Epidemiology and New Predictors of Atrial Fibrillation After Coronary Surgery

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Introduction and objectives. Postoperative atrial fibrillation (PAF) is a frequent complication of coronary artery bypass grafting (CABG). Our aims were to study its epidemiology and to identify predictors in everyday clinical practice, while taking into account statin use, extracorporeal circulation, and new biomarkers of inflammation and ventricular stress.

Methods. The study included 102 consecutive patients (65 [9] years, 72% male) who were undergoing CABG. Blood samples were taken the day before surgery to determine baseline levels of C-reactive protein (CRP) and N-terminal probrain natriuretic peptide (NT-proBNP). Details of baseline clinical characteristics, preoperative treatment and surgery were recorded. The end-point was PAF at 30 days.

Results. The incidence of PAF was 23% (n=23; 3.2 [2.9] days, range 1-15 days). Its appearance was associated with a longer stay in the intensive care unit (+1 day; *P*=.019), but not with an increased total hospital stay (*P*=.213). Among patients with PAF, 4.3% had an embolism and 8.6% remained in atrial fibrillation at discharge. Moreover, PAF was associated with a longer duration of ischemia (28.5 [22.3] vs 18.0 [27.9]; *P*=.045) and a lower statin pretreatment rate (39% vs 66%; *P*=.022). Multivariate analysis showed that the only factor associated with a higher risk of PAF was the absence of statin pretreatment (odds ratio, 4.31, 95% confidence interval, 1.33–13.88; *P*=.015). There was no association between either extracorporeal circulation or the baseline CRP or NT-proBNP level and an increased risk of PAF.

Conclusion. In everyday clinical practice, PAF is a frequent complication. Statin pretreatment could have a protective effect against its appearance.

Key words: *Postoperative atrial fibrillation. Statins. Coronary surgery.*

Epidemiología y nuevos predictores de la fibrilación auricular tras cirugía coronaria

Introducción y objetivos. La fibrilación auricular postoperatoria (FAP) es una complicación frecuente tras la cirugía de revascularización coronaria. Estudiamos su epidemiología y los predictores en la práctica actual, considerando el uso de estatinas, la circulación extracorpórea y los nuevos biomarcadores de inflamación y estrés ventricular.

Métodos. Se estudió a 102 pacientes consecutivos (65 ± 9 años, 72% varones) en los que se realizó cirugía coronaria. El día previo se obtuvieron las muestras plasmáticas para medida de proteína C reactiva (PCR) y porción amino-terminal del propéptido natriurético cerebral (NT-proBNP), se recogieron las características clínicas basales y el tratamiento preoperatorio, posteriormente se registraron los datos quirúrgicos y se estudió la aparición de FAP a 30 días.

Resultados. La incidencia de FAP fue del 23% (n = 23) (3,2 ± 2,9 días; intervalo, 1-15 días). Su aparición prolongó los cuidados intensivos (mediana + un día; p = 0,019) pero no la estancia hospitalaria total (p = 0,213). Entre los pacientes con FAP, los embolismos y la persistencia en FA en el momento del alta fueron del 4,3 y el 8,6%, respectivamente. La FAP se asoció con un mayor tiempo de isquemia (28,5 ± 22,30 frente a 18,0 ± 27,9 min; p = 0,045) y una menor tasa de estatinas preoperatorias (el 39 frente al 66%; p = 0,022). En el análisis multivariable, sólo la ausencia de estatinas conllevó un mayor riesgo de FAP (*odds ratio* [OR] = 4,31; intervalo de confianza [IC] del 95%, 1,33-13,88; p = 0,015). El uso de circulación extracorpórea (CEC) y los valores basales de PCR y NT-proBNP no se asociaron con un mayor riesgo.

Conclusión. En la práctica actual, la FAP es una complicación frecuente y la administración de estatinas en el preoperatorio podría proteger frente a su aparición.

