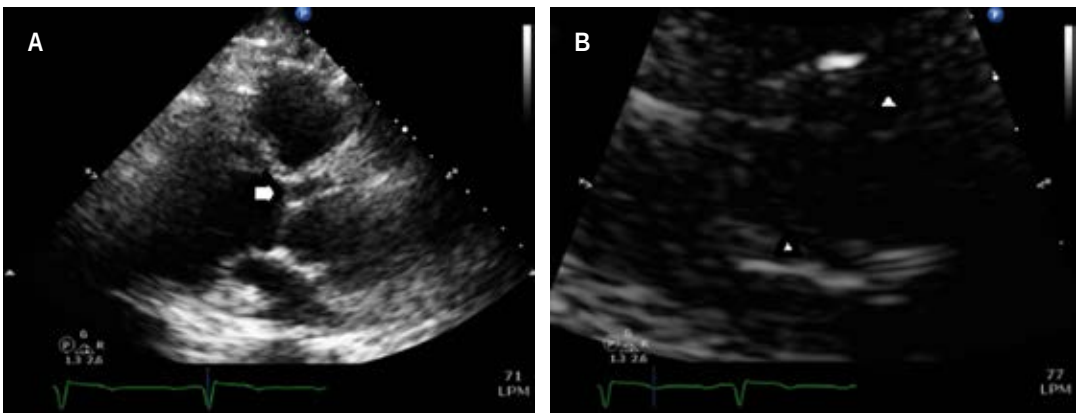

Figure 2: Enlargement of the aortic root and sinus of Valsalva, an anterior dissection flap is seen **(A)**, and the aortic valve is seen with a bivalve configuration at the end-diastolic view **(B)**.

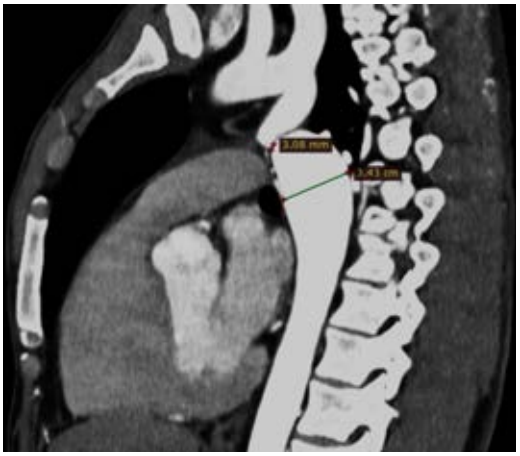

Figure 3: Maximal stenosis of the aorta due to coarctation and post-ductal aortic dilatation are seen.

and 5), consistent with Stanford A classification of unknown evolution. After the heart team meeting, a very specific sequential treatment was established: firstly, CoA was successfully corrected after angioplasty with a 50 × 14 mm covered stent placement, with appropriate positioning and reducing medium gradient from 50 mmHg to six mmHg *(Figures 6 and 7)* and four weeks later, surgical procedure took place: Sievers type one BAV was replaced with bileaflet St. Jude mechanical prosthesis sized 25 mm along concomitant proximal AscAo replacement with 24 mm sized Woven-Dacron graft (wheat procedure). After complete recovery, he received a medical discharge, long-term beta blockade, angiotensin enzyme inhibitor and mid-term aspirin therapy. An evaluation six months later revealed a satisfactory evolution.

DISCUSSION

Secondary hypertension (SH) comprises those forms of systemic hypertension related to a specific etiology, and thus, a particular management strategy. It is recommended to screen SH in certain patients, such as those with younger age (< 40 years), acute worsening of a previously controlled hypertensive patient, severe (grade 3) or drug-resistant hypertension and the presence of extensive hypertensive mediated organ damage.[3] Multiple conditions have been reckoned as secondary causes of SH, including congenital conditions like CoA. CoA might correspond to about one percent of congenital heart defects in live births and up to one out of 1,550 patients in necropsies.[1,4] The traditional classification relies on an anatomical relationship with the ductus arteriosus: preductal CoA (aortic arch and isthmus) is typically found in newborns[2] and, conversely, post ductal stenosis in children and adults.[2,4] CoA has a male-to-female ratio of 1.5:1; when BAV coexist, this might increase to a 4:1 ratio.[5] Although CoA can be found on a solitary basis, most cases feature several associated congenital conditions such as BAV (nearly 85% of cases),[3,6] Willis circle aneurysms (5-10%), persistent ductus arteriosus, subaortic stenosis, parachute mitral valve, supravalvular stenosis; the last three altogether known as Shonen complex.[4] Besides cardiovascular conditions, different perturbations have been described, i.e., neurological, hemangiomas and even ocular congenital syndromes.[1]

CoA does not only imply a local narrowing of the aorta but rather a generalized vasculopathy that compromises central and peripheral vasculature as well as heart valves. If untreated, significant CoA consistently leads to SH characterized by upper-lower extremities systolic difference > 20 mmHg,[7] along with collateral circulation developing, left-side heart failure and cerebrovascular disease; therefore, the mortality risk can be as high as 90% by the age of 50.[1] Besides narrowing severity, CoA affectation

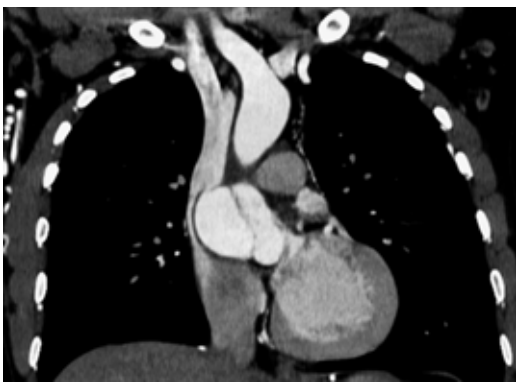

Figure 4: A dissection flap extending from the aortic root traversing through the ascending aorta just before the aortic arch.

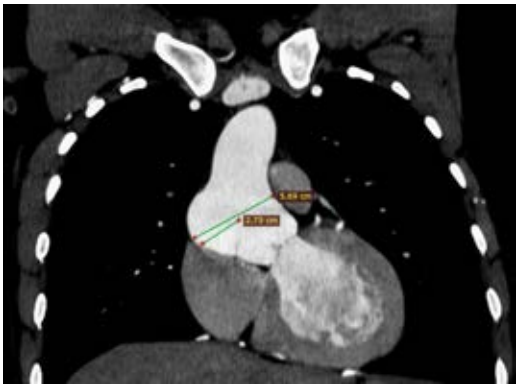

Figure 5: Aneurysmatic aortic dilation can be appreciated.

will also depend on its relationship with arch vessel disease and adequacy of vessel formation along collateral and concomitant diseases.[1,4] Treatment consists of appropriate SH control along stenosis correction, indicated when either hemodynamic significant CoA exists or hypertensive illness.[7] While surgical correction may be preferred in newborns and children, angioplasty is often favored in older populations, with stenting generally preferred over balloon techniques. Balloon techniques are typically reserved for cases of post-stenting restenosis.[4]

Despite the most common complication of BAV being aortic stenosis, several situations might arise since the interaction between BAV and CoA is complex and interdependent, i.e., both diseases involve a certain degree of aortopathy, along with the fact that CoA consistently leads to systemic hypertension. Several pathophysiological mechanisms can coexist, such as persistent shear stress and, possibly, chronic localized inflammation, leading to aortic intimal laceration and underlying media tunica,[1,4] endothelial dysfunction, vascular remodeling, and even cystic medial degeneration.[8] These mechanisms can lead to atherosclerosis, AA, and, in some cases, even aortic syndromes, including AD. AD is a condition characterized by the separation of the wall of the aorta at the outer media or media-adventitia border, a process that starts with an intimal tear. Blood subsequently passes through the tear, then moves in an anterograde or retrograde fashion, and later dissects the lumen of the aorta into both true and false lumens.[9] AD is usually classified according to location and acuity. The most commonly known classification is the Stanford system,[10] which separates AD according to whether the AscAo (type A) is involved or only the descending aorta (type B). The De Bakey system considers the origin site and extension of the intimal flap: type I involves the AscAo, aortic arch, and descending aorta, type II is confined to the AscAo, and type III only the descending aorta; distal to the left subclavian artery. Aortic syndromes are also classified into acute (≤ 14 days) and chronic (> 14 days), depending on the time of onset of initial symptoms and the time of presentation. Another described classification system recommended by the European Society of Cardiology (ESC) but less frequently used establishes three categories: acute (<14 days), subacute (15-90 days) and chronic (>90 days).[11]

Classically, type A AD is associated with a high mortality risk, which increases by one-to-two percent per hour until reaching up to 50% in the first 48 hours.[11] However, there is a small group of patients who present minimal or no symptoms, making it difficult to determine the duration of the condition.[12,13] Compared to those with acute presentation, these patients are associated with a history of cardiac surgery, BAV, wide AscAo diameter, severe AI and typically do not extend beyond the aortic arch.[14] The approximate incidence of chronic AD is estimated at four to six cases

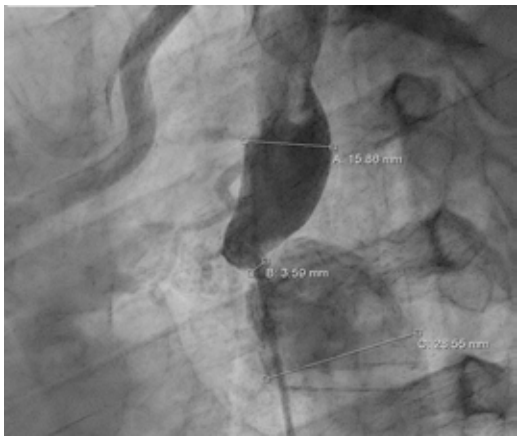

Figure 6: Depiction of the coarctation side at the greatest narrowing point and post-coarctation dilation.

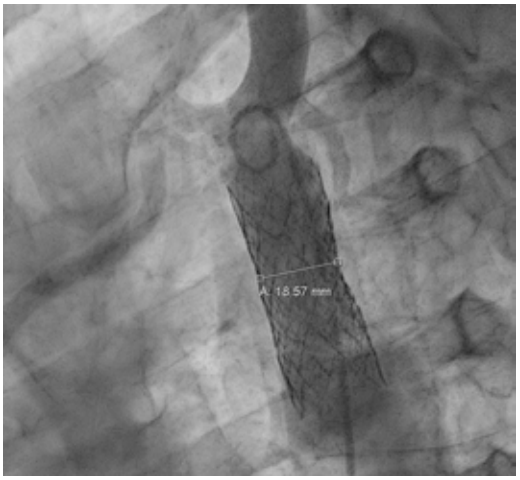

Figure 7: After angioplasty and stent placement, successful correction is seen.

per year with an average survival of seven years, with a prevalence of 28-42 cases per 100,000 people per year, consistent with the data for acute AD, which is three cases per 100,000 people per year.[15] Besides, approximately 50% of patients with AD have been observed to develop aneurysms.[11,15] Despite the fact that the first imaging study usually involves an echocardiogram, due to its low sensitivity, CTA or magnetic resonance imaging (MRI) is preferred; both offer optimal imaging, allowing diagnosis and management decisions.[1,13] Features like a thick, immobile intimal flap, aneurysmal dilatation or thrombus in the false lumen suggest dissection chronicity.[13] Treatment options include open surgery, which is the gold standard, and endovascular repair, hybrid methods, or even medical treatment alone. Surgical reparation is recommended in uncomplicated AA if the diameter exceeds 55 mm, but if complicated, such as ours, the decision should be individualized. However, if CoA coexists, expedited surgical treatment is advised to increase survival prognosis.[16] In patients with chronic AD undergoing surgery, mortality can reach up to six percent at 30 days, much lower than in acute cases (30% at one month).[11,17] Pavlou et al.[11] along with Abugroun et al.[12] reported the cases of patients with chronic AD, who had a favorable evolution after surgical repair, consistent with our very patient's situation. Similarly, Jiang et al.[17] described a case of a middle-aged man with the coexistence of CoA, BAV, AA and AD, with a successful surgical repair. Therefore, a multidisciplinary approach is fundamental to ensure long-term success with fewer complications when such atypical confluence is found. A two-staged approach was favored in our patient with relatively stable clinical status. In addition, the correction of CoA on the first time would lead to a better hemodynamic condition besides decreasing aortic clamping time during the latter surgical procedure, reducing its morbidity and mortality risk.

CONCLUSIONS

The simultaneous presence of CoA, BAV and Chronic AD complicated with AA is a medical trilemma. Therefore, multiple considerations should be considered before any definitive intervention is done. Since conservative management may lead to high morbidity and mortality, a combination of surgical and endovascular approaches should be preferred in most cases if it is consistent with care goals.

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Ethical aspects

Protection of humans and animals: the authors declare that no experiments were conducted on humans or animals for this research.

Confidentiality of data: the authors declare that no patient data appears in this article. The authors declare that they have followed their workplace protocols regarding the publication of patient data.

Right to privacy and informed consent: the authors declare that no patient data appears in this article.

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«A boot in a heart». A case report of non-ruptured aneurysm of Valsalva sinus with a special shape and review of the literature

«Una bota en el corazón». Reporte de un caso de seno de Valsalva no roto de forma particular y revisión de la literatura

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Keywords:
aneurysm, sinus of Valsalva, congenital, sinus Valsalva aneurysm.

Palabras clave:
aneurisma, seno de Valsalva, congénito, aneurisma de seno de Valsalva.

ABSTRACT

The aneurysms of the Valsalva sinus are congenital or acquired aortic sinus wall dilations at the level just above the three cusps of the aortic valve, which may be asymptomatic or fatal cases if ruptures, usually into the right cardiac chambers. These cases are relatively rare. We present the case of a 72-year-old male referred for a suspected pulmonary murmur. The evaluation revealed an aneurysm of the right sinus of Valsalva, causing compression to the right ventricular outflow tract (RVOT). The echocardiogram, computed tomography, and the aortogram revealed interesting, evocative images. The patient received a mid-cap surgical repair. This paper reviews and discusses the current literature and presents the case.

RESUMEN

Los aneurismas del seno de Valsalva son dilataciones congénitas o adquiridas de la pared del seno aórtico a nivel justo por encima de las tres cúspides de la válvula aórtica, que pueden ser casos asintomáticos o fatales si se rompen, más frecuentemente hacia las cavidades cardiacas derechas. Estos casos son relativamente raros. Presentamos el caso de un varón de 72 años remitido por sospecha de soplo pulmonar. La evaluación reveló un aneurisma del seno de Valsalva derecho, que causaba compresión del tracto de salida del ventrículo derecho (TSVD). El ecocardiograma, la tomografía computarizada y el aortograma revelaron imágenes interesantes y evocadoras. El paciente recibió una reparación quirúrgica mid-cap. Este artículo revisa y discute la literatura actual y presenta el caso.

INTRODUCTION

James Hope described a sinus of Valsalva aneurysm (SVA) case, ruptured into the right ventricle in 1839, considered then a congenital anomaly. Most of the unruptured cases of SVA remain asymptomatic and undetected, although confused with other pathologies such as pericardial cysts.[1] Most of these aneurysms are generally silent; however, autopsy studies of 8,138 individuals suggested a prevalence of 0.09% in the general population.[2] The SVA is usually congenital in etiology, but other acquired etiologies include atherosclerosis, syphilis, Marfan's syndrome, or infective endocarditis has been described. Pathophysiologically, SVA results from the Valsalva sinus's dilation, from a separation between the aortic media and annulus fibrosus due to elastin and collagen deficit causing wall stiffening, more frequently affecting the right sinus. The diagnosis includes image multimodalities with a size range of 20 to more than 50 mm in different series, usually starting with transthoracic Doppler-echocardiography,

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later confirming with transesophageal one, contrast computed tomography, magnetic resonance, and catheter-based angiography. The true history of SVA is not completely clear, but the rupture of SVA is a possibly preventable fatal complication.

We discuss an unusual unruptured sinus of Valsalva aneurysm due to the scarcely available literature on this presentation mode, with special descriptive and evocative cardiac imaging views with an innovative corrective surgical technique.

CASE PRESENTATION

We received a 72-year-old athletic male with no significant past medical condition, referred for evaluation of a new systolic pulmonary focus murmur. The patient reported no symptoms and performed daily jogging. Chest X-ray was read as normal *(Figure 1)*.

On physical examination, the blood pressure was 130/78 mmHg, heart rate 78 bpm, and no respiratory distress with a grade II/VI systolic ejection on the left upper sternal border, with normal pulses, without pericardial rub, jugular dilatation or paradoxical pulse. The echocardiogram revealed a mildly reduced Simpson's rule calculated ejection fraction of 46% and inferolateral mild hypokinesis. The valvular examination revealed mild aortic and mitral insufficiency, dilated ascending aorta dimension at the sinus of Valsalva level, severe aneurysmal dilatation (2.5 × 4.6 mm) of a non-ruptured right sinus of Valsalva with right ventricular outflow tract compression and increased flow velocity in the pulmonary valve *(Figure 2)*.

The CT angiography confirmed the echocardiogram findings and suggested a small right coronary artery (RCA), not shown in our figures, and a normal left anterior descending coronary artery with compression of the right ventricular outflow tract *(Figure 3)*.

