Atrial fibrillation in cardiac surgery

Fibrilación auricular en cirugía cardíaca

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Abstract

Atrial fibrillation (AF) is the most frequent arrhythmia in the post-operative period of cardiac surgery. It is associated with heart failure, renal insufficiency, systemic embolism, and increase in days of in-hospital and mortality. AF in the post-operative period of cardiac surgery (FAPCC) usually appears in the first 48 h after surgery. The main mechanisms involved in the appearance and maintenance of FAPCC are the increase in sympathetic tone and the inflammatory response. The associated risk factors are advanced age, chronic obstructive pulmonary disease, chronic kidney disease, valve surgery, fraction of ejection of the left ventricle < 40%, and the withdrawal of β -blocker (BB) drugs. There are instruments that have been shown to predict the appearance of FAPCC. Prophylactic treatment with BBs and amiodarone is associated with a decrease in the appearance of FAPCC. Given its transient nature, it is suggested that the initial treatment of FAPCC be the heart rate control and only if the treatment does not achieve a return to sinus rhythm, the use of electrical cardioversion is suggested. It is unknown what should be the long-term follow-up and complications beyond this period are little known. FAPCC is not a benign or isolated arrhythmia in patients undergoing cardiac surgery, so the identification of risk factors, their prevention, and follow-up in the outpatient setting, should be part of the units dedicated to the care and care of these patients.

Key words: Atrial fibrillation. Cardiac surgery. Cardiac surgery arrhythmias.

Resumen

La fibrilación auricular es la arritmia más frecuente en el periodo posquirúrgico de la cirugía cardíaca. Se relaciona con insuficiencia cardíaca, insuficiencia renal, embolismo sistémico y más días de estancia y mortalidad. La fibrilación auricular en el periodo posquirúrgico de la cirugía cardíaca (FAPCC) suele aparecer en las primeras 48 horas. Los principales mecanismos que producen la aparición y el mantenimiento de la FAPCC son el aumento del tono simpático y la respuesta inflamatoria. Los

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factores de riesgo adjuntos son la edad avanzada, enfermedad pulmonar obstructiva crónica, enfermedad renal crónica, cirugía valvular, fracción de expulsión del ventrículo izquierdo menor de 40% e interrupción de fármacos bloqueadores β . Existen instrumentos que han demostrado predecir la aparición de FAPCC. El tratamiento profiláctico con bloqueadores β y amiodarona se relaciona con disminución de la aparición de FAPCC. Dada su naturaleza transitoria, se sugiere que el tratamiento inicial de FAPCC sea el control de la frecuencia cardíaca y sólo en caso de que el tratamiento no consiga el retorno al ritmo sinusal está indicada la cardioversión eléctrica. Se desconoce cuál debe ser el seguimiento a largo plazo y sólo se conocen en escasa medida las complicaciones más allá de este periodo. La FAPCC no es una arritmia benigna ni aislada en los pacientes sometidos a operación cardíaca, por lo que la identificación de los factores de riesgo, su prevención y el seguimiento en el ámbito ambulatorio deben formar parte de las unidades dedicadas a la atención y los cuidados de estos pacientes.

Palabras clave: Fibrilación auricular. Cirugía cardíaca. Arritmias en cirugía cardíaca

Introduction

Atrial fibrillation (AF) can occur before, during, or after any operation. The AF that arises after the surgical act and during the hospital stay after said the event is called post-surgical AF. It can occur after a cardiac, chest, or non-cardiac intervention. This is a review of AF that appears after cardiac surgery, and its acronym, AFACS, will henceforth be used.

The appearance of AFACS entails a loss of atrial systole contribution to cardiac output and a decrease in diastolic filling time, which may cause heart failure or myocardial ischemia, an increase in mechanical ventilation days (18.2%), development of kidney (8.5%), and likelihood of systemic embolism. In consequence, AFACS is related to an increase in days of hospital stay, costs of care¹ and mortality rate². Hence, the importance of trying to prevent its appearance. This article reviews AFPCS-related risk factors and measures that have been assessed to prevent it with an approach based on known pathophysiology.

Clinical considerations

The prevalence of AFACS ranges from 15% to 40% in coronary revascularization surgical procedures, from 37% to 60% in valvular surgery interventions, and it is higher than 60% in combined interventions and 24% in patients undergoing heart transplantation^{3,4}. Despite advances in the knowledge of AFACS, its incidence has remained stable in the past 10 years⁵.