Palabras clave: *Fibrilación auricular postoperatoria. Estatinas. Cirugía coronaria.*

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ABBREVIATIONS

CPB: cardiopulmonary bypass
CABG: coronary artery bypass grafting
PAF: post-operative atrial fibrillation
NT-proBNP: N-terminal probrain natriuretic peptide
CRP: C-reactive protein

INTRODUCTION

Post-operative atrial fibrillation (PAF) is the most common complication encountered after coronary artery bypass grafting (CABG).[1,2] Despite improvements in anesthesia, surgical techniques, and myocardial protection, its incidence appears to be increasing, the consequence of an aging surgical population.[3] Although it rarely places the life of the patient at risk, it can lead to hemodynamic deterioration, thromboembolic complications, and anxiety.[4,5] Its treatment requires the use of further medications and a potential lengthening of the patient's stay in hospital, which places greater demands on resources.[3-5]

Coronary artery bypass grafting without cardiopulmonary bypass (CPB) may help to reduce the incidence of PAF. However, the studies that have investigated this have so far have been few in number and contradictory in their findings.[6,7] Recent studies have related baseline values of C-reactive protein (CRP), a marker of local and systemic inflammation, and of N-terminal probrain natriuretic peptide (NT-proBNP), a marker of myocardial stress, to the development of PAF.[8,9] From a pharmacological point of view it has been long established that treatment with beta-blockers before and immediately after CABG provides protection against the appearance of PAF.[10-12] However, these studies were performed some 20 years ago and involved surgical populations different to those of the present day. Studies analyzing other models of pharmacological prophylaxis have reported very different results.[13,14] More recently, a number of studies have reported a protective role for statins against atrial fibrillation in the general coronary disease population.[15,16]

The aim of the present work was to determine whether the appearance of PAF in patients undergoing CABG was associated with the pre-operative plasma concentrations of CRP and NT-proBNP, with pre-operative treatment with statins, and with the use of CPB.

METHODS

Patients and Study Design

This prospective study involved 102 consecutive patients who underwent elective CABG between February 2002 and July 2003 at a tertiary university hospital. No patient who underwent emergency surgery, reoperation procedures, or combined valve surgery was included. Patients receiving steroid treatment, in dialysis, or with systemic inflammatory conditions were also excluded, as were those with chronic atrial fibrillation. The day before surgery, the patients' baseline characteristics were recorded, their plasma collected, and the pre-operative medications they took registered. The details of their surgical interventions were then recorded. The primary event studied was the appearance of PAF during the patients' post-operative stay in hospital and at 30 days post release.

Surgical Procedure

In those patients who underwent CABG with CPB, the latter was performed by cannulation of the ascending aorta; a single cannula in the right atrium was used for the venous return. A standard CPB circuit (Cobe Cardiovascular, Inc., Colorado, USA) was used, employing 40 µm filters (Sorin Biomedia, Modena, Italy) and a Dideco D 903 Avant membrane oxygenator (Dideco Srl, Mirandola, Italy). A pulsatile flow with a mean flow rate of 2.4 L/m^2 per min was used. Patient systemic temperature was reduced to between 28ºC and 33ºC (moderate hypothermia). Myocardial protection was provided via antegrade or retrograde cold blood cardioplegy with high levels of potassium.

In those patients who underwent CABG without CPB, the exposure of the vessel in which the graft was to be anastomosed was performed using a CTS stabilizing device (Guidant, Indianapolis, Indiana, USA). The duration of myocardial ischemia was regarded as being 0 minutes in patients who did not undergo CPB.

Diagnosis and Treatment of Post-Operative Atrial Fibrillation

Patient heart rate and rhythm were monitored by continuous telemetry during the immediate post-operative period in the intensive care unit. A 12 lead electrocardiogram (ECG) was performed 2 h before surgery and then daily until release. After leaving the intensive care unit, a 12 lead ECG was immediately performed (as a matter of routine) whenever there was a clinical suspicion of post-operative cardiac arrhythmia (dyspnea, palpitations, precordial oppression). A new ECG and clinical examination were performed at 30 days post release. Whenever PAF occurred the ventricular response was controlled with beta-blockers and the symptoms treated as previously described.[5]