The cardiac catheterization presented normal coronaries with a small right coronary artery. The left ventricular angiogram presented inferior mild hypokinesia, and the aortogram revealed an abnormal appearance which we described as «a boot in the heart», produced by the severely dilated non-ruptured right sinus of Valsalva without fistulous tracts *(Figure 4)*.

The patient had repair of the non-ruptured right coronary sinus of the Valsalva aneurysm with a J-shaped mini sternotomy through the fourth intercostal space, exposing the ascending aorta followed by arterio-venous femoral cannulation for cardiopulmonary bypass and coronary sinus cannulation under transesophageal echocardiogram assistance. The right superior pulmonary vein was used for decompression and venting the heart, later exploring the anterior aorta and valve through a hockey stick incision to examine the aneurysm. With Prolene 5-0, concentric purse strings were applied from the lower dome of the aneurysm and up until the defect's obliteration.

After measuring the aortic sinus defect, a piece of autologous pericardium was meticulously prepared and tailored according to the measurements and shape of the defect, carefully suturing the pericardial patch continuously to the aortic defect with Prolene 5-0, confirming no-insufficiency of the valve finally weaning the patient from cardiopulmonary bypass as usual. After surgery, the patient recovered with minimal analgesic drugs requirement, removing the chest tube and the pacing wires on the second postoperative day and discharged to home on the fourth postoperative day, without complications at follow up, when he had a significantly modified sinus of Valsalva aspect *(Figure 5)*.

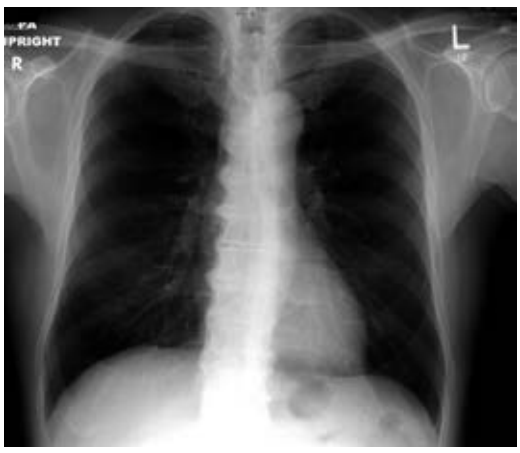

Figure 1: Anteroposterior view of chest radiograph, note that it is not able to detect the huge problem.

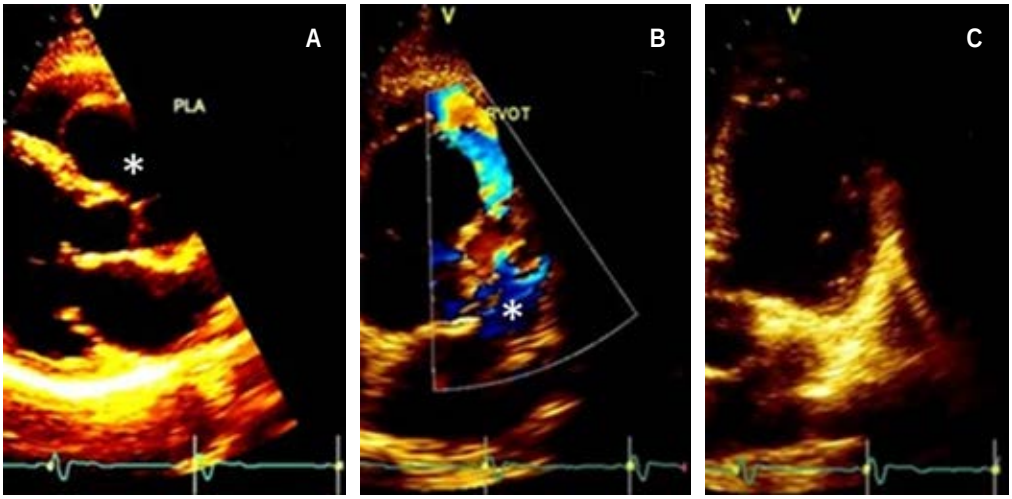

Figure 2: Doppler-echo pre-treatment; the asterisk shows the aneurysm in long **(A)** and short **(B)** parasternal and apical **(C)** view.

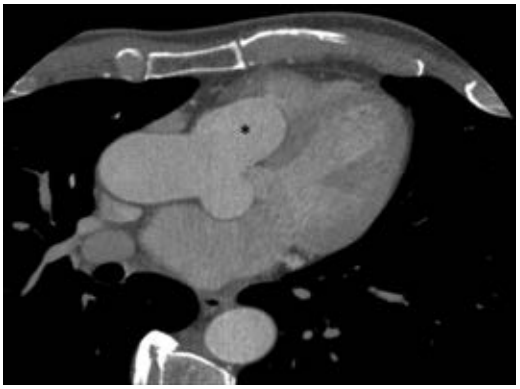

Figure 3: A chest computed tomography-sagittal view showing dilation of the aortic root and expansion of the aneurysm (asterisk) into the right ventricle.

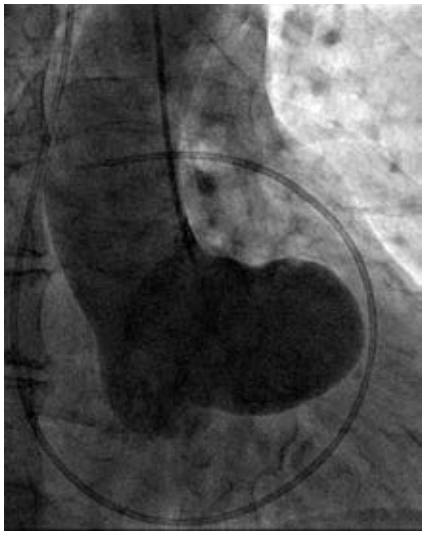

Figure 4: Aortogram.

DISCUSSION

The SVA are small dilations in the aortic wall just above any of the three aortic valve cusps between the aortic valve annulus and the sinotubular ridge, usually secondary to infection or trauma that implies the aortic media separation from the annulus fibrosus,[3] most often occurring in the right coronary or noncoronary sinus. These aneurysms are thin walled-outpouchings prone to rupture. When this occurs, they can form a fistulous connection with one of the heart chambers, causing symptoms. The patients may be asymptomatic or may have ischemic events, cardiac rhythm abnormalities, and embolic events. In ruptured aneurysms, symptoms may include dyspnea, chest pain, fatigue, peripheral edema, and, in the worst scenario, sudden cardiac death or tamponade.

Symptoms can be gradual or acute, sometimes associated with other cardiac abnormalities, such as ventricular septal defects and aortic valve dysfunction. The physical examination may

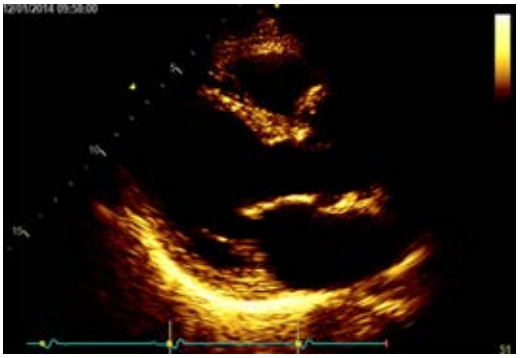

Figure 5: Postoperative transthoracic echocardiogram in parasternal view with a mild aortic insufficiency, as before surgery.

disclose a continuous mechanical-sounding murmur similar to the patent ductus arteriosus. The electrocardiogram is usually normal in unruptured aneurysms except if the aneurysm compresses the atrioventricular node, perhaps causing conduction disturbances.[3] In most cases, for the diagnosis of SVA, transthoracic and transesophageal echocardiography can provide adequate identification and description of the size and severity, as described in our referred case reports, either with[2,3] or without cardiac catheterization[1] or echocardiography and cardiac catheterization.[4] Chest computerized tomography (CCT), in addition to magnetic resonance, can also be used as part of the workup for SVA identification, and in other cases where the clinical suspicion is high but not seen in the previous images, angiography is an acceptable option. Nowadays, the only accepted and recommended treatment is surgery. The first SVA repair cases were described in the 1950s,[3] with the surgical treatment usually indicated in the presence of rupture, compression of adjacent structures, and significant dilation or aortic regurgitation.[2] Other surgery indications include non-ruptured SVA-producing malignant arrhythmia, obstructing coronary ostia or ventricular outflow tract, or infection.[4,5] The operative mortality after an SVA surgical repair is relatively low, with 80 to 97% alive patients at five and ten years, respectively. The presented case has the importance of being one of the few cases detected before rupture, possessing evocative and descriptive imaging, and considered perhaps, to our knowledge, if not the first, one of the few nonruptured cases corrected with a minimally invasive surgical procedure.

CONCLUSIONS

This case presents a characteristic shape that may rupture with a fatal outcome.

The early diagnosis and treatment may be life-saving. The image diagnosis usually starts with transthoracic echocardiography, later confirmed and detailed by contrast computed tomography, magnetic resonance and catheter-based angiography.

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Streptococcus gordonii infective endocarditis complicated with perforated mitral valve aneurysm and aortic valve perforation: a case report and literature review

Endocarditis infecciosa por Streptococcus gordonii *complicada con aneurisma mitral perforado y perforación de válvula aórtica: reporte de caso y revisión de la literatura*

José Martín Alanís-Naranjo,* Julio César Rivera-Hermosillo‡

Keywords:
infective endocarditis, perforated aneurysm, mitral valve aneurysm, aortic valve endocarditis, valve replacement surgery, *Streptococcus gordonii*.

Palabras clave:
endocarditis infecciosa, aneurisma perforado, aneurisma mitral, endocarditis aórtica, cirugía de reemplazo valvular, Streptococcus gordonii.

ABSTRACT

Mitral valve aneurysm (MVA) is a rare complication of infective endocarditis (IE), and it requires surgical intervention as soon as possible when it ruptures. *Streptococcus gordonii* is an extremely rare cause of IE complicated with abscesses, fistulas, aneurysms, or valve perforations. We describe a case of native valve IE complicated by a perforated MVA and aortic valve perforation caused by *Streptococcus gordonii*, along with a literature review. This case highlights the importance of identifying IE complications through the echocardiogram. Therefore, it is mandatory to evaluate all patients with streptococcal bloodstream infections with a high risk of IE to rule out its complications and provide prompt surgical intervention if necessary.

RESUMEN

El aneurisma de la válvula mitral (AVM) es una complicación rara de la endocarditis infecciosa (EI) y cuando se perfora requiere una intervención quirúrgica tan pronto como sea posible. Streptococcus gordonii *es una causa extremadamente rara de EI complicada con abscesos, fístulas, aneurismas o perforaciones valvulares. Describimos un caso de endocarditis de válvula nativa complicada por una AVM perforada y perforación de válvula aórtica por* Streptococcus gordonii, *junto con una revisión de la literatura. Este caso destaca la importancia de identificar las complicaciones de la EI a través del ecocardiograma. Por lo tanto, es importante evaluar a todos los pacientes con bacteriemia estreptocócica con alto riesgo de EI para descartar sus complicaciones y proporcionar una intervención quirúrgica oportuna si es necesario.*

INTRODUCTION

Infective endocarditis (IE) is a rare but life-threatening disease worldwide.[1,2] In addition to heart failure and systemic embolization, patients with IE also suffer from valvular destruction and valve aneurysms, which lead to increased morbidity and mortality.[3]

Over the years, the epidemiology of IE has gradually changed; *Staphylococcus aureus* is now the most common cause of IE in most studies at 26.6%; Viridans group streptococci (VGS) account for 18.7% of all cases, other streptococci account for 17.5%, and enterococci make up 10.5%; together, these organisms account for 80-90% of IE cases.[2] Many endocarditis pathogens are still found in the oral cavity and may have been acquired through everyday dental routines or invasive procedures. VGS bacteria have a low level of virulence and are typically found in the oral cavity, upper airways,

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gastrointestinal tract, and female genitalia.[1] Regarding the VSG classification, *Streptococci mitis* is the most common cause of IE, while *Streptococcus gordonii* has historically been an uncommon cause of IE.[4]

The mitral valve aneurysm (MVA) is a rare complication associated with IE of the aortic valve. MVA incidence in the setting of IE has decreased from approximately 3.5% to less than 0.3%.[5] Once MVA ruptures and severe mitral regurgitation with hemodynamic instability develops, immediate surgical intervention is required.[3,6] *Streptococcus gordonii* is an extremely rare cause of IE complicated with abscesses, fistulas, aneurysms, or valve perforation.[6,7] In addition to a literature review, we describe a case of native valve endocarditis complicated with perforated MVA and aortic valve perforation caused by *Streptococcus gordonii*.

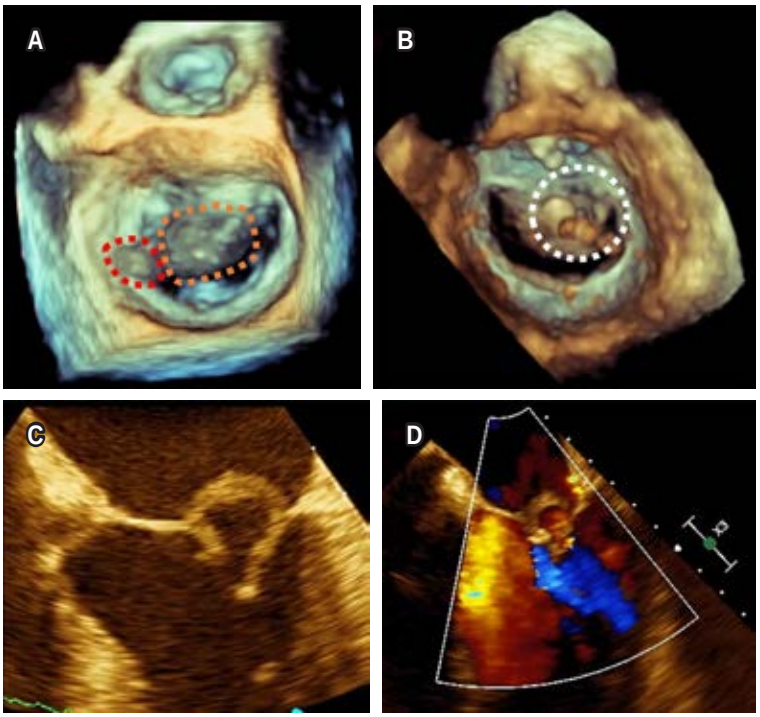

Figure 1: Transesophageal echocardiography: **A)** 3D view from the left atrium demonstrating an 11 × 5 mm vegetation on the P1 annulus of the mitral valve (red dotted line mark) and an anterior mitral leaflet perforated aneurysm (orange dotted line mark), **B)** 3D zoom-mode acquisition of mitral valve in mid-diastole from a ventricular perspective with discontinuity of the anterior mitral leaflet at segment A2 (white dotted line mark), **C)** 2D image at 30º showing an abnormal ring-like structure on anterior mitral leaflet compatible with a perforated aneurysm, **D)** 2D image with color Doppler showed mitral regurgitation and turbulent flow inside the saccular like image.

CASE PRESENTATION

A 60-year-old man presented to our center due to a four-week history of evening predominant fever, diaphoresis, asthenia, adynamia, and involuntary weight loss of 10 kg. Only active smoking for 36 years was relevant in his past medical history; IE-related risk factors were not identified, such as recent dental procedures, invasive procedures, or valve heart disease. Vital signs at admission were unaltered: BP 113/56 mmHg, HR 71 bpm, temperature 36.2 ºC, RR 23 rpm, and SaO_2 95% at ambient air. An electrocardiogram revealed no abnormalities, although the blood tests showed elevated C-reactive protein level (5 mg/dL) and white blood cell count (11,000 mm^3).

During the physical examination, a grade 5 holodiastolic murmur was detected in the aortic area, while the mitral area had a grade 5 holosystolic murmur with radiation to the armpit and aortic arch; no signs of IE vascular phenomena were observed.

Based on the suspicion of IE, we obtained paired blood cultures and, subsequently, started vancomycin 1 g IV bid and ceftriaxone 1 g IV bid. A transesophageal echocardiogram (TEE) revealed an 11 × 5 mm vegetation on the P1 annulus of the mitral valve, a ruptured anterior mitral leaflet aneurysm resulting in severe mitral regurgitation accompanied by turbulent flow within the ruptured aneurysm *(Figure 1)* as well as a perforated non-coronary cusp of the aortic valve resulting in severe aortic regurgitation with regurgitation jet impinging on the anterior mitral leaflet *(Figure 2)*. The blood cultures were positive for multi-sensitive *Streptococcus gordonii*, and antibiotics were deescalated to only ceftriaxone. Blood tests revealed a reduction in white blood cell count (8,400 mm^3) and a decrease in inflammation markers (C-reactive protein 1 mg/dL, erythrocyte sedimentation rate 5 mm/h).