Among all AFACS cases, 90% occur within the first 4 days of the post-operative period^{3,5}. The first episode average duration is 7-8 h⁵. Recurrence occurs in 40% of cases and it does within the first 24 h. Up to 80% of patients remain in sinus rhythm 24 h after the first episode⁴. Among the patients who develop AFACS, 14% remain with said rhythmic disorder for up to 2 weeks. Long-term follow-up reports (3-12 months) of AF persistence vary,

since there is no uniformity in the follow-up recommendations and in some cases, it is not carried out.

Pathophysiology

AFACS is related to factors, situations, or alterations that ultimately act on two pathophysiogenic mechanisms which are activation of the sympathetic system (adrenaline increase) and inflammation. Even when the degree of inflammation or sympathetic tone necessary to trigger AFACS is unknown, most measures aimed at its prevention focus on antagonizing any of these two effects⁶.

Inflammatory phenomenon

The inflammatory response in cardiac surgery can be systemic or local (at the myocardial level) and is an effect of cardiopulmonary bypass and cardioplegia^{7,8}. The molecular manifestation of cardiac intervention-associated inflammation is mediated by cytokines, such as interleukins 1 and 6 and tumor necrosis factor α , among others. At the cardiovascular level, these cytokines not only can affect the contractile function (inotropism) but also can influence on ventricular remodeling and myocardial stunning, whose consequence is an alteration of action potentials and triggering of arrhythmias. In addition to cytokines, reactive oxygen species (ROS) are linked to atrial tissue action potential alterations, secondary to changes in calcium metabolism. High figures of nicotinamide adenine dinucleotide phosphate in atrial appendages have been described as a predisposing factor for the appearance of AFACS⁸. In AFACS animal models, the inflammation that appears around the atriotomy scar, expressed by leukocyte myeloperoxidase activity, has been documented to be directly related to a higher dispersion of atrial activation and with the consequent onset of AF. In addition, anti-inflammatory treatment reduced these alterations⁷. Recent studies suggest that blood accumulation within the pericardium is associated with

the occurrence of AFACS, also mediated by cytokines and ROS produced by the metabolism of blood and plasma cellular components⁹.

Sympathetic activation

Neural activation is another factor involved in the development of AFACS. Adrenergic tone increase produces alterations in the atrial refractory period, increases heart rate, and decreases R-R intervals variability or heart rate variability, which are factors that promote the development of an electrical substrate for the appearance of AFACS¹⁰. Hence, the usefulness of β -blockers (BB) in prophylactic treatment.

Risk factors and instruments to predict the onset of AFACS

The main risk factor related to AFACS is age; for each 10-year increase after 50 years of age, the risk increases by ~ 13%¹¹. Other risk factors have been described, such as obesity, belonging to the female gender, diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and sleep apnea syndrome. AFACS occurs most frequently in procedures that affect the valvular apparatus, in particular, the mitral valve, when more than one cardiac surgery procedure is practiced (e.g. valve operation plus coronary artery bypass graft), when BBs are withdrawn in the post-surgical period, when left ventricular ejection fraction (LVEF) is lower than 40% or the diameter of the left atrium is larger than 4 cm, when mechanical ventilation is required for more than 24 h, and when there is elevation of cerebral natriuretic peptide serum values^{4,5,10-16} (Table 1).

Identification of these risk factors brought about the development of tools for AFACS prediction. With them, identifying those patients at high risk for developing AFACS, which in theory are the ones that would benefit most from prophylactic treatment, is sought. Next, some scales that can be used for the prediction of AFACS are presented.

Multicenter study of perioperative ischemia (MSPI)

In 2004, a risk score was published, based on ~ 4500 patients from 70 hospitals who participated in the MSPI. When age (the most important and higher-scored variable), history of COPD, valve operation, use or withdrawal of BB drugs and angiotensin-converting enzyme inhibitors, and consumption of nonsteroidal anti-inflammatory

Table 1. Risk factors for atrial fibrillation in cardiac surgery post-surgical period

	Variable
Preoperative	Advanced age* Systemic arterial hypertension Atrial enlargement > 40 mm Chronic obstructive pulmonary disease* Left ventricular ejection fraction < 40% Coronary artery disease Mitral or tricuspid valve disease* Chronic kidney disease (GFR < 30 mL/min/1.72 m ² *) Obesity Smoking Diabetes mellitus Alcohol consumption
Intraoperative	Operation with mitral valve intervention* Use of cardiopulmonary bypass pump Pericardiotomy
Postoperative	Hypovolemia Hypervolemia β -blockers withdrawal* Angiotensin-converting enzyme inhibitors withdrawal

*Main risk factors for AFACS.

drugs or potassium supplementation were used as predictive variables, they divided the patients in three groups (low, intermediate, and high). The area under the curve (AUC) was 0.77¹¹. This scale was amended in 2009 to include the use of statins, although the AUC was not modified (0.77) (Table 2)¹⁷.