Plasma C-Reactive Protein and NT-proBNP Concentrations

Immediately before surgery, peripheral blood was collected in tubes containing EDTA for the quantification

of plasma CRP and NT-proBNP. All plasma samples were stored at –80ºC and analyzed together at the end of the study. Plasma CRP (mg/L) was determined using an immunoturbidimetry kit (Roche Diagnostics GMBH, Mannheim, Germany). The anti-CRP antibodies attached to the latex microparticles react with the antigen in the sample forming an antibody-antigen complex, the amount of which is turbidimetrically determined after agglutination. The precision of this test was 0.03 mg/L; the detection limit was 0.1-20 mg/L. The plasma NT-proBNP concentration (pg/mL) was determined using the proBNP Assay kit (Roche Diagnostics, Germany), employing a Elecsys 2010 analyzer (Roche Diagnostics, Germany). The reactant is represented by polyclonal antibodies that recognize the epitopes of the N-terminal end (1-76) of proBNP. Samples of 20 µL were incubated with a biotinylated polyclonal antibody specific for NT-proBNP, plus another marked with ruthenium chelate, to form a complex sandwich. Following incubation, the bound fraction was separated with streptavidin-coated microparticles and quantified by chemiluminescence. The precision of this assay ranged from 1.8% at 800 pmol/L to 2.7% at 20.7 pmol/L; the detection limits were 0.6 and 4.130 pmol/L respectively. The pmol/L to pg/mL conversion ratio was 8.457.

Statistical Analysis

Continuous variables with a normal distribution were expressed as means(standard deviation), and were compared using the Student *t* test. Variables whose distribution was not normal were expressed as medians and quartiles; these were compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and were compared using Fisher's Exact Test or the χ^2 test as required. The potential predictors of PAF were analyzed using univariate logistic regression. Multivariate logistic regression included those factors that were significant or nearly significant ($P<.10$) in univariate analysis, as well as the reported risk factors of age, sex, a history of paroxysmal atrial fibrillation, a high baseline plasma NT-proBNP concentration, high blood pressure, high New York Health Association (NYHA) functional class, prior heart failure, chronic obstructive pulmonary disease, the non-use of pre-operative beta blockers, the discontinuation of post-operative beta blockers, the non-use of pre-operative angiotensin converting enzyme inhibitors, the discontinuation of post-operative angiotensin converting enzyme inhibitors, the non-use of pre-operative digitalis, the discontinuation of post-operative digitalis, a low left ventricular ejection fraction, the use of intra-aortic balloon counterpulastion, the use of post-operative catecholamines, the use of arterial grafts, and the duration of CPB. All calculations were performed using SPSS 12.0 software for Windows (SPSS Inc., Chicago, Illinois, USA). Significance was set at $P<.05$.

RESULTS

The accumulated incidence of PAF 30 days after release was 23% (n=23). This arrhythmia made its appearance at 3.2 (2.9) days (range 1-15 days) (Figure 1). In 70% of cases PAF appeared while the patient was in the intensive care unit; the remaining 30% occurred on the ward. The problem was associated with a longer stay in the intensive care unit (4 [interval 3-7] compared to 3 [interval 2-4] days; $P=.019$), but not with a longer stay in hospital (13 [interval 9-30] compared to 12 [interval 8-20] days; $P=.213$). Of the patients who suffered PAF, 1 (4.3%) developed an embolic complication, and at the time of release 2 patients (8.6%) still suffered atrial fibrillation (and therefore received oral anticoagulants).

Tables 1 and 2 show the baseline clinical characteristics and intra-operative data (respectively) of the patients who developed and did not develop PAF. The appearance of PAF was associated with a longer period of myocardial ischemia (28.5 [22.30] min compared to 18.0 [27.9] min in those who did not develop the problem; $P=.045$) and the absence of pre-operative treatment with statins (taken by 39% of those who developed PAF and 66% of those who did not; $P=.022$). However, it was not associated with age, use of tobacco, the degree of right coronary artery involvement, or cholesterol level, although trends towards significance were seen. The use of CPB—or not—had no effect on the appearance of PAF (Table 2).

The patients who developed PAF, and those who did not, had similar baseline plasma NT-proBNP concentrations (343 pg/mL [173-631 pg/mL] compared to 394 pg/mL [151-1118 pg/mL] respectively; $P=.576$). However, in univariate analysis those who developed PAF had lower baseline plasma CPR concentrations than those who did not develop this problem (0.14 mg/L [0.10-0.37 mg/L] compared to 0.24 mg/L [0.10-1.11); $P=.021$). Multivariate logistic regression, however, identified only 1 independent predictor of the appearance of PAF—the absence of pre-operative statin treatment (odds ratio [OR]=4.31; 95% confidence interval [CI] 1.33-13.88; $P=.015$). Prior paroxysmal atrial fibrillation and a longer duration of myocardial ischemia showed trends towards significance ($P=.067$ and $P=.055$ respectively) (Table 3). Sixty one patients (60%) were administered pre-operative statin treatment (median 35 days, range 14-420 days), the majority (95%) receiving an intermediate dose (40 mg). The total cholesterol concentrations of those who developed and those who did not develop PAF were similar (160.2 [33.9] mg/dL compared to 168.8 [44.7] mg/dL; $P=.812$), as were their low density lipoprotein cholesterol (LDL-C) (95.1 [35.8] compared to 98.2 [44.6]; $P=.783$) and high density lipoprotein cholesterol (HDL-C) (33.5 [10.0] compared to 36.4 [11.8]; $P=.350$) concentrations. Kaplan-Meier analysis (Figure 2) revealed pre-operative statin treatment to be associated with better PAF-free survival at 30 days post release (85.3% compared to 65.8%; log rank 0.0247).