The patient underwent surgery after two weeks of antibiotic treatment. Severe damage

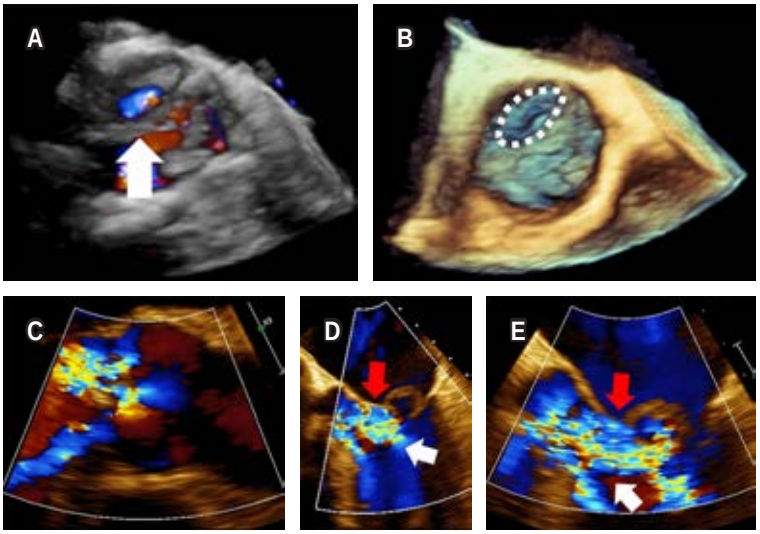

Figure 2: Transesophageal echocardiography: **A)** 3D image with color Doppler showing flow on the non-coronary cusp of the aortic valve (white arrow), **B)** 3D image with discontinuity of non-coronary cusp (white dotted line mark), **C)** 2D image with color Doppler at 125º showing lateral and central jets of aortic regurgitation, **D, E)** 2D image with Color Doppler at 45º showing the aortic regurgitation jet (white arrow) impinging on the anterior mitral leaflet (red arrow).

was observed intraoperatively in the aortic and mitral valves, along with active signs of inflammation; the anterior mitral valve leaflet (AMVL) displayed a perforated aneurysm, while the aortic valve had a perforation on the non-coronary cusp. Mitral and aortic valves were replaced with a 21-mm mechanical prosthesis (St. Jude Medical). The postoperative TEE showed a normal function of the prosthetic valves. Intravenous ceftriaxone was continued, and postoperative blood cultures were negative.

Unfortunately, the patient developed several complications following surgery: hypovolemic shock caused by left internal mammary artery injury, which caused severe postoperative bleeding and necessitated surgical artery repair; complete heart block requiring permanent cardiac pacing; and at day 20 post-surgery, he died of septic shock caused by *Klebsiella pneumonia* acute mediastinitis.

DISCUSSION

Streptococcus gordonii is a VSG species that colonizes oral biofilms on tooth surfaces and forms dental plaques. During tooth brushing, tooth extraction, or oral trauma, bacteria can be released from oral biofilms and enter the bloodstream, resulting in systemic infection.[4] *Streptococcus gordonii* bacteremia contributes to the pathogenesis of IE by inducing platelet aggregation and excessive inflammatory conditions by stimulating various host cells.[4,8]

As soon as *Streptococcus gordonii* enters the bloodstream, it attaches to platelets or erythrocytes using their numerous cell surface proteins, and then hematogenously spreads to damaged heart valves. Upon binding to human vascular endothelial cells, it forms biofilms on heart valves, which can further exacerbate the inflammatory response by aggregating platelets into bacterium-platelet-fibrin complexes. In addition, it activates human valve interstitial cells to cause them to release IL-6 and IL-8, which in turn leads to the infiltration of immune cells via the Nuclear Factor-kappa B (NF-κB) signaling pathway. *Streptococcus gordonii* secretes nitric oxide through the toll-like receptor-2 pathway to activate immune cells in heart lesions recruited from chemokines. When human monocytes are stimulated, they produce proinflammatory cytokines and express more cell surface markers, including clusters of differentiation (CD) 40, CD54, and CD80. Furthermore, it stimulates dendritic cells to produce inflammatory cytokines such as IL-6, IL-12, tumor necrosis factor-α (TNF-α), and co-stimulatory receptors.[8]

The prevalence of IE in streptococcal bloodstream infections is highly dependent on species, as reported by Chamat-Hedemand et al. in 6,506 cases involving streptococcal bloodstream infections (BSIs). BSI due to *S. gordonii* showed a very high prevalence (44.2% [95% CI 34-54.8]) and high risk for IE (OR 80.8 [95% CI 43.9-149]), with the highest requirement of cardiac surgery (31%) compared to the most common isolated streptococcal species (*S. pneumonia*, *S. pyogenes*). These findings suggest that an echocardiogram should be performed in all patients with streptococcal BSI with a «high» or «very high» risk of IE.[9]

MVAs are extremely rare, usually associated with IE of the aortic valve, and the incidence is between 0.2 and

0.3% on echocardiography in general.[6] There are several mechanisms of MVA formation: in the presence of aortic valve IE, the jet lesion may result in secondary destruction of the mitral valve due to: A) the jet damaging the endothelial surface of the mitral valve, B) retrograde dissemination of bacteria, or C) the presence of neovessels (prominent in AMVL) which results in localized inflammation, valvulitis, protrusion of weakened MV into the left atrium cavity, and subsequently aneurysmal formation.[3,5,10] Respect retrograde dissemination might result from 1) direct contact between the aortic vegetation and the AMVL during diastole, known as «mitral kissing vegetations» when they exceed 6 mm in length, 2) secondary infection of the damaged endothelium by bacteria from regurgitation blood flow, or 3) local spread of the infection through the mitral-aortic intervalvular fibrosa.[5]

Approximately two-thirds of MVAs rupture or perforate; the size of the aneurysm does not correlate with the risk of perforation; the AMVL is much more commonly involved than the posterior leaflet for unknown reasons.[5]

The echocardiographic appearance of MVA is characterized by a saccular bulge of the mitral leaflets that extends into the left atrium during systole and collapses during diastole.[5,11] Other echocardiographic features vary from small saccular bulges, often challenging to identify due to vegetation, to large leaflet protrusions towards the left atrium, which may be associated with various degrees of mitral regurgitation and thrombosis.[12] Among the differential diagnoses of MVA are mitral valve diverticulum, blood cysts of the papillary muscle, cardiac masses, chordal rupture, non-bacterial thrombotic endocarditis, mitral valve prolapse, flailing mitral leaflets, myxomatous degeneration, and infective vegetations. The color flow Doppler can support a correct diagnosis. A high-velocity regurgitant jet and direct communication between the aneurysm and the left ventricle support the diagnosis of a perforated aneurysm.[3,5]

Abscess, pseudoaneurysm, and formation of valve aneurysm in a patient with IE indicate uncontrolled infection and the need for urgent cardiac surgery (within seven days), except if there is severe co-morbidity. In other cases, the surgery can be postponed for one or two weeks while the patient receives antibiotic treatment under careful observation to allow the infected tissue to recover and heal and avoid unnecessary extensive surgical procedures.[6,11,13]

Streptococcus gordonii IE has been reported in 27 patients worldwide *(Table 1)*, most male (74%). The median age was 48 (range 11-83 years), and fever was the most common symptom; 66% of patients experienced embolisms, 50% had to undergo valve replacement or repair surgery, and 13.6% died. In most cases, IE was diagnosed by TEE. The most common valve affection was the isolated native mitral valve (42%), followed by native mitro-aortic compromise (27%) and the isolated native aortic valve (23%). 94% of IE cases featured vegetations (mean diameter 11 mm), 27% a valve perforation, and 16.6% a valve aneurysm (the most common of both was the anterior mitral leaflet). Among patients who presented a perforated MVA with valve perforation, mortality was the highest.

CONCLUSIONS

Streptococcus gordonii is considered a commensal of the oral cavity and a non-pathogenic bacterium, but it could be an opportunistic pathogen and cause various infectious diseases. A perforated MVA with AV perforation is a rare but life-threatening complication of IE, even rarer in *Streptococcus gordonii*-related IE. In order to identify these complications, TEE is the method of choice that allows for more accurate morphological characterization of the tissue. All patients with streptococcal BSIs with a high risk of IE should be evaluated with an echocardiogram to rule out IE and its complications and offer prompt surgical intervention if necessary.

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Table 1: Reported cases of infective endocarditis due to *Streptococcus gordonii*.

Author	Country	Pt. no.	Year	Age/gender	Symptoms (time)	Valve	Embolism	Diagnostic modality	Vegetation (valve/number/size)	Aneurysm (valve)	Perforation (valve)	AR	MR	Antibiotic treatment (duration)	Surgery	Outcome
Tomsic et al.[6]	United States	1	2016	48/M	Fever, Fatigue, cough (2 months)	Bicuspid AV, MV	Yes	TTE, TEE	AV/1/< 10 mm, MV/NR/NR	Yes (NCC AV, anterior MVL)	Yes (anterior MVL)	Severe	Severe	IV penicilin (6 wk), IV gentamicin (2 wk)	AVR, MVR	Cure
Baca et al.[7]	Peru	2	2017	58/M	Fever, vomiting, low back pain (2 months)	AV, MV	Yes	TEE	AV/multiples/9 mm, MV/NR/NR	Yes (anterior MVL)	Yes (NCC AV)	Severe	Severe	NR	AVR, MVR	NR
Dadon et al.[14]	Israel	3	1998	23/F	Fever (NR)	MV	NR	TEE	NR	NR	NR	NR	NR	IV gentamicin (2 wk)	None	Cure
		4	2006	37/M	Dyspnea (NR)	AV	NR	TTE	NR	NR	NR	NR	NR	NR	AVR	Died
		5	2006	45/M	Fever (NR)	MV	NR	TEE	NR	NR	NR	NR	NR	IV penicilin (6 wk), gentamicin (1 wk)	MVR	Cure
		6	2007	75/M	Fever (NR)	MV, AV	NR	TEE	NR	NR	NR	NR	NR	IV penicilin (6 wk)	No	Cure
		7	2013	83/F	Fever (NR)	MV	NR	TEE	NR	NR	NR	NR	NR	IV ceftriaxone (6 wk)	No	Cure
		8	2014	78/M	Fever (NR)	MV, AV	NR	TEE	NR	NR	NR	NR	NR	IV penicilin (6 wk)	AVR, MVR	Cure
		9	2014	71/M	Fever (NR)	NR	NR	TEE	NR	NR	NR	NR	NR	IV penicilin (6 wk)	No	Cure
		10	2015	31/M	Fever (NR)	MV	NR	TTE	NR	NR	NR	NR	NR	IV penicilin (4 wk)	MVR	Cure
		11	2016	82/M	Low back pain (2 wk)	MV	Yes	TEE	MV/1/14 mm	None	None	None	None	IV penicilin (8 wk)	None	Cure
		12	2016	63/M	Fever, low back pain (2 wk)	AV	Yes	TEE	AV/1/13 mm	None	None	None	None	IV penicilin (8 wk), IV gentamicin (2 wk), oral amoxycyline (4 wk)	None	Cure
		13	2017	71/M	General deterioration (NR)	AV	NR	TEE	NR	NR	NR	NR	NR	IV penicilin (6 wk)	AVR, MVR	Cure
Callejo-Goena et al.[15]	Spain	14	2018	60/M	Fever (2 wk)	MV	Yes	TEE	MV/1/NR	None	None	None	Severe	Ceftriaxone (3 months)	None	Cure
Mosailova et al.[1]	United States	15	2019	31/M	Bilateral lower extremity edema (2 days)	MV	Yes	TTE	MV/1/NR	None	None	None	Severe	IV ceftriaxone (6 wk)	MVR	NR

Continue to Table 1: Reported cases of infective endocarditis due to *Streptococcus gordonii*.

Author	Country	Pt. no.	Year	Age/gender	Symptoms (time)	Valve	Embolism	Diagnostic modality	Vegetation (valve/number/ size)	Aneurysm (valve)	Perforation (valve)	AR	MR	Antibiotic treatment (duration)	Surgery	Outcome
Komorovsky et al.[16]	Ukraine	16	2019	11/F	Fever, weakness, joint pain (NR)	MV	None	NR	MV/1/6 mm	None	None	None	Moderate	NR	MV annuloplasty	Cure
Peechakara et al.[17]	India	17	2019	42/M	Fever, back pain, hemoptysis, joint pain (3 months)	AV, MV	None	TTE, TEE	AV/NR/NR	None	Yes (anterior MVL)	Moderate	NR	IV ceftriaxone (6 wk), IV gentamicin (2 wk)	None	NR
Quan Li et al.[18]	China	18	2020	36/M	Fever (2 months)	Bicuspid AV	None	TTE, TEE	AV/ NR/NR	None	None	Severe	NR	NR	AVR	Cure
Yue Wang et al.[19]	China	19	2020	39/F	Fever, headache (6 months)	MV	Yes	TEE	MV/multiples/ NR	None	None	None	None	IV vancomycin (12 days)	None	Died
Bridwell et al.[20]	United States	20	2020	63/M	Fever (3 wk)	MV	None	TEE	MV/NR/NR	None	None	None	NR	IV gentamicin (2 wk), IV penicilin (4 wk)	None	Cure
Arbune et al.[21]	Romania	21	2021	23/F	Fever, malaise (9 wk)	AV	None	TTE	AV/1/5 mm	None	None	NR	NR	IV ceftriaxone (6 wk)	None	Cure
Jiménez Melo et al.[22]	Spain	22	2021	76/F	Dyspnea (4 months)	Mechanical MV and AV	Yes	TEE, FDG-PET/CT	MV/2/7 mm, AV/1/NR	None	None	None	None	IV ceftriaxone (NR)	None	NR
Chang et al.[4]	Malaysia	23	2021	28/M	Fever (1 wk), abdominal pain (3 days)	Bicuspid AV, MV	Yes	TTE	AV/2/11 × 6 mm, 16 × 8 mm, MV/1/5 × 8 mm	None	None	Severe	Moderate	IV penicilin (6 wk)	NR	NR
Lim et al.[23]	Malaysia	24	2022	40/M	Fever (1 month)	PV	Yes	TTE, CT	PV/1/23 × 12 mm	None	None	None	None	IV penicilin (6 wk)	PVR	Cure
Chawla et al.[24]	United States	25	2023	27/F	Sudden loss of vision, Severe headache (4 days)	MV	Yes	TEE	MV/NR/NR	None	None	None	NR	IV ceftriaxone (6 wk)	None	Cure
Qu Yi-Fan et al.[25]	China	26	2023	61/M	Fever, malaise (4 wk)	Bicuspid AV	Yes	TEE	None	None	Yes (AV)	Moderate-severe	Mild	NR	AVR, AV valvuloplasty	Cure
Alanís-Naranjo et al. (present case)	Mexico	27	2023	60/M	Fever, weight loss (3 wk)	AV, MV	None	TEE	MV/1/11 × 5 mm	Yes (anterior MVL)	Yes (NCC AV, anterior MVL)	Severe	Moderate	IV ceftriaxone (1 month)	AVR, MVR	Died

AR = aortic regurgitation. AV = aortic valve. AVR = aortic valve replacement. CT = computed tomography. F = female. FDG-PET/CT = F-fluorodeoxyglucose positron emission tomography/computed tomography. IV = intravenous. M = male. MR = mitral regurgitation. MV = mitral valve. MVL = mitral valve leaflet. MVR = mitral valve replacement. NCC = noncoronary cusp. NR = not reported. Pt = patient. PV = pulmonary valve. PVR = pulmonary valve replacement. TEE = trans-esophageal echocardiogram. TTE = trans-thoracic echocardiogram.

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Declaration of patient consent: the authors declare they have followed their workplace protocols for using patient data. Also, they certify that the relatives have received sufficient information and have given written informed consent for the patient images and other clinical information to be reported in the journal, without names or initials, to protect the right to privacy.

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In-flight cardiac arrest on commercial flights

Paro cardiaco en vuelos comerciales

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Keywords:
cardiopulmonary resuscitation, in-flight cardiac arrest, automated external defibrillation, good Samaritan law, aircrew.

Palabras clave:
reanimación cardiopulmonar, paro cardiaco en vuelo, desfibrilador automático externo, leyes de buen samaritano, tripulación aeronave.

ABSTRACT

The number of air travelers has increased over the past years, and after the limitations imposed by the COVID-19 pandemic, are expected to increase further. Given these conditions, the possibility for a health professional to find himself needing to assist an in-flight cardiac arrest is also increased. The present work describes some of the most common problems in managing an inflight cardiac arrest and emphasizes the relevance of cardiopulmonary resuscitation (CPR) performance and automated external defibrillators (AED) use on board of commercial airliners.