AF risk index

This score was published in 2012, based on 1300 patients who underwent coronary artery bypass graft surgery, and whose AUC was 0.68 (Table 3)¹⁸.

Post-operative AF (POAF) index

This score, published in 2014, analyzed around 17,000 patients from three university hospitals in Europe. Similar to other scales, age was the variable with the highest weight for AFACS prediction, and AUC was 0.64. Two or more points were associated with an incidence higher than 30% (Table 4)¹⁹.

CHA₂DS₂-VASc

The CHA₂DS₂-VASc scale, originally developed to establish the risk of annual embolism in patients with AF in the non-surgical setting²⁰, has been studied as an AFACS prediction tool, even in patients in sinus

Table 2. MSPI scale score of the risk for the occurrence of AFPCS

Variables	Score
Age (years)	
< 30	6
30-39	12
40-49	18
50-59	24
60-69	30
70-79	36
≥ 80 years	42
Medical history	
Atrial fibrillation	7
Chronic obstructive pulmonary disease	4
Valve operation	6
Treatment withdrawal	
β-blockers	6
Angiotensin-converting enzyme inhibitors	5
Pre-surgical and post-surgical treatment	
β-blockers	-7
Angiotensin-converting enzyme inhibitors	-5
Post-surgical treatment	
β-blockers	-11
Other treatments	
Potassium supplementation	-5
Nonsteroidal anti-inflammatory drugs	-7

Low risk: < 14 points.

Intermediate risk: 14-31 points.

High risk: > 31 points.

MSPI: multicenter study of perioperative ischemia.

rhythm. CHA₂DS-VASc cutoff point to predict PAF is three points, which has sensitivity, specificity, positive, and negative predictive value of 84%, 84%, 43.9%, and 97%, respectively. The AUC is 0.87²¹.

Comparison of scales

Using a cohort of approximately 1400 patients, validation of three of the four previously mentioned scales (POAF score, AF risk index, and CHA₂DS-VASc) was performed in 1416 individuals undergoing cardiac intervention (coronary artery bypass graft surgery, valve surgery, or combined procedures). No

Table 3. Atrial fibrillation risk index

Variable	Males	Females
Age (years)	> 60	> 66
Weight (kg)	> 76	> 64
Height (cm)	> 176 cm	> 168
Peripheral vascular disease	Present	Present

Table 4. POAF score

Variables	Score	OR (95% CI)
Age		
60-69 years	1	2.04 (1.81-2.31)
70-79 years	2	2.93 (2.60-3.30)
More than 80 years	3	3.94 (3.31-4.69)
COPD	1	1.33 (1.14-1.56)
Dialysis or GFR < 15 mL/min/1.73 m ²	1	1.90 (1.17-3.10)
Emergency operation	1	1.50 (1.19-1.88)
Use of intra-aortic balloon counterpulsation	1	1.90 (1.28-2.83)
Ejection fraction < 30%	1	1.45 (1.18-1.77)
Valve operation	1	1.68 (1.55-1.83)

COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; OR: odds ratio; CI: confidence interval.

significant differences were found in the capacity to predict AFACS. The POAF score and CHA₂DS₂-VASc were related to the most frequent prophylactic treatment initiation in comparison with not using any risk scale²². However, when the index published by Mathew, who added the use of statins as an additional protective factor^{11,17}, was included, it was shown to be superior to predict AFACS. In addition, the CHA₂DS₂-VASc score had a lower AUC than reported in previous publications¹⁷, which might be explained by differences in AFPCS prevalence in the populations included in the validation cohorts.

In the authors' opinion, age older than 60 years, COPD, left ventricular dysfunction (LVEF < 40%), chronic kidney disease, and valve operation, especially if it includes mitral valve intervention, are the main factors related to AFACS and are included in most risk scales. In the presence of two or more of these variables, the patient should be classified in a high-risk category and, therefore, should be offered one of the prophylactic treatments described below.

Prophylactic treatment

The relationship of the appearance of AFPCS with negative outcomes has led to the investigation of pharmacological and non-pharmacological interventions with the purpose to decrease its occurrence. One meta-analysis of about 14,000 patients showed that prophylactic treatment reduces the risk of AF in this group of patients by up to 32.3%²³. However, since prophylactic treatment is not without side effects and given that in the main treatment guidelines, it has not been clearly established which group of patients obtains benefit, the indication for each intervention should be individualized according to the clinical context²⁴. Next, the agents used in AFACS prophylaxis are analyzed.