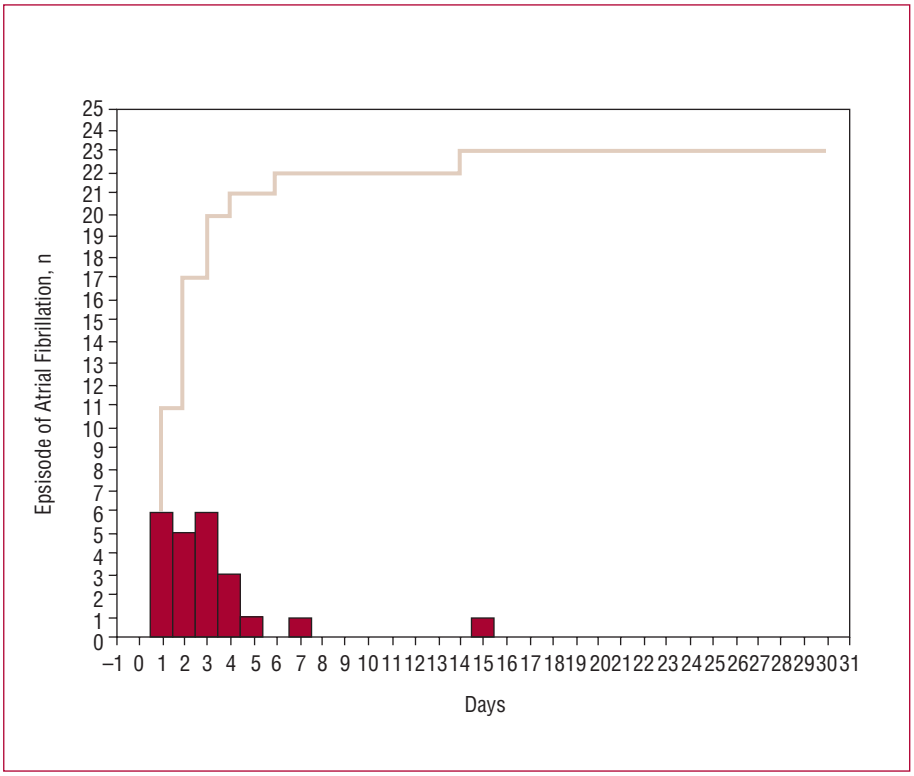

Figure 1. Bar graph showing the frequency of post-operative atrial fibrillation cases per day after surgery, and the cumulative incidence curve.

TABLE 1. **Baseline Clinical Characteristics of Patients in Whom Post-Operative Atrial Fibrillation Appeared and Did not Appear***

Variable	With PAF (23)	Without PAF (79)	*P*
Age, mean (SD), years	67.7 (8.8)	63.9 (9.4)	.089
Male sex	18 (78%)	55 (70%)	.419
Diabetes mellitus	11 (48%)	39 (49%)	.896
High blood pressure	13 (57%)	55 (70%)	.241
Hypercholesterolemia	10 (44%)	51 (65%)	.070
Smoking	2 (9%)	21 (27%)	.071
Previous AMI	9 (39%)	31 (39%)	.992
Recent ACS (<1 month)	13 (57%)	54 (68%)	.293
Kidney failure	3 (13%)	13 (17%)	.692
Pre-operative AF	2 (9%)	2 (2.5%)	.180
Preoperative CHF	2 (9%)	17 (22%)	.164
LVEF	57 (50-60)	55 (45-60)	.172
COPD	2 (9%)	5 (6.3%)	.693
Creatinine	1.1 (0.9-1.2)	1.1 (0.9-1.3)	.796
EuroScore	5.78 (3.10)	5.63 (2.59)	.817
Beta-blockers	19 (86%)	58 (77%)	.357
ACEi or ARA-II	12 (55%)	40 (53%)	.713
Antiaggregants	20 (91%)	69 (92%)	.870
Statins	9 (39%)	52 (66%)	.022
Amiodarone	1 (4.5%)	1 (1.3%)	.351