RESUMEN

El número de viajeros por avión ha aumentado en años pasados, y después de las limitaciones impuestas por la pandemia de COVID-19, se espera que esas cifras crezcan aún más. En vista de esta situación, la posibilidad de que un profesional sanitario se encuentre en posición de tener que asistir una parada cardiaca durante un vuelo comercial es también mayor. El presente trabajo describe algunos de los problemas más frecuentes en el tratamiento de un paro cardiaco durante un vuelo y enfatiza la relevancia de realizar reanimación cardiopulmonar y emplear un desfibrilador automático externo a bordo de una aeronave comercial

INTRODUCTION

Cardiac arrest aboard a commercial flight is a rare problem with many possible outcomes. Although it has a low frequency, it is estimated that approximately five billion people travel by commercial airlines yearly and about 2000 will have a sudden cardiac arrest.[1,2] This number of fatalities is substantially higher than the one from aircraft crashes, in 2021, for example, they were 176 dead persons worldwide.[3] In 2021 there were no deaths from accidents in the United States (US) civil aviation records.[4]

More sudden cardiac arrest events will occur in the future since there are increasing numbers of people flying, elderly travelers, and passengers with various cardiac diseases.[5] Between 1 in 14,000 and 1 in 50,000 passengers will experience an in-flight acute medical problem.[6] Nonetheless, in-flight cardiopulmonary resuscitation (CPR) and automatic external defibrillator (AED) use occur in one per 5 to 10 million passengers every year, or, according to the German Society of Aerospace Medicine, up to 0.3% of all in-flight emergencies.[6,7] Ventricular fibrillation (VF) is usually the first documented rhythm (up to 70% of sudden cardiac arrest victims), making defibrillation one of the first interventions to be done with real life-saving possibilities. In-flight cardiac arrest (IFCA) has shown a different pattern, although a significant 25 to 50% of subjects showed VF as the initial rhythm.[2,8-10] A study that recorded IFCA over a 65-month period, found that 27 passengers suffered from cardiac arrest aboard an airplane. Sixteen events were witnessed, and six had an initial VT/VF successfully treated with CPR, defibrillation, and diversion to the nearest suitable airport. Seven out of 27 subjects had an initial asystole and did not recover.[6,11]

In the context of out-of-hospital cardiac arrest (OHCA), successful reversion of the arrest

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has been reported in up to 30% of cases, given timely interventions are performed (hands-only cardio-pulmonary resuscitation [CPR], early defibrillation and proper emergency cardiac care). Those survival numbers strongly rely on early defibrillation: if an effective shock is applied within the first three minutes of the OHCA, most patients will regain spontaneous circulation. If that first shock is delayed beyond 16 minutes, survival possibilities are minimal, even if effective CPR has been performed.[12-15] When the OHCA happens during a flight, return of spontaneous circulation (ROSC) occurs in 44% of cases, and 15% of patients are discharged alive from the hospital.[2]

The conditions on board an aircraft are particular, and legislations are mostly unknown, although Lufthansa has estimated that in 80% of their flights,[7] there is a healthcare professional (physician, nurse, technician, or others) that will volunteer to assist in an in-flight medical emergency. In the present work, we will review some of the most common problems concerning IFCA and some of the solutions currently available.

GENERAL CONSIDERATIONS

For a physician, his conduct should be the same in an in-flight emergency as it is on the ground, but some considerations must be kept in mind.

First, the cabin has a pressurized atmosphere equivalent to an altitude of about 8,000 feet (2,400 meters). This implies that oxygen's partial pressure is 110 mmHg, about 25 to 30% lower than at sea level. The risk of gas expansion has to be taken into account to avoid pneumothorax in susceptible subjects, as well as complications from recent intracranial, abdominal, or ophthalmic surgeries. Because of the reduced partial pressure of oxygen, there will be a reduced oxygen blood saturation and, thus, compensatory tachycardia and tachypnea that might trigger other cardiovascular events.[7]

According to the Federal Aviation Administration (FAA), the European Aviation Safety Agency (EASA), and the Joint Aviation Authorities (JAA), aircraft have to be equipped with a minimum of medical equipment to face an in-flight emergency. The FAA requires that every plane flying in the US carry an (AED), a bag-valve-mask resuscitator, and an infusion system with normal saline solution.[7]

The laws applicable in an aircraft are those of the country under whose jurisdiction the airline operates; for example, Mexican laws will apply to any Mexican ships, while US laws will be applied to American Airlines. Some countries (France and Germany, among others) require that a physician on board must administer assistance, while the British, US and Canadian laws do not require physicians to help if there is an incident unless there is a pre-existing physician-patient relationship. In Mexico, there is no clear legislation aside from the ethical obligation to assist a person in an emergency. In order to facilitate assistance, many airlines provide a declaration of assumption of liability that is insurance against any claims arising from medical assistance except if there is gross negligence or deliberate harm to the ill person. If the assisting person does not obtain any monetary or equivalent compensation for the given assistance, it must be specified that insurance applies. In the US, physicians providing assistance under the «good Samaritan law» are not liable except in cases of gross negligence or willful misconduct.[7,16]

ROLE OF DOCTORS IN ASSISTING AN IFCA

There are different numbers around the world, but approximately 43% of IFCAs have been managed with the help of a passenger physician who responded to the call for help from the aircrew. As mentioned, Lufthansa personnel mentions that in up to 80% of the recorded emergencies in that airline, there was a health-related professional that could assist a fellow ill passenger.[5,7] The role of medical volunteers in an IFCA is to manage the emergency to the best of their ability and keep open communication with the aircrew and ground-based consultant to ensure that everyone involved in the emergency is fully aware of the situation's needs.[17]

Physicians have the ethical obligation to provide medical assistance when they can be reasonably expected to do so in any type of emergency, including IFCA.[18] That is why, even if every aircraft is subject to its country-of-origin laws, as previously mentioned, they are protected by the «good Samaritan laws».[7]

THE CHAIN OF SURVIVAL

Early recognition of cardiac arrest is the first link in the «chain of survival». It must be followed by the activation of the emergency medical services and immediate administration of CPR, preferably «hands-only CPR» followed by timely defibrillation, since CPR alone is unlikely to eliminate ventricular tachycardia or fibrillation and restore spontaneous circulation. It is known that for every minute delay between collapse and defibrillation, if no CPR is provided, survival rates decrease by 7 to 10%, but if CPR is administered, that decay in survival rate reaches 3 to 4% per minute *(Figure 1 and Table 1)*. These facts should prompt early recognition of an in-flight cardiac arrest and consequent interventions since the only opportunity to save a prehospital cardiac arrest victim is to treat him at the scene.[19] The main actions, such as CPR administration, AED use, and flight plan changes, will be discussed further.

FAILURE TO RECOGNIZE IN-FLIGHT CARDIAC ARREST

A collapsed passenger may be mistakenly considered a sleeping person. If the IFCA is not recognized, CPR and AED use will be delayed, and thus, the survival of the patient will be jeopardized. The aircrew should be trained to assess an unresponsive passenger who is not breathing as the first step in the survival chain. The aircrew should be trained to administer hands-only CPR and use the AED.[19,20]

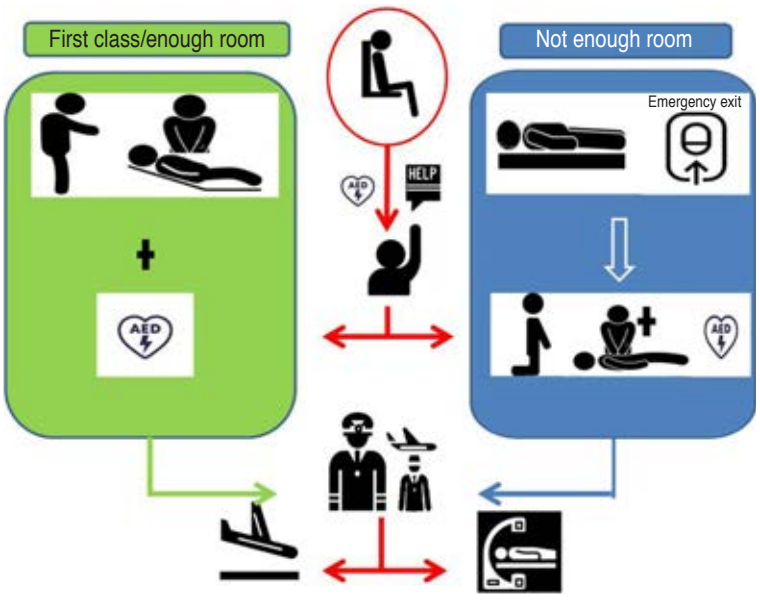

Figure 1: Suggested in flight cardiac arrest flowchart.

DELAYED TIME TO DEFIBRILLATION

By international regulations, aircraft should have an AED on board, and the aircrew has to be trained to start early CPR and connect an AED. Failure to recognize the cardiac arrest reduces the chances of identifying VF as the initial rhythm and, thus, reverses it by proper use of an AED, as is the case with passengers asleep or seemingly sleeping. That is why certain studies have shown that only 25 to 35% of the patients with IFCA have VF or VT as the initial rhythm. Training the aircrew to perform early recognition of IFCA in an unresponsive patient who is not breathing, start hands-only CPR, and attach the AED is mandatory to reach better survival rates.[10,20]

CABIN SETTING AND SURROUNDINGS

The management of an IFCA can be challenging in the restricted space of an aircraft cabin as there might be poor access, interference from vibration noise that precludes an adequate assessment to look for breathing and cardiac sounds and no privacy to work. The spectators of the intervention might not only not help but instead contribute to exacerbating a stressful situation by itself, even in proper medical settings. When possible, moving the patient to an ample space, such as an emergency exit, is recommended, and then start resuscitation maneuvers. Some large aircraft might be equipped with a special area to treat medical emergencies.[6,7,20]

The following are general recommendations for treating a passenger with IFCA in the main cabin:

1. Layback the unresponsive person in the seat and start hands-on CPR. At his point, the main concern should be if effective chest compression can be performed on

Table 1: Suggested action sequence for an in-flight cardiac emergency.

Problem	Action 1	Action 2
1. Unresponsive passenger	1.1. Ask for help to the crew and a AED	
2. Passenger first class Or seat able to lean back	2.1. Start high quality hands only CPR use of AED	
3. Passenger not in first class	3.1. Move him to the floor	3.2. Start high quality hands only CPR use of AED
	3.1.1. Place him next to emergency exit	
4. Patient receiving high quality hands only CPR and AED use	4. Get in touch with the rest of the crew	4.1. Ground support
		4.2. Possible diversion of the aircraft

AED = automated external defibrillators. CPR = cardiopulmonary resuscitation.

the seat. In the same way that a patient can receive high-quality CPR in a hospital bed, another patient might receive it as well in an aircraft, although this is probably more easily achievable out of the economy class.

2. If the CPR maneuvers can not be administered correctly in the seat, the passenger must be moved to the floor in the aisle near his seat to get a hard surface suitable for appropriate chest compressions, with the rescuer kneeling between seats. Another rescuer should be placed in front of the first one to take care of the airway. No matter if the patient is in the economy, business, or first class, the cabin space is usually scarce, and at least two rescuers AED and other equipment layout has to be optimized to make the most of it.
3. In very cramped cabins, the patient might be moved near an emergency exit or other suitable spaces (galley) to perform effective CPR. This will provide more space, but it will delay the initiation of CPR, with the consequent decreased chance of a successful outcome.[20]

GROUND SUPPORT

Airlines should have a ground-based medical support consultant, and they must get involved in the management of an IFCA or any other medical emergency. Their role is to assist medical decision-making through direct advice, support on-board medical volunteers and crew, and guide the pilot about flight diversion decisions. The latter recommendations must be made in the best patient's interest (to solve the emergency) and must take into account the patient's status, presumptive diagnosis, ground needs, and other in-flight and ground safety options.[16,21]

DIVERSION OF THE AIRCRAFT

The decision to divert an aircraft from its original flight plan depends primarily on the medical condition and the stability of the patient. There are standard protocols that must be strictly followed.[13] Even if there is a clear need to divert the flight to the nearest appropriate airport, this is unlikely to happen before 20 minutes –remember that the utility window for an AED to perform defibrillation is a maximum of 16 minutes–. Even after landing, it can take 10 to 15 minutes to get back to a bay after permission has been asked and obtained from the air traffic control.

The «nearest appropriate airport» has to be determined by the patient's disease. In the case of acute myocardial infarction, the pilot, controllers and ground personnel have to be aware that the aircraft has to land in the nearest possible position to a 24 hours available cath lab, with the proper services in the hospital (Intensive Care Unit, 24 hour emergency room). In certain situations, the plane can be diverted to the nearest airport, but then coordination to have a ground or heli-ambulance available and ready to transport the patient to another city with a cath lab available as soon as possible has to be made.

In some instances, the AED might be used as a monitor (supervised by a medically trained volunteer/passenger) and provide valuable information for the diversion of the aircraft, as can be the case with acute coronary syndromes.

Other reasons to divert a flight are emergencies such as continuing myocardial ischemia, acute myocardial infarction or stroke, where time to reperfusion treatment is of the essence,[22] as in other respiratory, metabolic or surgical emergencies.

EXTERNAL DEFIBRILLATORS (AEDs)

One of the major concerns regarding the use of AEDs in an inflight emergency is a possible malfunction of the device or a failure to recognize a shockable rhythm induced by the vibrations in the cabin, although no interference of the sort has been documented so far.[23] Katis also found that AED's with monitoring capabilities could be safe and useful for evaluating patients without cardiac arrest, with the help of a medically trained passenger, to decide whether to divert the flight or take other pertinent decisions.[23,24]

An important consideration is that the AED requires periodic maintenance to ensure its proper function if needed in an in-flight emergency. As Sheehan reported, even if there is limited information and there are rare cases of IFCA, AED use is safe, feasible, and is associated with improved outcomes, given that apparatus is in working order.[25] In this regard, current international regulations require that at least one flight attendant is trained in the use and operation of the AED.[19,26]

CONCLUSIONS

The number of air travelers has increased over the past years, as has the risk of witnessing an IFCA as a health professional. In-flight cardiac arrest has some peculiarities due to the characteristic confined space, the limited medical resources and personnel and the international regulations that tend to protect by the Good Samaritan Laws any person volunteering to assist a fellow passenger in distress. Performing CPR and using an AED is the most helpful treatment that can be administered on board, while a decision is made to divert the flight plan to a location with suitable services to treat the patient. Timely cardio-pulmonary resuscitation and defibrillation on board are the best options for an IFCA victim to regain spontaneous circulation, given that cardiac arrest is recognized. Aircrews need training in CPR and AED use, and assistance by volunteer medical personnel is of utmost importance to increase recovery chances for a patient.

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Cardiac myxoma

Mixoma cardiaco

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Keywords:
cardiac myxoma, cardiac magnetic resonance imaging, echocardiogram.

Palabras clave:
mixoma cardiaco, resonancia magnética cardiaca, ecocardiograma.

ABSTRACT

Introduction: the most common primary cardiac tumors are myxomas, of which 75-85% are located in the left atrium and are prevalent in females. They may present with a triad of obstructive, embolism or constitutional symptoms. **Case presentation:** this study presents the case of a patient who, two years before being diagnosed with a cardiac myxoma, presented dyspnea that subsided with the use of a beta-blocker. After a surgical intervention, the symptoms of heart failure were exacerbated, and an echocardiogram showed a mass covering most of the left atrium and protruding through the mitral valve. **Conclusion:** the transthoracic echocardiogram is the first line of imaging for the diagnosis of myxoma. Magnetic resonance imaging (MRI) provides information on the location, size and characterization of the mass, in addition to helping the differential diagnosis with the presence of thrombus, essential data for the diagnosis approach and patient treatment.

RESUMEN

Introducción: *los mixomas son los tumores cardiacos primarios más comunes, en 75-85% se localizan en la aurícula izquierda y suelen tener predominio por el sexo femenino. Se pueden presentar con la triada de obstrucción cardiaca, embolismo o síntomas constitucionales.* ***Presentación del caso:*** *en este trabajo se presenta el caso de una paciente joven, quien dos años antes del diagnóstico comenzó con disnea de medianos esfuerzos, la cual cedió con el uso de un betabloqueador, posterior a una intervención quirúrgica comienza con datos de falla cardiaca, se le realiza un ecocardiograma donde se evidencia una masa que abarca la mayor parte de la aurícula izquierda y protruye a través de la válvula mitral hacia el ventrículo izquierdo.* ***Conclusión:*** *el ecocardiograma transtorácico es la primera línea de imagen para el diagnóstico del mixoma, sin embargo, la resonancia magnética provee información sobre la localización, tamaño y caracterización de la masa, además de ayudar al diagnóstico diferencial con presencia de trombo, datos indispensables para el abordaje y tratamiento del paciente.*

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INTRODUCTION

Primary cardiac tumors in adults have an approximate incidence of 0.001 to 0.3%, with cardiac myxomas being the most common. In comparison, metastatic tumors of the heart are 30 times more frequent.[1,2]

In 75-85% of cases, cardiac myxomas are located in the left atrium. The development begins in the interatrial septum of the fossa ovalis; 22% develops in the right atrium, 2% in the ventricles, and 1% in the valves, specifically attached to the anterior leaflet of the mitral valve.[3-5]

The transthoracic echocardiogram is the first line of imaging for the diagnosis of myxoma. Magnetic resonance provides information on the location, size and characterization of the mass, in addition to helping the differential diagnosis with the presence of thrombus, essential data for the diagnosis approach and patient treatment.[6,7]

CASE PRESENTATION

A 39-year-old Hispanic female with no medical history of chronic diseases was presented with dyspnea grade two and dry cough, per the New

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York Heart Association (NYHA). The patient was treated with a beta blocker, which relieved the symptoms, until two months ago, when she underwent a laparoscopic cholecystectomy. A few days after the procedure, the patient reported shortness of breath, ankle swelling and lipothymy after physical activities. Initial physical exam revealed jugular ingurgitation grade III/IV, lungs with bilateral wheezing, bilateral pleural effusion syndrome with side predominance, the elevation of heart rate, cardiac murmur in mitral foci and lower extremities with symmetric edema +/++++. The electrocardiogram showed the presence of sinus tachycardia with an electrical axis to the right and mitral p wave determining left atrial enlargement *(Figure 1)*.