1. Agents that predominantly act by antagonizing the adrenergic tone. β -adrenergic blockers or BBs are the most widely studied drugs as prophylactic treatment of post-surgical supraventricular arrhythmias, including AF¹⁰. The use of BBs reduces AFACS from 31.7% to 16.3% (odds ratio [OR], 9.33; 95% confidence interval [CI], 0.26-0.43)²³. However, the use of BBs does not reduce the occurrence of cerebrovascular episodes or acute myocardial infarction or mortality²⁵. For every seven patients treated with BBs in the perioperative period, one episode of AFACS is prevented (number needed to treat: 7)²⁶. Currently, metoprolol is the most widely studied drug in AFACS prevention. Metoprolol dosage is 50-200 mg daily, according to the hemodynamic status, and must be administered at least 48-72 h before the surgical procedure. The majority of patients undergoing cardiovascular surgical procedures use BBs for some indication related to the underlying disease. AF treatment guidelines, in the AFACS prevention section, suggest the administration of BBs, if they were no longer used (Class I, level of evidence B)²⁰. From the authors' point of view, BBs are the first-line prophylactic treatment, especially in patients considered at high risk. In addition, their discontinuation should be avoided during the post-operative period, since this is related to the appearance of AFACS.

Antiarrhythmic drugs

Amiodarone

In addition to the antiarrhythmic effect mediated by the blockage of multiple ion channels, amiodarone has sympatholytic effects by blocking α and β adrenergic receptors, and hence it also prevents AFACS.

Amiodarone reduces AFACS by 57% when compared against placebo (OR, 0.43; 95% CI, 0.34-0.54), which translates into a number needed to treat of 7²³. Most studies included in the meta-analysis of amiodarone effectiveness as prophylactic treatment included patients previously treated with BBs; hence, the real contribution of amiodarone in the prevention of AFACS may be lower. Oral amiodarone suggested dose (10 mg/kg/day) should be administered 6 days before and six after the operation to reach adequate tissue values, which may limit its use in situations of emergency²⁷. A behavior that proved useful in a small group of patients of the National Institute of Cardiology consisted of the administration of 200 mg thrice daily, at least 3 days before the intervention, 200 mg twice daily for 24 h after the operation and 200 mg once daily until the day of hospital discharge²⁸. Attention should be given to side effects such as hypotension (10-30%), atrioventricular block (2%), and corrected QT interval (QTc) prolongation, with the latter being associated with ventricular arrhythmias (< 1%); all these side effects may require dose reduction or discontinuation of the drug in up to 11.4% of patients²⁹. In view of the above, the European guidelines suggest that amiodarone should be a prophylactic scheme for AFACS (Class II, level of evidence A) and should be considered in patients with contraindications for the treatment with BBs²⁰. The authors suggest that, if it is considered as a prophylactic alternative, the above-described oral dosage should be used, until information that enables modifying this practice is obtained.

Sotalol

Sotalol, a BB with Class III antiarrhythmic properties, is useful for the prevention of AFACS. In a meta-analysis that included 2988 patients, it reduced AFACS from 26.2% to 16.5% (OR, 0.55; 95% CI, 0.41-0.73)²³. Patients who received sotalol were not stratified by AFACS risk and were more susceptible to abandon treatment, in particular, due to side effects such as hypotension and bradycardia; in addition, it is associated with ventricular arrhythmias such as torsades de pointes ventricular tachycardia in 1-5% of cases³. The ACC/AHA/HRS 2014 guidelines recommend using it prophylactically (Class II, recommendation B); however, in the European guidelines, its use is not foreseen²⁶. In the authors' opinion, sotalol should only be considered in individuals with contraindication for metoprolol and amiodarone, although it should be noted that it is not available in Mexico.

Drugs and substances that predominantly act based on their anti-inflammatory effects