*ARA-II indicates angiotensin II receptor antagonists; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; PAF, post-operative atrial fibrillation; LVEF, left ventricular ejection fraction; AMI, acute myocardial infarction; CHF, congestive heart failure; ACEi, angiotensin converting enzyme inhibitors; ACS, acute coronary syndrome.
Values are expressed as n (%) and mean (standard deviation), or median (quartiles).

DISCUSSION

In the present population, the absence of pre-operative statin treatment was significantly and independently associated with a greater risk of developing PAF. Neither the pre-surgery plasma CRP nor NT-proBNP concentrations, nor the use—or not—of CPB had any effect on the appearance of PAF.

TABLE 2. **The Appearance of Post-Operative Atrial Fibrillation With Respect to Coronary and Surgical Characteristics***

Variable	With PAF (23)	Without PAF (79)	*P*
Number of affected vessels	2.44 (0.60)	2.60 (0.56)	.242
LMCA disease	11 (48%)	41 (52%)	.731
ADA disease	19 (83%)	65 (82%)	.971
RCA disease	12 (52%)	57 (72%)	.071
Cx disease	18 (78%)	52 (66%)	.258
Surgery without CPB	10 (44%)	41 (52%)	.477
Use of arterial grafts	16 (70%)	66 (84%)	.137
Surgery on the RCA	16 (70%)	66 (84%)	.137
Number of vessels bypassed	2 (0.75)	2.17 (0.87)	.117
Duration of CPB, mean (SD), min†	76.5 (18.2)	96.2 (44.7)	.919
Duration of ischemia, mean (SD), min	28.5 (22.3)	18 (27.9)	.045

*RCA indicates right coronary artery; Cx, circumflex artery; CPB, cardiopulmonary bypass; ADA, anterior descending artery; PAF, post-operative atrial fibrillation; LMCA, left main coronary artery.
Values are expressed as n (%) and mean (standard deviation).
†Only for patients with CPB (n=51).

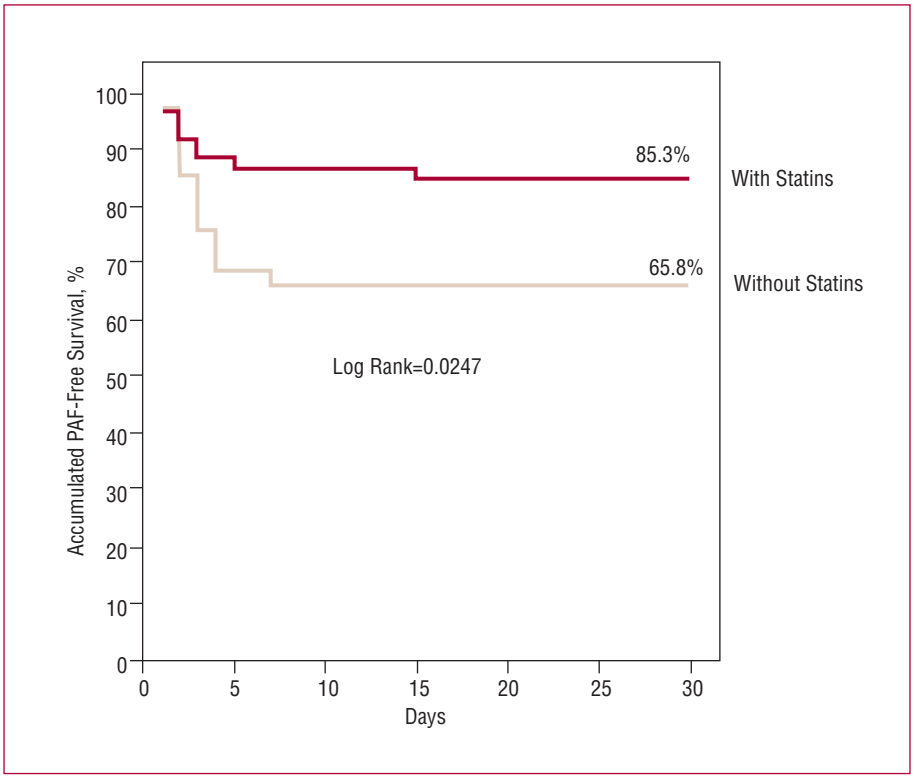

Figure 2. Kaplan-Meier curves for the appearance of PAF in those who were administered (darker line) and not administered (lighter line) pre-operative statins.