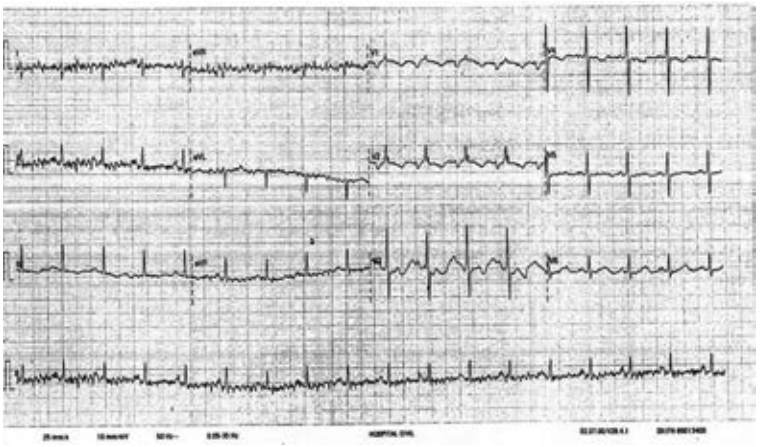

Figure 1: Electrocardiogram. Presence of sinus tachycardia with electrical axis to the right and mitral p wave determining left atrial enlargement.

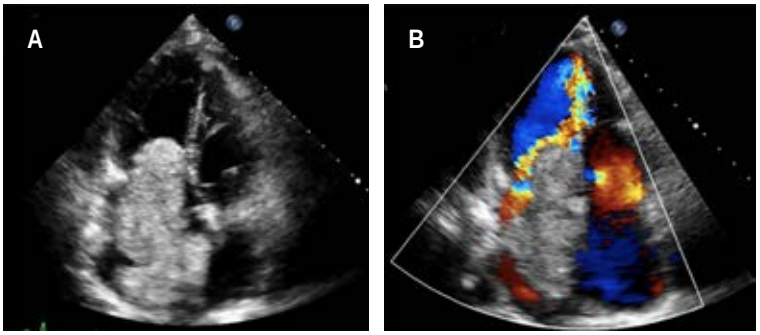

Figure 2: Transthoracic echocardiogram. **A)** Four-chamber diastole showing a mass in the left atrium protruding through the mitral valve into the ventricle. **B)** Color Doppler in four chambers.

A transthoracic echocardiogram showed a preserved ejection fraction. A mass was identified in the left atrium of approximately 52 × 29 mm in systole with slight protrusion into the anterior mitral valve leaflet and left ventricle during diastole, producing severe mitral stenosis. A concentric remodeling of the left ventricle without mobility alterations and both atriums with normal size was observed *(Figure 2)*.

DISCUSSION

Approximately 10% of primary cardiac tumors are malignant, and 90% are benign.[2] Myxomas are the most common benign cardiac tumors, accounting for about 50% of the primary cardiac neoplasms.[2]

Cardiac myxomas can develop at any age, but individuals older than 40 are at an increased risk. Furthermore, females are at a higher risk for cardiac myxomas, with a female-to-male ratio 3:1.[3,7,8]

The World Health Organization defines a cardiac myxoma as a neoplasm composed of stellate to plump, cytologically bland, mesenchymal cells set in a myxoid stroma.[9]

The classic triad of cardiac myxoma are: 1) symptoms due to cardiac obstruction, 2) symptoms due to cerebral or peripheral embolism, and 3) constitutional symptoms. The clinical spectrum depends on the location, size, and mobility of cardiac myxoma.[2,4] 10-33% of the patients are asymptomatic.[7]

The embolic events are present in 30-40% of cases. Intracardiac flow obstruction occurs in approximately 50% of cases, with dyspnea, palpitations and syncope being the most common symptoms. Constitutional symptoms are present in 20-60% of cases.[2,7]

Circulatory vascular collapse and signs of heart failure (dyspnea, paroxysmal nocturnal dyspnea, orthopnea, acute pulmonary edema and pulmonary hypertension) may occur. In those with ventricular location, outflow tract obstruction with syncope and sudden death may occur.[3,7,8] It can also cause damage to the subvalvular and valvular apparatus structures.[9]

The constitutional symptoms, characterized by fatigue, fever, myalgia, arthralgia, lethargy, anorexia, and weight loss, could correlate to the

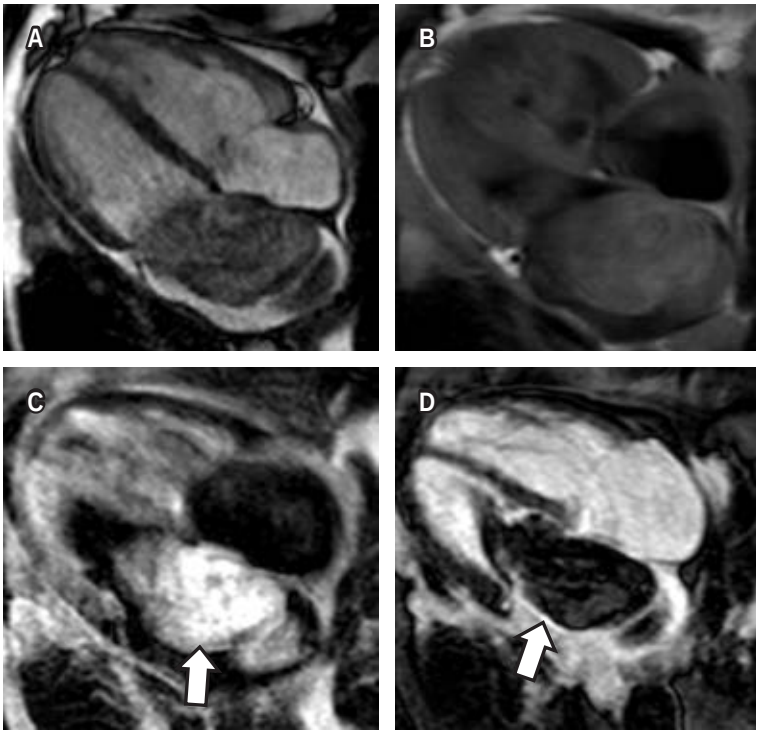

Figure 3: Cardiac magnetic resonance imaging showing left atrial mass. **A)** Cine (SSFP) four chambers. **B)** T1 FSE I-R four chambers. **C)** STIR T2W FSE I-R four chambers showing hyperintense mass suggesting high fluid content. **D)** T1 GRE I-R (late enhancement). White arrows point to hyperintense mass and areas of late enhancement in C and D, respectively.

interleukin-6 cytokine and vascular endothelial growth factor secreted by the myxoma.[2,3]

The thromboembolic event results from tissue fragmentation, detachment of the tumor as a whole and dissemination of overlaying thrombi from the tumor surface, which can result in stroke or ischemic complications.[3,9]

Upon physical examination, a proto-diastolic murmur -also called a tumor plop- may be present and simulates a mitral opening click. In addition, the penetration of the tumor into the ventricle through the valve generates a rumble due to the obstruction of blood flow.[10]

Electrocardiography abnormalities are common but also non-specific, present in 20-65% of the patients. It most commonly shows left or right atrial enlargement or non-specific ST segment abnormalities.[7] In some cases, conduction abnormalities can be presented, including a complete block of the left or right branch, grade one atrioventricular block and atrial fibrillation.[8]

Echocardiography is the first-line imaging modality for myxomas, with up to 95% sensitivity in diagnosing atrial myxoma.[6-8] According to echocardiography findings, there are two different anatomic appearances of atrial myxomas. The first appearance is solid and round with a non-mobile and smooth surface. The second appearance is polypoid, soft, an irregular shape and friable surface, and this one is associated with a higher incidence of embolization.[11] The most common differential diagnosis of atrial myxoma on echocardiography is intracardiac thrombus, which has a homogenous appearance instead of the myxomas' heterogeneous appearance.[6,11]

An MRI provides information with respect to localization, insertion site, and size of the mass. Myxomas typically show a heterogeneous appearance in MRI due to areas of necrosis, hemorrhage or calcification.[11]

On T1-weighted cine images, cardiac myxoma shows as a hypointensity mass relative to the myocardium; meanwhile, on T2-weighted images, it shows as a hyperintensity mass. Gadolinium-enhanced MRI demonstrates contrast enhancement due to high neovascularization, which is an important discriminator from a thrombus *(Figure 3)*.[11]

On cardiac tomography, cardiac myxoma usually appears as a hypodense filling defect in the cardiac cavities. Due to repeated episodes of hemorrhage, dystrophic calcification is common, which tends to be more common in right atrial myxoma.[3]

Tumor biopsy, with histological assessment, remains the gold standard for confirmation of the diagnosis.[6] Cardiac myxoma can be sessile or pedunculated, gelatinous in consistency, and the surface may be smooth, villous, or friable, with a pale gray, white, yellow or brown appearance.[1,5]

The treatment of choice is the prompt, complete surgical excision of the myxoma with its surroundings to avoid tumor recurrence, which is generally curative.[6,7] As rare complications of the surgical excision due to atriotomy, scar can appear atrial fibrillation, atrial flutter or supraventricular arrhythmias.[7]

CONCLUSIONS

Myxoma is the most common primary cardiac tumor, with 75-85% located in the left atrium and predominantly affecting females. They may present with the triad of cardiac obstruction, peripheral embolism or constitutional symptoms.

Depending on the degree of cardiac obstruction, it can cause sudden death. In this case study, the patient had a mass that covered almost the entire left atrium with protrusion into the left ventricle through the mitral valve. However, medication with a beta-blocker decreased the transmitral reflux, attenuating the symptoms of heart failure until its exacerbation after the surgical procedure.

Transthoracic echocardiography is the first line of imaging for the diagnosis of myxoma. However, magnetic resonance imaging provides information on the location, size and characterization of the myxoma. In addition, MRI helps with the differential diagnosis with the presence of a thrombus, indispensable data for the diagnosis approach and treatment of the patient.

The gold standard for diagnostic confirmation is biopsy. The treatment of choice is surgical resection of the tumor, which can be curative with a 10-year survival in 90% of patients. Although cardiac myxomas are rare, the early diagnosis can lead to a better prognosis of the patients.

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Consensus statement

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Lifestyle modifications and risk factors control in the prevention and treatment of atrial fibrillation. Endorsed by the Mexican Society of Cardiology (SMC) and National Association of Mexican Cardiologists (ANCAM)

Modificaciones al estilo de vida y control de los factores de riesgo en la prevención y tratamiento de la fibrilación auricular. Avalado por la Sociedad Mexicana de Cardiología (SMC) y Asociación Nacional de Cardiólogos de México (ANCAM)

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Keywords:
atrial fibrillation, lifestyle, risk factors, primary prevention, secondary prevention, treatment.

Palabras clave:
fibrilación auricular, estilo de vida, factores de riesgo, prevención primaria, prevención secundaria, tratamiento.

ABSTRACT

Atrial fibrillation (AF) is the most prevalent arrhythmia and is related to significant morbidity, mortality and costs. In spite of relevant advances in the prevention of embolic events and rhythm control, little has been done to reduce its prevalence, progression and impact since it increases with aging as well as with common risk factors such as alcohol intake, tobacco use and stress as well as with arterial hypertension, diabetes mellitus, heart failure, sleep apnea, kidney failure, chronic pulmonary obstructive disease, ischemic heart disease and stroke, among other important comorbidities. Fortunately, new evidence suggests that lifestyle modifications and adequate risk factors and comorbidities control could be effective in primary and secondary AF prevention, especially in its paroxysmal forms. This is why a multidisciplinary approach integrating lifestyle modifications, risk factors and comorbidities control is necessary for conjunction with rhythm or rate control and anticoagulation. Unfortunately, that holistic approach strategy is not considered, is scarcely studied or is subtilized in general clinical practice. The present statement's objectives are to: a) Review the relationship

RESUMEN

La fibrilación auricular (FA) es la arritmia más frecuente y se asocia con importante morbilidad, mortalidad y costos. A pesar de los grandes avances en la prevención de eventos embólicos y en el control del ritmo, poco se ha realizado para reducir su prevalencia, progresión e impacto, debido a que incrementa con la edad y con la presencia de múltiples factores de riesgo muy comunes en la población, como obesidad, sedentarismo, alcoholismo, tabaquismo y estrés, así como hipertensión arterial sistémica, diabetes mellitus, insuficiencia cardiaca, apnea del sueño, enfermedad renal crónica, enfermedad pulmonar obstructiva crónica, cardiopatía isquémica y enfermedad vascular cerebral, entre otras comorbilidades importantes. Nuevas evidencias demuestran que las modificaciones en el estilo de vida y el control adecuado de factores de riesgo y comorbilidades pueden ser efectivos en la prevención primaria y secundaria de la FA, especialmente en sus formas paroxísticas; para ello es necesario un manejo multidisciplinario que integre las modificaciones en el estilo de vida, el manejo de factores de riesgo y control de comorbilidades en el tratamiento de la FA

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between habits, risk factors and illnesses with AF, b) Review the individual and common physiopathology mechanisms of each one of those conditions that may lead to AF, c) Review the effect of control of habits, risk factors and co-morbidities on the control and impact of AF, d) Supply guidelines and recommendations to start multidisciplinary and integrative AF treatment.

en conjunto con el control de ritmo o frecuencia y la anticoagulación. Desafortunadamente, en la práctica clínica, estas estrategias frecuentemente no son tomadas en cuenta, son subutilizadas y poco estudiadas. Los objetivos del presente posicionamiento son: a) revisar la relación entre factores de riesgo y comorbilidades con FA, b) revisar los mecanismos fisiopatológicos de cada una de estas condiciones, c) revisar el impacto del control de factores de riesgo y comorbilidades en el control e impacto de la FA y d) proporcionar guías y recomendaciones para la puesta en práctica de programas de tratamiento multidisciplinario e integral en pacientes con FA.

Abbreviations:

AF = Atrial fibrillation.
HBP = High blood pressure.
DM = Diabetes mellitus.
HF = Heart failure.
IHD = Ischemic heart disease.
KCD = Chronic kidney disease.
COPD = Chronic obstructive pulmonary disease.
CMS = Cardiometabolic syndrome.
HCM = Hypertrophic cardiomyopathy.
BMI = Body mass index.
QOL = Quality of life.
BP = Blood pressure.
RAAS = Renin-angiotensin-aldosterone system.
ACEI = Angiotensin converting enzyme inhibitors.
ARAII = Angiotensin II receptor antagonists.
MRA = Mineralocorticoid receptor antagonists.
SGLT-2 = Sodium-glucosecotransporter-2 inhibitors.
DPP-4 = Dipeptidyl peptidase-4 inhibitor.
GLP-1 = Glucagon-like peptide-1.
LVEF = Left ventricular ejection fraction.
CPAP = Continuous positive airway pressure.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia. It is estimated that there are 43 million people affected worldwide, and its prevalence is 600 to 900 cases per 100,000 persons; thus, the risk of having AF in people older than 55 years is about 1 in 3.[1] The current numbers suggest that there will be 5 million new cases every year in the world.[2,3]

There have been significant advances in the prevention of embolic events and rhythm control strategies. Nonetheless, few efforts have been made to reduce AF's prevalence, progression and impact.[1-3] Although AF can be present in young individuals without apparent heart disease, it has been acknowledged that its prevalence increases with aging and is related to multiple common risk factors such as obesity, sedentarism,[1] stress, long working hours,[4] alcohol intake and tobacco use.[3] Atrial fibrillation is also associated with other co-morbidities such as high blood pressure (HBP), diabetes mellitus (DM), heart failure (HF), sleep apnea, cardio-metabolic syndrome (CMS),[3] chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD), stroke,[1] fatty liver,[5] dyslipidemia, hypothyroidism,[6] hypertrophic cardiomyopathy[1] and peripheral artery disease (PAD).[7]

Aging and added risk factors and co-morbidities increase the chances of having AF.[3,6] The significant association of AF with multiple risk factors has been proven, especially with HF in both men and women.[8] Atrial fibrillation is a high-impact condition because it has higher morbidity rates. Its mortality rates go from 8 to 19.5% yearly from cardiac and non-cardiac causes.[9] *Figure 1* shows a proposed sequence of risk factors, co-morbidities and mortality in AF patients. Both risk factors and co-morbidities share common pathophysiologic mechanisms, such as atrial endothelial dysfunction, inflammation and fibrosis, that induce atrial cardiomyopathy with anatomic, electric, mechano-electric and autonomic remodeling that will promote AF,[10] as shown in *Figure 2*. Different forms of AF (paroxysmal, persistent and permanent) have different clinical implications, slight differences in the risk profile and variable responses to treatment. Nonetheless, in every form of AF, there is a benefit from the prevention measures and risk factors control.