Colchicine

Although colchicine has sympatholytic and anti-inflammatory properties, with a potential role in AFACS prevention, the evidence is inconsistent. A sub-analysis of the Colchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS) trial demonstrated a reduction from 22% to 12% in the occurrence of AFACS^{30,31}. One of the main limitations of this research was the reduced number of patients (169 subjects per group), in addition to the fact that the occurrence of AFACS was not part of the primary outcome measures. For this reason, the COPPS II trial was carried out, whose primary objective was to assess colchicine efficacy and safety in the prevention of PAF and other complications after pericardiotomy. Colchicine reduced the cases of PAF by 7.8%; however, the difference was not statistically significant. In addition, gastrointestinal adverse effects were more frequent in the colchicine treatment group³². One of the possible differences between COPPS and COPPS II is the larger proportion of valve procedures in COPPS II, fewer patients with revascularization surgery and the fact that up to 20% of individuals discontinued medical treatment. In 2017, a meta-analysis was published, which included 1400 patients from five clinical trials (including COPPS I and COPPS II), with the purpose to establish the benefit of colchicine in AFACS prophylaxis. The therapeutic regimen used in all studies was 0.5 mg every 12 h. AFACS prevalence was 27% in the control group in comparison with 18% in the colchicine treatment group (RR, 0.69; 95% CI, 0.57-0.84). The number needed to treat was 11. In addition, it was accompanied by a reduction of 1 day of hospital stay. Gastrointestinal effects were increased 2.5 times in the colchicine treatment group. Apparently, the main benefit of colchicine treatment is found in patients undergoing coronary bypass graft surgery³³. Although the conclusion of this meta-analysis was that colchicine offers benefit in the reduction of AFACS, there are other analyses that are not consistent with this result. In 2018, a review of seven studies was published, where no differences were identified regarding the prevention of AFACS³⁴. The use of colchicine is suggested in the post-surgical period with the purpose to prevent the occurrence of AFACS, according to the American guidelines (Class II, Grade B recommendation)²⁶. With the evidence presented so far, the role of

colchicine still must be demonstrated with other clinical trials of larger size. In addition, it should be clarified whether dose reductions can mitigate gastrointestinal effects without losing effectiveness in terms of preventing AFACS. Colchicine administration might be considered only in patients undergoing coronary artery bypass graft intervention, in whom treatment with BBs and amiodarone is contraindicated.

Glucocorticoids

High concentrations of C-reactive protein, as an inflammation marker, are associated with the onset of AFACS, and the use of glucocorticoids reduces its occurrence³⁵. In 2007, a randomized clinical trial was conducted, which included 241 patients undergoing coronary artery bypass graft, aortic valve replacement, or both, and who received 100 mg hydrocortisone starting the day of the procedure and then every 8 h until 3 days of treatment were completed. The steroid was shown to reduce AFACS by 18% (OR, 0.54; 95% CI, 0.35-0.83), with a number needed to treat of six patients. In addition to receiving intravenous steroids, the patients were under treatment with BBs before the surgical procedure³⁶. However, in another clinical trial, where approximately 4500 patients were included in the study, dexamethasone did not reduce the occurrence of AFACS³⁷. Although there are meta-analyses published before 2015, where steroids reduce PAF and even days of hospital stay³⁸⁻⁴⁰, in 2018, another meta-analysis was published that included about 16,000 patients, and whose purpose was to elucidate the role of steroids in patients undergoing cardiac surgery with the use of cardiopulmonary bypass. No mortality reduction was identified in neither group (OR, 0.85; 95% CI, 0.71-1.01), but an increase in the incidence of myocardial infarction was documented (OR, 1.17; 95% CI, 1.04-1.31) and a lower frequency of AFACS occurrence (OR, 0.91; 95% CI, 0.86-0.96)⁴¹. When all studies were broken down, the benefit of steroids in reducing the incidence of AFACS was found to come from studies where the study populations were of < 120 patients. In previous reviews, the use of steroids (hydrocortisone or methylprednisolone equivalent dose) to prevent AFACS was suggested. Nevertheless, after analyzing available evidence and possible side effects of the medication (increased incidence of mediastinal infections and hyperglycemia), the authors consider that this group of drugs should not be used in AFACS prophylactic treatment.

Statins

Statins have been proposed as prophylactic treatment in AFACS. The hypothetical mechanism of action is a reduction of inflammatory mediators through the inhibition of HMG-CoA reductase and pleiotropic effects such as platelet inhibition, vasodilation, and decreased lymphocyte activity⁴². In 2015, 16 clinical studies were analyzed to assess the effect of statins on mortality, myocardial infarction, AFACS, embolic episodes and days of hospital stay in patients undergoing cardiac surgery and who were statin-naïve. Statins reduced mortality from 3.4% to 1.8% (OR, 0.53; 95% CI, 0.30-0.94), myocardial infarction from 8% to 4.1% (OR, 0.54; 95% CI, 0.38-0.76%), days of hospital stay with almost 1 day less and AFACS from 23.7% to 12.1% (OR, 0.53; 95% CI, 0.43-0.66), with a number needed to treat of nine patients to prevent an AFACS episode⁴². In 2016, the statin therapy in cardiac surgery trial was published, which randomized 1920 patients scheduled for coronary artery bypass graft or aortic valve replacement and who received rosuvastatin (20 mg) 8 days before and 5 after the intervention. The primary objective was to document the occurrence of AFACS or myocardial injury, as measured by changes in troponin kinetics. In addition to no find any differences between both groups for the primary objective, rosuvastatin was accompanied by more episodes of kidney function worsening (24.7% in the statin group in comparison with 19.3% in the control group⁴³). In 2018, an analysis of the effect of statins in patients undergoing elective cardiac and non-cardiac procedures was carried out. Almost 82,000 patients were included in the study. Statins had a protective effect against myocardial infarction in patients with non-cardiac procedures (2.3% in the statin group vs. 5.1% in the control group; OR, 0.44; CI 95%, 0.30-0.64), with a number needed to treat of 35. However, there was no effect on mortality, myocardial infarction or embolic episodes in the group of cardiac intervention⁴⁴. The authors suggest that statin consumption is considered part of AFACS prophylactic treatment in case of contraindication for treatments of greater effectiveness, especially in coronary artery bypass graft and aortic valve replacement procedures.