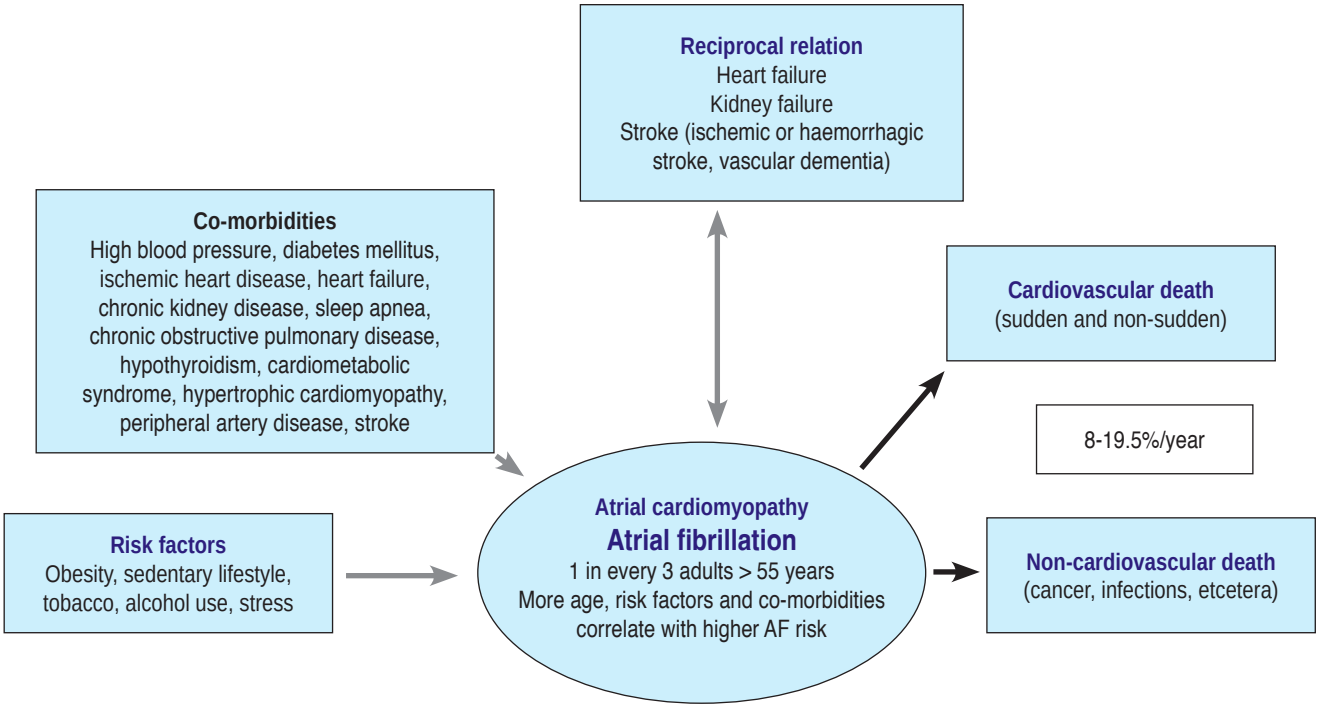

Figure 1: Risk factors, co-morbidities and mortality sequence in patients with atrial fibrillation.
AF = atrial fibrillation.

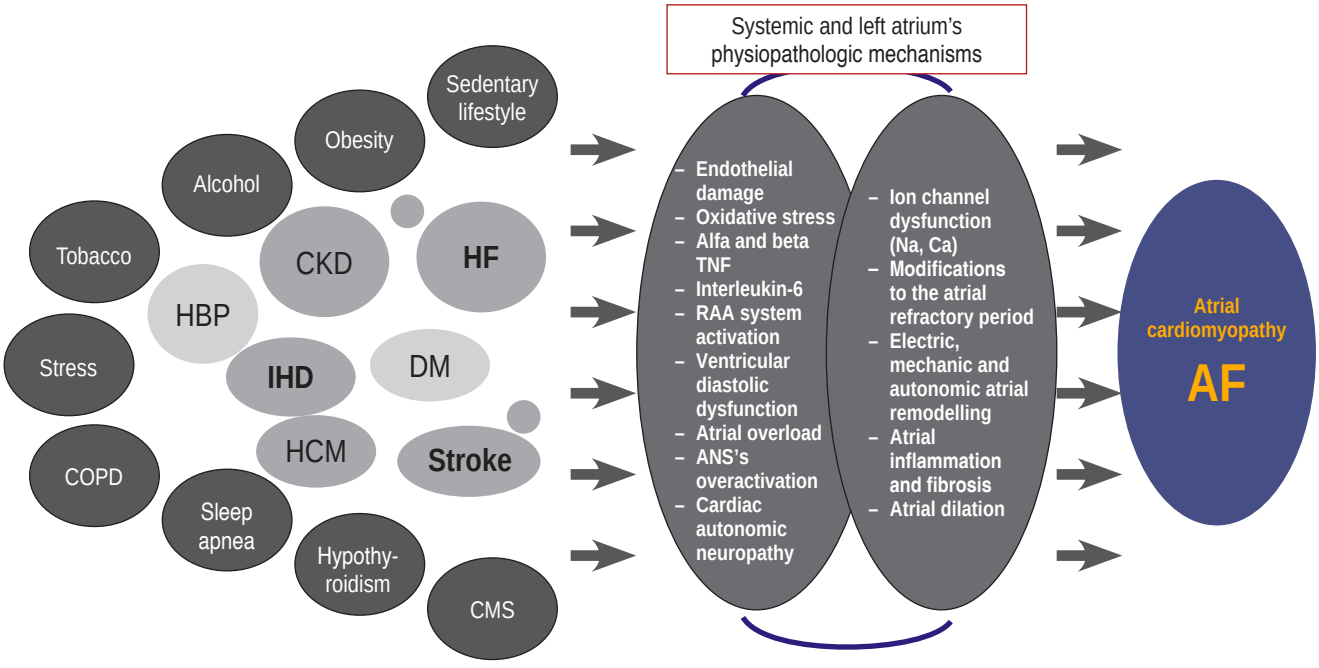

Figure 2: Risk factors and co-morbidities' common physiopathologic mechanisms that induce atrial cardiomyopathy and AF.
AF = atrial fibrillation. COPD = chronic obstructive pulmonary disease. CMS = cardiometabolic syndrome. CKD = chronic kidney disease. HBP = high blood pressure. IHD = ischemic heart disease. HF = heart failure. DM = diabetes mellitus. HCM = hypertrophic cardiomyopathy. TNF = tumor necrosis factor. RAA = renin, angiotensin-aldosterone. Na = sodium. Ca = calcium. ANS = autonomic nervous system.

Most of those risk factors are reversible when they are properly controlled and there is a positive impact on AF behavior.[1-3] The most recent European and American guidelines rank risk factors and comorbidities control as a class I indication with evidence level B along with rhythm or rate control and anticoagulation.[10-13] Because of the great number of elements related to AF, its management is more complex and might be suboptimal if only directed towards a fraction of them.[1,13] A joint approach treatment to achieve rhythm control, anticoagulation, and derive the patient to a multidisciplinary team for adequate risk factor control might facilitate an intensive and complete treatment with better results.[2,3] The acronym HEAD-2-TOES (heart failure, exercise, arterial hypertension, DM2, tobacco use, Obesity, Ethanol consumption, sleep apnea) refers to several modifiable risk factors, lifestyle and comorbidities that are related to the development, persistence and progression of AF.[14] These and other elements that we show in the present work are targets for primary and secondary AF prevention. Several services and specialists might be needed to achieve an integrated multidisciplinary approach to AF, shown in *Figure 3*. Some recent controlled

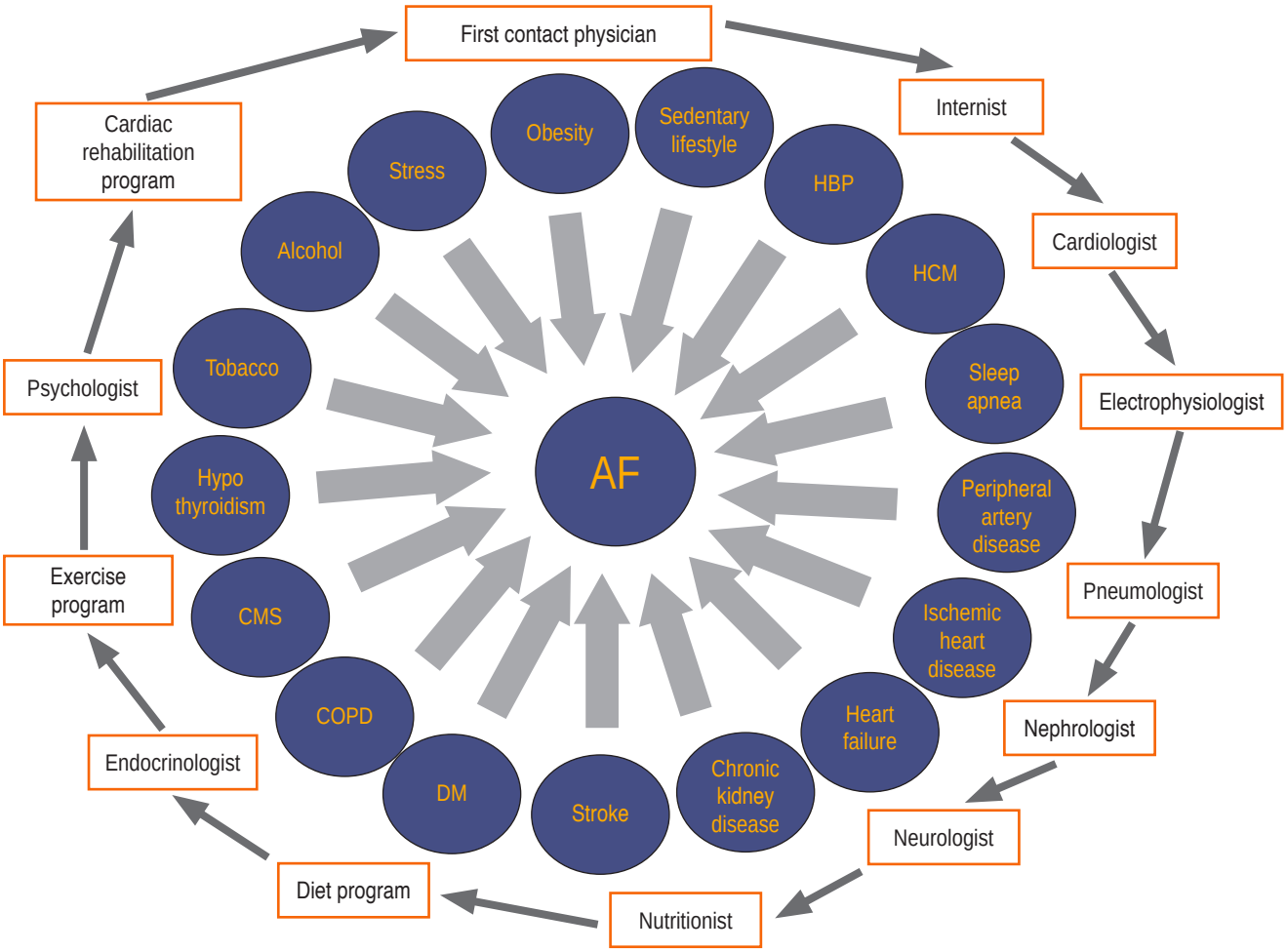

Figure 3: Necessary interactions between physicians and services to achieve an integral and multidisciplinary attention in the atrial fibrillation patients.
HBP = high blood pressure. HCM = hypertrophic cardiomyopathy. DM = diabetes mellitus. COPD = chronic obstructive pulmonary disease. CMS = cardiometabolic syndrome. AF = atrial fibrillation.

and randomized clinical studies have shown a positive impact on the arrhythmia burden when lifestyle modifications such as weight reduction *(Table 1)*, exercise and modifiable risk factors control are implemented, showing up to a 35% reduction in re-hospitalizations and mortality,[3] as well as a reduced progression from paroxysmal to permanent forms of AF and lower recurrence rates after ablation.[3] Those benefits regarding AF behavior are associated with lesser atrial damage.[10-12]

In the following pages, we will detail the risk factors and co-morbidities most frequently associated with atrial cardiomyopathy and AF development, as well as the recommended actions to control them and reduce their progression. In every case, it is recommended to adopt the most recent AF treatment guidelines that emphasize the permanence in sinus rhythm as the best option to delay the arrhythmia and atrial cardiomyopathy's progression, along with lifestyle modifications and risk factors control, which is the main focus of the present work.

OBESITY AND AF

There is a strong correlation between obesity and AF. Patients with BMI > 35 kg/m^2 have a 3 to 4-fold increase in the risk of AF.[15] Several mechanisms are implicated in this phenomenon: the increase in pressure and size of left atrium's favors greater release of transforming factor β1 and platelet derived growth factor (PDGF) concentrations.[16] Increased pericardial and epicardial fat have arrhythmogenic effect through increased release of stearic acid and by induction of changes in the electric currents of a left atrium with stretched myocardial fibers.[17] Sympathetic activation, the effect of the renin angiotensin aldosterone system (RAAS), leptin excess and insulin resistance induce cardiac remodeling and atrial cardiomyopathy.[10,18] The association of obesity with cardio-metabolic syndrome,[19] sleep apnea, HBP, DM,[20] HF[21] and IHD[22] increase both the prevalence and impact of AF. Non-alcoholic fatty liver, present in 75-92% of patients with obesity,[5] is associated with higher cardiovascular risk,[23] AF[24,25] and recurrence risk among patients that undergo a radiofrequency ablation procedure to control AF.[26]

Weight control and AF

Some studies have shown a positive impact of weight loss on AF control. People that achieve weight reductions above 10% or a BMI < 27 kg/m^2 have a 6/fold reduction in AF events when compared to those that did not lose it or with reductions lesser than 3% of the initial total body weight.[11,27] Weight loss is also related with less symptoms and higher sinus rhythm conversion rate (75 vs 63%).[12,28] Weight reduction in patients that receive an ablation procedure has shown better AF-free survival.[29] A Mediterranean diet, rich in vegetables, grains, fruit, coffee, tea and virgin olive oil has antioxidant and anti-inflammatory properties that reduce the overall AF risk as well as its progression and recurrences.[30]

Key points and recommendations:

1. Obesity increases the risk of AF.
2. Reduction of at least 10% of baseline weight or reach a BMI < 27 kg/m^2 is a 1-B recommendation to reduce the progression and impact of AF.
3. In candidates for AF ablation, weight reduction increases AF-free survival rate.
4. A Mediterranean diet (rich in vegetables, grains, fruit, coffee, tea, and olive oil) is recommended because of its antioxidant and anti-inflammatory properties that reduce the risk of AF and its complications.

PHYSICAL ACTIVITY AND AF

Physical inactivity is associated with cardiovascular disease. Inactivity periods are associated with AF appearance: the longer the sedentary period, the higher the AF risk.[31,32] Physical inactivity promotes electrical and structural remodeling of the atrial wall through an increase in systemic inflammatory processes and sympathetic activity that favors autonomic de-regulation processes that will eventually lead to AF.[32] On the other hand, excessive exercising can also increase the risk of AF, as has been noted in marathoners, [33] that have a 5-fold increase in AF risk.[34] That phenomenon among high-end athletes is somehow explained by dilation and fibrosis of the atrial muscle secondary to elevated hemodynamic loads, an increase in

Table 1: Randomized clinical studies about risk factors control and their results in patients with atrial fibrillation.

Study	Objective	Impact on AF's behavior	Other findings
Legacy[11] 355 patients with AF Follow-up 48.4 ± 18.2 months	Body weight reduction (> 10 vs 3-9 vs < 3% reduction) and risk factor's management	Reduction of the frequency, duration and severity of AF's symptoms Higher AF-free survival (86.2 vs 65.5 vs 39.6%)	Reduction of the left atrium's indexed volume Reduction of interventricular septum's thickness Reduction of the left ventricle's end-diastolic diameter Reduction of high sensitivity C-reactive protein
Reverse-AF[12] Same patients as in the Legacy study[11] Follow-up 48 4 ± 18.2 months	Body weight reduction (> 10 vs 3-9% vs < 3% reduction) and risk factor's management	Lower progression to AF's persistent forms (3 vs 32 vs 41%) Higher AF's reversion from persistent to paroxismal forms (88 vs 49 vs 26%)	Reduction of the left atrium's indexed volume Reduction of interventricular septum's thickness Reduction of the left ventricle's end-diastolic diameter Reduction of high sensitivity C-reactive protein
Weight reduction in cardiometabolic risk[27] 150 patients with paroxismal or persistent AF Follow-up 15 months	Body weight reduction and risk factors control	Reduction in frequency, severity, impact and duration of AF's symptoms	Reduction of interventricular septum's thickness Left atrium's area reduction
Race 3[28] 250 patients with AF and HF 119 multiple combined therapies, 126 conventional therapy Follow-up 12 months	Risk factors control vs conventional therapy	Sinus rhythm in the risk factors control group 75 vs 63% with conventional therapy group Improvement of AF's symptoms	Improvement in systolic and diastolic blood pressure control Weight reduction, body mass index reduction. Lower total cholesterol levels, LDL, NT-proBNP and urinary sodium
Arrest-AF[29] Patients submitted to AF ablation 149 Ablation + risk factor's control 88 control group (ablation only) Follow-up 41.6 ± 14.2 months	Risk factors control HBP, lipid, glycemic and sleep apnea control along with weight reduction, reduction of tobacco and alcohol use	Reduction in the frequency, duration and severity of AF's symptoms Higher AF-free survival after one or several procedures (87 vs 17.8%)	Reduction of interventricular septum's thickness Left atrium's volume reduction
Cardio-Fit[38] 308 patients with FA Follow-up 49 ± 19 months	High physical conditioning vs adequate vs low Physical conditioning gain during follow-up	Reduction in the frequency, duration and severity of AF Higher AF-free survival in the high physical conditioning group (84 vs 76 vs 17%)	Higher physical performance: higher weight reduction, lower blood pressure, LDL and triglyceride reduction, better glycemic control, lower high-sensitivity C reactive protein levels, left atrium's volumen reduction

AF = atrial fibrillation. HF = heart failure. LDL = low density lipoprotein. HBP = High blood pressure.

atrial ectopic activity and abrupt shifts in the sympathetic-parasympathetic balance.[35]

Exercise and AF control

Better physical capacity as a result of regular aerobic training is associated with lesser AF impact in middle age and older adults.[36] Atrial fibrillation's incidence is higher in subjects with low training (capable of less than 5 METs), but it is reduced by every MET (1 kcal/kg/h) increase. Regular exercise reduces the risk of AF by 7%[37] and by 9% the risk of AF recurrence after ablation procedures.[38] A two-month regular exercise program in subjects with permanent AF reduces symptoms and ameliorates quality of life (QoL).[39] A meta-analysis shows that an increase in exercise capacity also increases left ventricular ejection fraction, QoL and vitality.[40] Even if regular physical activity is beneficial to prevent and treat AF, in daily clinical practice, physicians recommend exercise in less than 10% of patients.[14] Short intervals-high intensity exercise can improve physiologic parameters such as cardiorespiratory capacity,[41] ejection fraction,[42] diastolic function,[43] as well as endothelial and general vascular function.[43]

Body-mind exercises as Yoga, Tai-chi and Chi-kung can also have beneficial effects because they improve elasticity, flexibility, equilibrium, general health conditions and autonomic cardiac functioning,[44] that has an important role in AF's genesis.[45] The study YOGA My Heart[46] showed that a three-month yoga training program reduces AF's impact and improves symptoms and QoL. When comparing yoga against short Interval-high intensity exercise, it was found that yoga does not have adverse effects on left atrial remodeling, so it could further reduce AF's recurrences.[47]

Key points and recommendations:

1. A sedentary lifestyle is associated with increased risk of AF.
2. A regular exercise program must be suggested in every AF patient as a class 1-B recommendation.
3. An increase in the physical capacity and cardiovascular endurance reduces the impact and recurrences of AF, and improves QoL and symptoms among AF patients.