Omega-3 fatty acids

Omega-3 fatty acids (Omega-3s) are long-chain, polyunsaturated fatty acids, which include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), mainly obtained from fish⁴⁵. There is evidence on the

usefulness of omega-3s supplementation in cardiovascular mortality, myocardial ischemia, and AFACS. The proposed mechanism is inflammation reduction, antioxidant effects and decreased atrial remodeling. In 2002, the results of the OPERA trial were published, which randomized almost 1500 patients to receive 8-10 g of omega-3s preoperatively and 2 g a day postoperatively. The primary outcome measure was AFACS with duration longer than 30 s and the secondary outcome measure was AFACS with a duration longer than 1 h, symptomatic or with the need for cardioversion treatment. Omega-3s did not reduce the occurrence of AF and neither were they accompanied by adverse effects. In this study, fatty acid serum concentrations were not measured⁴⁶. In 2018, the results of a systemic review on the effects of omega-3s on AFACS were published. The omega-3s dose among the included studies was variable, 0.5 mg/kg of weight (maximum 100 mg) intravenously or 2-15 g orally every 24 h. Omega-3s reduced the incidence of AFACS from 35.7% to 31.85 ($p = 0.01$; OR, 0.89; 95% CI, 0.81-0.97). In the subgroup analysis, the incidence of PAF was lower in patients who received omega-3s whose EPA/DHA composition was lower than 1 and in patients with revascularization procedures. The number needed to treat was 25⁴⁵. From the authors' point of view, omega-3 fatty acids are part of the third-line prophylactic treatment for the prevention of AFACS. In case their use is considered, it must be reserved for patients undergoing coronary artery bypass graft and with omega-3s whose EPA/DHA composition is lower than 1.

Magnesium

Hypomagnesemia is associated with the occurrence of AF in the post-surgical period of a heart procedure, whereas the use of diuretics and cardiopulmonary bypass are accompanied by hypomagnesemia⁴⁷. One meta-analysis that included 2988 patients showed that the prevalence of AFACS in the control group was 26.2% in comparison with 16.5% in the group treated with magnesium (OR, 0.55; 95% CI, 0.41-0.73%). In 57% of the included studies, magnesium was administered for the 1st time at the time of the intervention at a dose 40-80 mg/kg²³. It should be noted that the studies included in the meta-analysis excluded patients with known risk factors for AFACS, such as old age, coronary artery bypass graft or previous valvular, and ventricular dysfunction. In addition, no consistent relationship was found between serum magnesium values and AFACS²⁶. The Canadian AF guidelines suggest the use of magnesium

in cardiac procedures, in case patient clinical context contraindicates the use of drugs with proven effectiveness such as BBs and amiodarone^{23,26,47}. For the moment, there is not enough evidence to suggest the use of magnesium supplementation as an isolated pharmacological measure, but it can be considered in high-risk patients, together with drugs such as BBs and amiodarone, and in situations of documented hypomagnesemia.

Ivabradine

Ivabradine has been studied as a potential agent to reduce AFACS. In 2016, a randomized clinical trial was published, where the primary objective was to compare the efficacy of ivabradine in the prevention of AFACS (initiated 48 h before surgery and maintained for a week after it). Three dosing schedules were compared Group 1, ivabradine at 5 mg every 12 h the first 24 h and then 7.5 mg every 12 h; Group 2, bisoprolol at 5 mg every 12 h; and Group 3, ivabradine and bisoprolol at the above doses. The combination of ivabradine and bisoprolol statistically significantly reduced AFACS (4.2%) in comparison with ivabradine (15.1%) and bisoprolol (12.2%) used in isolation⁴⁸. The proposed mechanism is secondary to the ivabradine mechanism of action on the *If* channels, whose density seems to be higher in myocytes of pulmonary veins, which are the cause of AF in 70% of cases⁴⁹. More studies on the combination of ivabradine and BB are needed to recommend it as a useful alternative in the prevention of AFACS.

Interventional maneuvers

Atrial stimulation

Atrial extrasystoles cause dispersion in the atrial refractory period, which favors the occurrence of re-entry circuits and gives rise to the occurrence of AFACS. For this reason, it has been proposed that stimulation of one or both atria might prevent AFACS-related electrophysiological effects and thus decrease its occurrence⁵⁰. One meta-analysis showed that atrial stimulation reduced AFACS occurrence from 32.8% to 18.7% (OR, 0.47; 95% CI, 0.36-0.61). Atrial stimulation was carried out using different approaches, such as biatrial, left or right atrial, and Bachmann's bundle stimulation. Only four studies of the 21 included in the meta-analysis showed benefit with this technique²³. Despite the American AF treatment guidelines suggesting atrial

stimulation to prevent the development of AFACS (Class IIb recommendation)²⁶, the authors consider that given that atrial pacemakers electrode placement is not systematic, and due to the technical complexity of some of these approaches (Bachman's bundle) and the low statistical power of previously-assessed clinical trials, atrial stimulation should not be part of prophylaxis for the prevention of AFACS.

Pericardiotomy

There are isolated reports that left posterior pericardiotomy reduces the incidence of AFACS, since this allows drainage on the left side of the chest and decreases blood accumulation in the left atrium, which could trigger AF due to myocyte inflammation⁵¹. Currently, patients are being recruited for inclusion in the Posterior Left Pericardiotomy for the Prevention of POAF after Cardiac Surgery Trial (PALACS), whose objective is to assess the effect of posterior pericardiotomy in the prevention of AFACS. In addition, total time on AFACS, hospitalization time, mortality, and adverse effects will be assessed as secondary endpoints⁵².

Considerations on AFACS prophylaxis

Prophylactic treatment reduces the incidence of AFACS; however, it can be accompanied by secondary effects, which in the case of BBs correspond to hypotension and atrioventricular block and, in the case of Class III antiarrhythmic drugs such as amiodarone, to predisposition to lethal arrhythmias such as tachycardia or ventricular fibrillation. In view of the above, the authors consider that a measure that can be used is a staggered (always administer the drugs with the highest level of evidence) and reasoned utilization, reserved for patients considered at high risk for AFACS, for example, those with two or more risk factors²⁴.

AFACS treatment: rhythm or frequency control?

The need for treatment, either antiarrhythmic or frequency control, is lower because episodes are self-limiting, and recurrence does not occur in all cases⁴. The treatment of an acute episode should include a comprehensive approach to treat potentially causes such as hypoxemia and hydroelectrolytic alterations (especially potassium and magnesium). AFACS can be treated with two measures: ventricular frequency control

and rhythm control (sinus rhythm restoration). The rhythm control behavior shows no differences in mortality in comparison with frequency control, but is related to a higher incidence of adverse effects, resulting from the use of antiarrhythmic drugs, and a higher number of hospitalizations during follow-up, together with treatment side effects⁵³. In 2016, a clinical trial was published whose main objective was to assess the effect of the treatment of rhythm or frequency in patients with AF-PCS. The primary endpoint was a total number of days spent at the hospital (including emergency visits) within the first 60 days after the start of treatment. Secondary outcome measures included all-cause mortality, permanent pacemaker insertion, and medication-related adverse effects. No differences were observed between both treatment groups⁵⁴. Based on the information of this clinical trial, the authors suggest that ventricular frequency control should be the first line of treatment in patients with AFACS and hemodynamic stability.

Ventricular frequency control

The use of drugs with atrioventricular node conduction blocking activity should be indicated as first-line treatment in patients with AFACS and no data consistent with hemodynamic instability, such as cardiogenic shock, heart failure or signs of cerebral, and renal or coronary hypoperfusion^{4,13,26}. The target for frequency is suggested to range between 80 and 110 beats/min¹⁶; however, the evidence that supports this recommendation is scarce and comes from clinical trials of patients out of the surgical setting and with preserved ejection fraction^{53,55}. Similar to prophylactic treatment, the drugs with better efficacy and safety profile are BBs, preferably short-acting agents such as esmolol. They are contraindicated in patients with untreated asthma, AV conduction block (PR segment duration longer than 240 ms, second or third grade AV block), and symptomatic acute heart failure. The American, European, and Canadian guidelines recommend the use of BBs with high levels of evidence (Class I, Grade A recommendation)²⁶. If additional treatment is required, the second line is non-dihydropyridine calcium antagonists such as verapamil and diltiazem; however, since their actions include depressing myocardial contractility, and usually they have a higher activity to decrease the ventricular frequency, caution should be exerted in patients with risk factors for bradycardia. Contraindications are similar to those for BBs, except that its use is allowed in patients with active pneumopathy. Digoxin has sympatholytic properties, and thus it could be useful to slow

ventricular frequency in patients with AFACS, although its use has not been studied in this context^{10,26}.