ALCOHOL INTAKE AND AF

Regular alcohol intake is widely accepted in occidental cultures, with a prevalence of 57% in the US population.[48] Some observational studies have observed a dose-dependent relationship between alcohol intake and AF: drinking of a weekly average of 7 to 14 alcoholic beverages significantly increases the risk of AF.[49] Acute alcohol intake has also been reported as a trigger in up to 35% of AF new cases[50] and is known to increase recurrences after ablation procedures.[51] Alcohol intake induces both sympathetic and para-sympathetic stimulation that reduce heart rate variability, increases pericardial fat, inflammation, electrical and mechanical remodeling of the left atrium and thus, increases AF inducibility.[52] It is also related to AF-favouring comorbidities such as obesity[53] and HBP.[54]

Alcohol consumption control and AF behavior.

Reduction of alcohol intake to less than 3 drinks per week reduce atrial remodeling, AF impact and has become a class 1-B recommendation in the European guidelines for AF treatment and control.[1] Complete abstinence in usual alcohol users further reduces AF recurrences.[55]

Key points and recommendations:

1. Alcohol intake is related with higher prevalence and recurrence of AF.
2. Restrict alcohol intake is a class 1-B recommendation to reduce AF's progression and impact.
3. Alcohol abstinence further reduces AF recurrences.

High blood pressure (HBP) and AF

Epidemiological and clinical studies have found a close relation between HBP and AF since they share many risk factors.[56] Because of its high prevalence, HBP is a major independent risk factor to develop AF. In the same way, poor HBP control is associated

with higher AF and mortality risk.[56] It has been reported that 21.6% of hypertensive subjects will have AF.[57] High blood pressure might induce atrial cardiomyopathy by promoting architectural, contractile and electrophysiologic changes that affect both atria and produce arrhythmogenic foci.[10] A hypertrophic left ventricle that is less compliant promotes a pressure increase and muscle fiber stretching of the atria, predisposing towards AF development.[58,59] Higher levels of aldosterone and angiotensin II, in the context of HBP, induce inflammation as well as fibroblastic and extra-cellular proliferation, that in turn will promote more myocyte hypertrophy and atrial remodelling.[56,57] Angiotensin II favors inward calcium currents and reduces potassium outward currents. These changes prolong the action potential plateau (phase 2), increase inotropism but favors anisotropism, thus increasing the risk of AF.[10,58,59]

ARTERIAL HYPERTENSION CONTROL AND AF

Arterial hypertension control is a class 1-B recommendation in the 2020 AF European[1] and 2019 American guidelines.[13] In order to achieve an adequate BP control, international guidelines must be followed.[60] A target blood pressure between 120-129/< 80 shows better outcomes than > 130/80 mmHg or < 120/80 records, that have been related with a higher risk of adverse cardiovascular events.[58,60] Stroke risk in patients with AF significantly increases with every 10 mmHg elevation above 120 mmHg or with systolic BP values lower than 115 mmHg.[60] Treatment with Angiotensin Converting Enzyme Inhibitors (ACEI) or with Angiotensin II Receptor Blockers (ARB's) reduce RAAS activation and has beneficial effects delaying atrial damage progression and AF prevalence.[61,62] Hypertension treatment with mineralocorticoid receptors antagonists has also been noted to reduce FA risk and recurrence both in observational studies and meta-analyses.[62,63] Patients with severe hypertension and AF treated with AF ablation and renal artery denervation have shown better BP control and less AF recurrences after a 12 month follow-up.[64]

Key points and recommendations:

1. Arterial hypertension is related with higher AF risk.
2. HBP control is a recommendation 1-B to reduce AF's progression and impact.
3. Pharmacological therapy with ACEI, ARB's and mineralocorticoid receptor antagonists exerts a positive effect to reduce atrial damage progression and AF effects.

DIABETES MELLITUS (DM) AND AF

Diabetes is a major risk factor related with an increase in cardiovascular events and mortality.[65] Patients with DM have more chances to develop AF with a 1.4 and 1.6-fold increase respectively in women and men.[65] Atrial fibrillation incidence is 14.9% among diabetic patients versus 10.3% in non-diabetic ones.[66] A metanalysis that included 1,6 million subjects showed that DM is an independent risk factor that increases 40% the chances of having AF.[67] Diabetes increases AF symptoms and reduces QoL,[68] it increases the hospitalization rate, the risk of acute coronary events, Stroke, HF, and all-cause mortality.[65,69] The mechanisms involved in the genesis of AF in patients with DM include an increase in oxidative stress,[70] atrial cardiomyopathy with electro-mechanic and autonomic remodeling of the left atrium,[10,71] and release of advanced glycation products that favor more inflammation, dilation and atrial fibrosis.[72] All these changes reduce the atrial functional reserve and impair electrical conduction through the atria, inducing a marked intra and inter-atrial electro-mechanical conduction delay.[73] The longer DM has been present, and the worse its control, the higher the risk of having AF.[65] Elevated levels of glycated hemoglobin, are associated with a 10% increased risk of having AF. For each 1% increase in glycated hemoglobin HbA1c, there is a 1% increase in the chances of having AF.[74,75] DM is associated with a higher prevalence of obesity, hypertension, HF and CKD, which in turn increase the prevalence of AF.[76] *Figure 4* shows the mechanisms implicated in AF among DM patients.

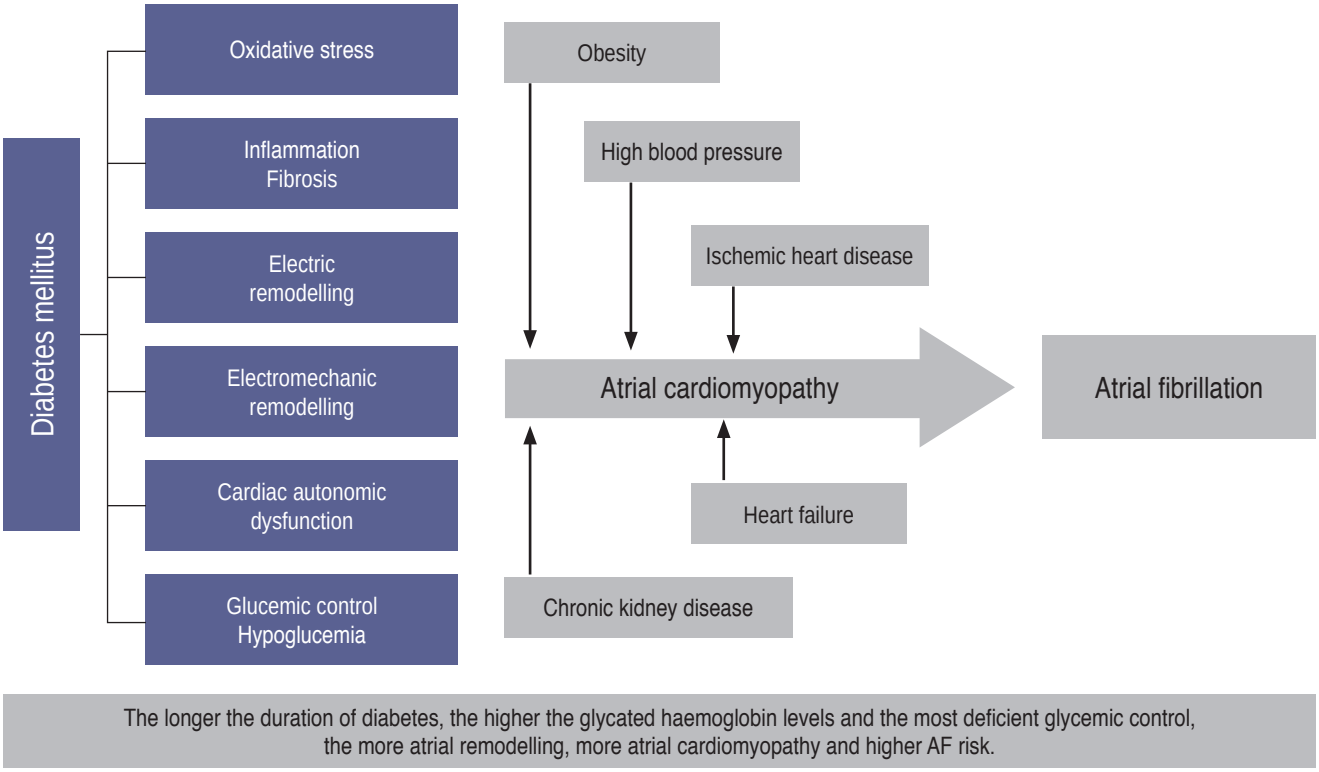

Figure 4: Physiopathologic mechanisms that induce atrial fibrillation in patients with diabetes mellitus.

Diabetes control and AF

Adequate control of blood glucose is important to reduce AF's impact and recurrences.[76,77] Metformin use has shown a 19% reduction in the risk of AF during a 13-year follow-up period.[78] A metanalysis showed that pioglitazone was associated with a 27% risk reduction to develop AF, apparently because it reduces atrial inflammation and fibrosis.[79] Drugs as SGLT2 inhibitors, seem to reduce the incidence of atrial arrhythmias and sudden death.[80] The DPP-4 inhibitors and the GLP-1 inhibitors have not shown, so far, any protective effect against AF.[81]

Key points and recommendations:

1. Diabetes mellitus is associated with higher risk of AF.
2. Diabetes control is a class1-B recommendation to reduce AF's recurrence rates, progression and impact.
3. So far, only metformin, pioglitazone and SLGT2 inhibitors (empaglifozin, dapaglifozin and canaglifozin) have proved to reduce AF's prevalence and impact.

HEART FAILURE AND AF

Heart failure's incidence has globally increased as well as its care costs. Atrial fibrillation is the most common arrhythmia related to HF, present in approximately 25% of HF patients.[82] The combination of HF and AF has a negative synergistic effect that reduce QoL and functional capacity while they increase stroke risk, hospitalizations and all-cause mortality.[83] Heart failure and AF share risk factors such as obesity, DM, HBP, IHD, tobacco and alcohol use and male gender.[84] The higher HF prevalence, higher AF prevalence and vice versa.[83] Atrial fibrillation can be present in patients with reduced or preserved ejection fraction HF.[85] Among the different mechanisms that lead to AF in HF patients, there is atrial cardiomyopathy,[10]

blood pressure overloads, atrial myocardial stretching, abnormal myocardial conduction velocity, structural remodeling and atrial maladaptation gene expression.[86] Acute increases of intra-atrial pressure promote dilation and fibrosis of the atrial myocardium, that in turn will induce electro-mechanical remodeling, shortening of atrial refractory periods, triggered activity and AF.[87] On the other hand, fast ventricular response AF will reduce cardiac output, loss of atrial contraction and irregular ventricular filling intervals.[10,85]

A chronic inflammatory state prevalent in HF[88] favors, as well, development of atrial cardiomyopathy[10] alongside with the left's atrium structural and anatomic remodeling that triggers and perpetuates AF.[89] *Figure 2* shows the physiopathologic features shared by HF and other co-morbidities that will lead to AF.[88,89]

Heart failure control and AF

The treatment for patients with HF and AF must be installed according to the international guidelines recommendations.[1,90] Treatment with ARB's, ACEI's and neprilisin inhibitors in patients with HF and AF might improve ventricular function and reduce the prevalence and impact of AF.[91-92] In patients with AF and rapid mean ventricular response, hemodynamic impairment or worsening HF, immediate external electrical cardioversion is a reasonable choice.[90,92] Among subjects with AF and preserved, moderately reduced or reduced LVEF, early rhythm control with antiarrhythmic drugs or ablation has shown better results in hospitalization, stroke prevention and mortality when compared to conventional treatment.[93]

Beta-blockers are preferred over digoxin to achieve rate control since they improve prognosis. Only if the mean ventricular rate persists high with beta-blocker therapy or when these drugs are not tolerated or are contra-indicated, then digoxin may be used.[92,93] Pulmonary vein isolation by a catheter ablation procedure in selected patients with AF and HF might be superior to both pharmacologic rate and rhythm control[94] since it improves QoL, exercise capacity, LVEF and reduces mortality.[95] Unfortunately, less than 10% of patients with HF and AF are eligible for pulmonary vein isolation.[94-96]

Key points and recommendations:

1. Heart failure increases the risk of AF, in the same way that AF increases the risk of HF.
2. Heart failure control is a class 1-B recommendation in patients with AF.
3. Early rhythm control has shown better results concerning hospitalization, stroke prevention and mortality in patients with preserved, moderately reduced and reduced LVEF.

SLEEP APNEA AND AF

Sleep apnea is a common problem with strong correlation to cardiovascular disease.[97] The prevalence of moderate to severe sleep apnea (SA) is 10 and 7% among men and women in the 30-49 years old range respectively and in 17 and 9% of men and women in the 50 to 70 years-old range respectively.[98] Sleep apnea induces hypoxia and hypercapnia as well as repetitive events of increased intrathoracic negative pressure and atrial overdistension thus increasing sympathetic activity that activates ion channels that promote atrial cardiomyopathy[10] and AF.[99] Sleep apnea and AF share risk factors as obesity, older age, male gender, HBP, HF, genetic factors, IHD, stroke and alcohol intake.[100] Patients with SA show a 2-fold increase in the risk of having AF and a 5.2-fold increase in cardiovascular death risk.[101] It has been reported that AF is present in 21 to 87% of SA patients,[102] according to the severity of the later, that is, the more severe the SA, the higher the risk of AF[103] and the lower the response to antiarrhythmic drugs.[104]

Sleep apnea control and AF

Patients with SA and AF treated with continuous positive airway pressure (CPAP) have slower AF progression to permanent forms and show less recurrences after cardioversion or ablation.[1,2,105] It is recommended to include every patient with SA in exercise, nutrition and body weight reduction programs in order to improve the results of other AF control interventions.[1,2,3,105]

Key points and recommendations:

1. Sleep apnea increases the risk of AF in a directly proportional way: The more severe the AS, the higher the risk of AF.
2. Sleep apnea diagnosis and treatment is a relevant component among the lifestyle modifications in AF patients and is a class 1-B recommendation.
3. Patients with SA treated with CPAP show slower AF progression and less recurrences after ablation or cardioversion.

CHRONIC KIDNEY DISEASE AND AF

Chronic kidney disease (CKD) and AF are closely related. They both share risk factors and co-morbidities such as advanced age, obesity, sedentary lifestyle, tobacco use, HBP, HF, stroke and both show global increasing prevalence with a reciprocal relationship.[1,106] Almost 20% of patients with CKD have AF and nearly 50% of patients with AF show some degree of kidney damage.[107] Patients with both conditions are at greater risk of thromboembolism, cardiovascular morbidity, hemorrhage and all-cause mortality.[108] Kidney disease promotes atrial cardiomyopathy[10] through several mechanisms: it increases the release of B1 growth factor that has a pro-inflammatory effect, as well as cellular infiltration, interstitial fibrosis and atrial conduction velocity heterogeneity. Kidney disease also activates RAAS, sympathetic nervous system and induces water and salt retention that in turn will stretch atrial walls and induce atrial remodeling, inflammation and necrosis.[106,109] On the other hand, AF promotes CKD progression to terminal phases.[1,110]

Chronic kidney disease control and AF

Several drugs reduce CKD progression and might be useful to reduce AF.as Angiotensin converting enzyme inhibitors and ARB's, reduce RAAS's activity and CKD progression as well as AF prevalence.[110] It is mandatory to control risk factors and co-morbidities in the early stages of renal damage in order to reduce the prevalence of CKD and AF.[111] Medications that increase renal damage such as non-steroidal anti-inflammatory drugs (NSAID's) should be avoided, as well as vitamin K antagonists such as warfarin or acenocoumarin, which also increase bleeding and embolism risk when compared to direct anticoagulants as rivaroxaban, apixaban, dabigatran or edoxaban, that are preferred in those patients.[1,112]

Key points and recommendations:

1. Chronic kidney disease and AF are linked and show a reciprocal relationship: the more significant the kidney damage, the higher the risk of AF, and vice versa.
2. An adequate control of risk factors and specific measures to reduce kidney damage along with measures to prevent AF and reduce its impact are a class 1-B recommendation.
3. Direct oral anticoagulants are preferred over vitamin K antagonists since the later increase renal damage.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND AF

Chronic obstructive pulmonary disease (COPD) is a major health problem: approximately 10% of the general population suffers from it.[113,114] Up to 23% of patients with AF have COPD.[115] The greater the COPD's severity, the greater its association with HBP, IHD, HF and AF.[116,117] Pulmonary disease increases the progression and recurrences of AF after pharmacological treatment,[1] cardioversion[118] or ablation.[113] Atrial fibrillation in patients with COPD, in turn, will promote lung damage and increases the rates of cardiovascular events and long-term mortality.[119] Several factors might promote AF in subjects with COPD: there is a systemic inflammatory state with increased oxidative stress.[114,116] Hypoxia induces the production of factor 1-alfa, that will promote atrial remodeling, atrial cardiomyopathy and AF.[116] Pulmonary artery hypertension and ventricular diastolic dysfunction induce atrial overload that may trigger arrhythmogenic automatic foci in the right atrium and favor AF.[120]

Chronic obstructive pulmonary disease control and AF

Patients with COPD and cardiovascular disease must be carefully monitored to

timely detect AF.[119,120] Some drugs used to control COPD, especially short-acting beta-2 agonists, might increase AF's prevalence and exacerbate symptoms because they have positive chronotropic action and favor depolarization-repolarization heterogeneity.[119] It is thus recommended to use long-acting beta-2 agonists, that do not increase AF's prevalence.[117] Anticholinergic drugs, theophylline and glucocorticoids can precipitate AF, either by a direct action or by modifying other risk factors.[121] It is recommended to correct hypoxia and hypercapnia with oxygen and non-invasive ventilation systems in acutely decompensated patients, an intervention that can help to reduce AF's impact.[122]

Key points and recommendations:

1. Chronic Obstructive Pulmonary Disease increases AF's prevalence and impact.
2. Interventions to control COPD risk factors and reduce chronic lung damage in order to avoid AF and lessen its impact are a class 1-B recommendation.
3. It is advised to reduce short-acting beta-2 agonists, anticholinergic drugs, theophylline and steroids since they increase the prevalence and impact of AF.

ISCHEMIC HEART DISEASE AND AF

Ischemic heart disease (IHD) and AF coexist in an important number of cases: It is estimated that 15% of patients with IHD will have AF and 30% of the patients with AF will have IHD.[123,124] Ischemia increases the prevalence of AF, especially recent onset AF after myocardial infarction.[124] Patients with IHD and AF have worse outcomes.[125] In the context of acute myocardial infarction and cardiogenic shock, AF is an independent one-year mortality predictor.[126] Several mechanisms have been implied in the genesis of AF in subjects with IHD. They include shortening of refractory periods in the atria along with myocardial fibrosis and slow conduction areas, that along with post-depolarizations (early and delayed) will lead to triggered activity, abnormal automaticity and reentry circuits.[124] Increased sympathetic activity will also induce autonomic, electrophysiologic and anatomical remodeling that promotes atrial cardiomyopathy.[127]

Ischemic heart disease control and AF

Ischemic heart disease and AF have common risk factors that must be controlled. Beta-blocker treatment, as well as ACEI's or ARBS's, might be useful in both conditions.[1,3] In patients with acute coronary syndrome that will be submitted to angioplasty, a short period of triple combination therapy with a direct oral anticoagulant and dual anti-platelet treatment is recommended.[1] Suggested drugs are rivaroxaban, apixaban, dabigatran or edoxaban along with clopidogrel and aspirin.[123] After the initial treatment period, it is advised to shift to a combination of clopidogrel and direct oral anticoagulant, that has shown less hemorrhagic complications and more effectiveness.[13]

Key points and recommendations:

1. Ischemic heart disease increases the risk of AF.
2. Control IHD and its risk factors is a class 1-B recommendation in patients with AF.
3. Drugs as beta-blockers and ACEI's or ARB's are beneficial in subjects with both conditions (IHD and AF)
4. A combination of a direct oral anticoagulant and an antiplatelet agent offers better results in patients with AF and acute IHD.

OTHER RISK FACTORS AND THEIR CONTROL IN ORDER TO REDUCE AF'S PREVALENCE

Tobacco use increases the risk of AF. When compared against non-smokers,[2] it also increases the risk of stroke and mortality in AF patients.[2,128] Smoking aggravates endothelial dysfunction, accelerates atherosclerosis and causes arrhythmia because of the combined effects of nicotine, carbon monoxide and polycyclic aromatic hidrocarbons contained in the smoke.[2] Patients that quit smoking show a 30% reduction in the risk of stroke and 16% in total mortality.[128]

Dislipidemia is another AF risk factor.[129] Their association is limited and inconsistent, nonetheless, it is considered that elevated

total cholesterol, triglycerides and LDL along with low levels of HDL are associated with increased AF risk.[130] Current international guidelines consider lipid control as a necessary intervention.[1,2]

Hypothyroidism is present in 9% of the people with AF.[131] It can be associated with chronic amiodarone use or other antiarrhythmic drugs, but it is unknown at the moment if it increases AF risk by itself or if it is associated with other conditions such as obesity, HBP, dyslipidemia, atherosclerosis and IHD that have proved to increase AF's prevalence.[132]

Cardiometabolic syndrome (CMS) is a combination of three or more of the following conditions: obesity, HBP, dysglucemia or DM, high LDL levels and low HDL. Each one of the CMS components increases the risk of AF by itself, although HBP seems to be the most significant one. It is clear that the higher the number of risk factors, the higher the risk of AF and its complications.[19]

Atrial fibrillation is present in 22 to 32% of patients with hypertrophic cardiomyopathy (HCM), with an annual incidence rate of 2%.[133] Major predictors of AF in HCM patients are: older age, high body mass index (BMI), moderate to severe mitral regurgitation, atrial volume increase and reduced left atrial contraction index.[134] Early recognition of AF in these patients is of outmost importance, since it is a bad prognostic feature associated with systemic embolism and heart failure.[1] Early anticoagulation is recommended[135] along with rhythm control through radiofrequency pulmonary vein isolation or cryoablation in subjects with symptomatic paroxysmal or persistent AF that does not respond to medications.[136]

Stress is a newly recognized cardiovascular disease risk factor. It induces over-activation of the autonomic nervous system that in turn, will stimulate atrial and pulmonary vein automatic foci and induce reentry circuits to increase AF risk.[137] It is advised to reduce stress levels, and it has been demonstrated that beta-blocker use reduces the probability of stress-related AF.[138] More than 55 work hours per week increase AF risk through a combination of stress and fatigue.[4]

Peripheral artery disease (PAD) is a mortality predictor in AF patients and an independent stroke risk factor in patients who are not receiving anticoagulant.[7] Stroke and AF share risk factors and show similar epidemiologic features.[1] Atrial fibrillation in patients with PAD is usually the final part of a pathway that starts with risk factors, atherosclerosis, atrial cardiomyopathy and atrial remodeling. It is recommended thus, to control all risk factors and co-morbidities in order to reduce AF's prevalence and impact.[1,139]

Atrial fibrillation might increase up to 10-fold the risk of a stroke.[140] On the other hand, stroke can favor AF appearance through autonomic nervous system lesions and systemic inflammatory response triggered by brain necrosis.[141] Atrial fibrillation also impairs cognition and increases dementia risk by 10%.[142] Early oral anticoagulation, especially with direct oral anticoagulants, reduces stroke risk, neurological impairment and dementia.[142] Direct anticoagulants are preferred over vitamin K inhibitors. Recent observational studies suggest that direct oral anticoagulants in subjects with AF might reduce dementia risk by 10 to 39% when compared to antiplatelet drugs or no antithrombotic therapy.[142]

Strategies that help risk factor control and lifestyle changes

Every person in the medical staff should promote lifestyle modifications.[1-3] Initial goals can be set at a 10% body-weight loss and a 2 MET increase in exercise capacity. These changes reduce AF's impact.[1,13] It is recommended to participate in successive weight reduction programs until a BMI < 27 kg/m^2,[1,11] is attained. Patients should also be advised to reach 200 minutes of exercise per week or 10,000 daily steps.[12,38] Podometers or smartphone applications might be useful to support and stimulate them to increase daily activity. Other applications designed to help choosing healthier meals such as vegetables, fruits and grains with anti-inflammatory properties,[2] instead of pro-inflammatory nutrients as animal fats, processed or canned foods, might also be useful.[143,144]

The 2020 AF management guidelines of the European Society of Cardiology[1] suggest the creation of multidisciplinary programs

for an integral management of AF patients. Those programs must consider the needs and preferences of each individual as well as the active participation of the subject and relatives to achieve better results. Available resources such as cardiac rehabilitation programs can be used, or specific multidisciplinary programs «AF clinics» might be created to offer integral treatment and at the same time, educate patients, relatives and health personnel to achieve better treatment adherence and better overall results *(Figure 5)*.

Atrial fibrillation patients should participate at least for six months in these programs in order to improve their lifestyle habits, treat co-morbidities, improve symptoms and reduce the impact and progression of AF.[1,3] Aside from anticoagulation and rhythm or rate control, guidelines suggest as a class 1-B recommendation, to focus on lifestyle modifications, risk factors treatment and co-morbidities control, as shown in *Figure 6*. Adherence to the international AF diagnostic and treatment guidelines is advised since not doing so has been reported to increase morbidity and mortality.[145] *Table 2* shows the key messages for an integral and multidisciplinary treatment of AF patients.

CONCLUSIONS

Atrial fibrillation is the most common arrhythmia and has a high impact on the general population. Its prevalence increases with age, habits and risk factors common in the general population such as obesity, sedentary lifestyle, stress, alcohol intake, tobacco use and stress as well as HBP, DM, IHD, HF. It is also related to dyslipidemia, hypothyroidism, stroke, HCM, CKD and peripheral artery disease. The current evidence shows that lifestyle modifications, adequate control of risk

1. **Detect and characterize AF:** stroke risk, symptoms severity, substrate and severity of AF (type of heart disease and atrial damage level)
2. **Patient and relatives education:** improve AF's comprehension, select the best treatment, achieve better treatment adherence
3. **Treatment's ABC:** anticoagulation, rhythm or rate control, co-morbidities control.
4. **Treatment objectives:** avoid stroke, improve symptoms, keep sinus rhythm, avoid alcohol and tobacco use, improve physical condition, reduce stress, 10% reduction in body weight or reach a BMI < 27 kg/m^2, reach BP 120-129/< 80 mmHg, adequate glycemic control with HbA1c 6-7%, treat and control heart failure, sleep apnea, CKD, COPD, IHD, HCM, dyslipidemia, hypothyroidism and cardiometabolic syndrome
5. **Health personnel/team education:** improve AF's comprehension and emphasize the relevance of an integral management, aside from appropriate anticoagulation and rhythm or rate control, to reduce AF's impact

Figure 5: Integral approach to the patient with atrial fibrillation with emphasis on patient's, relatives and health professionals education to achieve a better comprehension of the arrhythmia and select better treatments and improve adherence.
AF = atrial fibrillation. BMI = body mass index. BP = blood pressure. CKD = chronic kidney disease. COPD = chronic obstructive pulmonary disease. IHD = ischemic heart disease. HCM = hypertrophic cardiomyopathy.

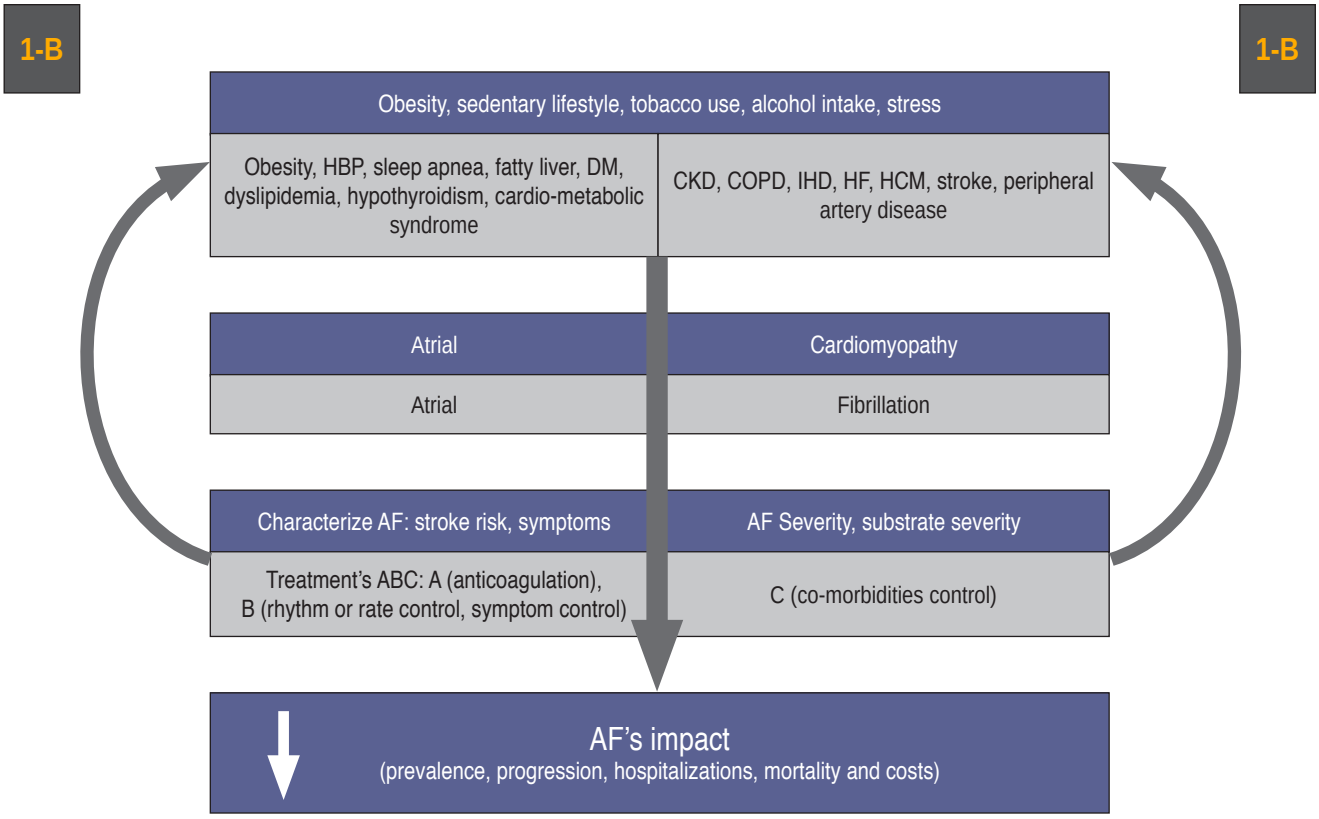

Figure 6: Integral treatment sequence in patients with atrial fibrillation. Aside from anticoagulation and rhythm or rate control, efforts must be made to control risk factors and co-morbidities as a class 1-B indication to reduce AF's impact.
HBP = high blood pressure. DM = diabetes mellitus. CKD = chronic kidney disease. COPD = chronic obstructive pulmonary disease. IHD = ischemic heart disease. HF = heart failure. HCM = hypertrophic cardiomyopathy. AF = atrial fibrillation.

Table 2: Key messages to achieve an integral-multidisciplinary management of patients with atrial fibrillation.

Key messages
1. Atrial fibrillation is the most common arrhythmia. It has a high impact because it is associated with higher morbidity, mortality and care costs
2. Atrial fibrillation has a close relation with sedentary lifestyles, alcohol intake, tobacco use and stress. It is also related to obesity, high blood pressure, diabetes mellitus, Ischemic heart disease, chronic kidney disease, sleep apnea, chronic obstructive pulmonary disease, peripheral artery disease, hypothyroidism, cardiometabolic syndrome, stroke, hypertrophic cardiomyopathy and heart failure
3. Lifestyle modifications such as weight loss, regular exercise, avoid alcohol and tobacco use, as well as controlling other modifiable risk factors and co-morbidities, reduce the prevalence, recurrence rate and progression of AF and improve these patient's prognosis
4. Lifestyle modifications along with a joint aggressive management of risk factors and co-morbidities must be done at the same time as anticoagulant therapy and rhythm or rate control in order to achieve the best possible results
5. It is recommended to create multidisciplinary programs for the management of patients with AF, cardiac rehabilitation programs can be used or create AF clinics to provide comprehensive treatment, promote greater education to patients, family members and health personnel, achieve greater adherence to treatment and best results

AF = atrial fibrillation.

factors and co-morbidities management, are effective interventions in AF treatment. Risk factors control and co-morbidities treatment must be done in conjunction with other AF therapies such as anticoagulation and rhythm or rate control. It is advisable to consider the creation of specific AF services or the optimization of cardiac rehabilitation units to offer a multidisciplinary integral treatment for AF patients.

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Books

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

Book chapters

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