Rhythm control

Treatment to restore sinus rhythm, known as rhythm control, should be considered in patients in whom despite treatment with BBs or calcium antagonists, there is no success in the reduction of ventricular frequency and in subjects with signs of hemodynamic instability^{4,10,13,20,26}. This behavior can be carried out by means of pharmacological or electrical cardioversion.

Pharmacological cardioversion in AFACS includes the use of ion channel-blocking drugs of Vaughan-Williams classification Class IA, IC, or III. There are no differences in effectiveness between the various antiarrhythmic classes and the safety profile of each drug is what determines the drug to be used. Class IC antiarrhythmic drugs are contraindicated in patients with structural heart disease, which limits their use in patients undergoing cardiac surgery. The reported efficacy for each agent in the recovery of sinus rhythm is as follows: quinidine (64%), procainamide (61-87%), amiodarone (41-93%), sotalol (35-85%), and ibutilide (57%). In patients in whom it was decided to opt for rhythm control treatment and that persist on AF for more than 24 h, considering electrical cardioversion is suggested⁴. Most previously advised treatment recommendations are derived from guidelines for non-surgical AF treatment, since the evidence that supports its use in the surgical context is poor.

Anticoagulant treatment in patients with AFACS

Cardiopulmonary bypass pump, aortic clamping, and AF are associated with systemic embolisms, with the most important of these being cerebrovascular episodes. Recently, in the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) registry, PFA in patients undergoing revascularization was found to be associated with the occurrence of cerebrovascular episodes up to 3 years after the intervention (6.6%; hazard ratio [HR], 4.19; 95% CI, 1.74-10.11) and with higher mortality rates (HR, 1.8; 95% CI, 1.22-2.64)⁵⁶. The incidence of embolism in patients with AFACS is 18.3 episodes per 1000 person-year, with anticoagulation reducing its occurrence (HR, 0.55; 95% CI, 0.32-0.95)⁵⁷. The guidelines on AFACS treatment suggest stratifying the risk for embolism²; the main risk factors described

are a history of embolism (transient ischemic attack or documented cerebrovascular episode), age older than 75 years, diabetes, heart failure, hypertension, and previous vascular disease^{20,26}. In addition to the risk of systemic embolism, the risk for hemorrhage should also be assessed. The European guidelines for AF recommend the use of the HAS-BLED scale to stratify hemorrhagic risk in patients with AF²⁰. However, this scale is not validated for patients with AFACS. Anticoagulation in cardiac surgery post-surgical period is related to major hemorrhagic episodes, including cardiac tamponade. Most information on the risk of systemic embolism and hemorrhagic risk in patients with AFACS derives from cohorts and records of chronic non-surgical AF. Information on AFACS is scarce and clinical trials on the prevention of cerebrovascular events are isolated.

Due to the transitory nature of AFACS, the treatment guidelines proposed by the American Association for Thoracic Surgery (AATS) suggest anticoagulation in case the AFACS episode lasts longer than 48 h or in case electrical or pharmacological cardioversion is considered². Anticoagulant treatment duration is not well defined, but in case sinus rhythm is recovered, maintaining anticoagulation for up to 4 more weeks is suggested^{2,20,26}. The drugs indicated for anticoagulation are Vitamin K antagonists (acenocoumarol or warfarin) and direct anticoagulants, such as dabigatran, apixaban, and rivaroxaban. There are no clinical trials on the use of direct anticoagulants in patients with PAF, but AATS suggests their use (Class II, Grade A recommendation)².

Conclusions

AF is the most common arrhythmia in patients undergoing cardiovascular surgery, and it has a clear relationship with negative outcomes. Prophylactic treatment with BBs and amiodarone, especially in high-risk patients, is accompanied by a decrease in its occurrence. Given its transitory nature, AFACS initial treatment is suggested to be the behavior of heart rate control. It is unknown which should be the form of long-term treatment, since only a minority of patients will remain with AF beyond 3-6 months. There are novel treatments for AFACS, such as pre-surgical treatment in high-risk patients with new drugs such as ivabradine with or without the use of BBs, but more evidence is needed to suggest its systematic use. The authors suggest that hospitals with the capacity to perform cardiovascular operations should have records and conduct prospective studies that generate the knowledge that enables eliminating

the gaps that still exist in this important field of cardiology.

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