In clinical practice, atrial fibrillation is the most commonly seen form of cardiac arrhythmia. Its prevalence is 1.7% in the general population,[17] rising with age to some 10% in those aged over 80 years. An incidence of 5% has been reported for the non-thoracic major surgery population.[18] Among those undergoing CABG, its incidence has been reported to vary between 25% and 40%, with a peak between the second and fourth days after surgery.[19] The incidence of PAF is greater (approximately 50%) among patients who undergo combined valve surgery.[2] However, such patients were excluded from the present study, which focused on coronary bypass surgery. The 23% PAF incidence recorded falls into the lower part of the described range, a likely consequence of the exclusion of patients requiring emergency surgery or combined valve surgery. As in

TABLE 3. **Factors Influencing the Incidence of Post-Operative Atrial Fibrillation: Logistic Regression Analysis***

Variables	Univariate		Multivariate	
	P	OR (95% CI)	*P*	OR (95% CI)
Pre-operative statin treatment	.022	0.34 (0.13-0.86)	.015	0.23 (0.07-0.75)
Duration of ischemia	.045	1.03 (0.99-1.03)	.055	1.02 (1.0-1.041)
Previous paroxysmal AF	.207	3.66 (0.487-27.5)	.067	11.43 (0.84-155)
RCA disease	.071	2.37 (0.91-6.17)	_	_
CRP	.021	1.38 (0.85-2.22)	_	_
Age	.089	1.05 (1.00-1.10)	_	_
Elderly	.072	2.35 (0.90-6.06)	_	_
Dyslipidemia	.070	2.36 (0.92-6.09)	_	_
Smoking	.071	3.80 (0.82-17.5)	_	_
NT-proBNP	.576	_	_	_
NYHA	.604	_	_	_
LVEF	.164	_	_	_
Without CPB	.477	_	_	_

*RCA indicates right coronary artery; CPB, cardiopulmonary bypass; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; CI, confidence interval; NT-proBNP, N-terminal probrain natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; CRP, C-reactive protein.

other studies, the majority of PAF episodes occurred soon after surgery, with the incidence peak appearing on the third day after the intervention. Together, the available data would seem to suggest that, despite improvements in surgical techniques, anesthesia and myocardial protection, the incidence of PAF in heart surgery has not declined over the last 20 years.

For the majority of patients PAF is a benign problem, but it can be associated with thromboembolic complications or hemodynamic deterioration.[20] The condition of course involves additional treatment (with its potential side effects), potentially longer hospital stays, and increased health service costs. In 1996, Aranki et al[1] calculated that PAF after coronary surgery added almost 5 days to hospital stays. Given its high incidence (25%-40%) this significantly increased costs. Therefore, any measure that reduces the incidence of PAF could provide important medical and economic benefits. In the present study, however, although PAF was associated with an increase in the time spent in the intensive care unit (median 1 day)—it was not associated with a longer overall hospital stay. This might reflect that current treatment of this arrhythmia is associated with better clinical progress. Indeed, the majority of the present patients (91%) were released with a normal sinus rhythm, and only 1 (4%) had an associated embolism; the overall hospital stay was therefore not prolonged.

Although the incidence of PAF remains high, modern treatment means its repercussions are usually of little importance. In the present study there was no policy of fast-track release (median hospital stay 12 days); however, within such fast-track release programs, PAF might lead to longer hospital stays—ie, early release would be impossible, thus increasing relative costs.

Few studies have reported pre-operative treatment with statins to protect against the appearance of PAF.[21-23] In 2000, Dotani et al[21] were the first to describe an association between such pre-operative treatment and a reduced incidence of post-operative arrhythmias, including PAF. In the present work, treatment with statins before surgery reduced the risk of developing AF by 67% after adjusting for other risk factors in multivariate analysis. This finding agrees with the results of recent studies showing that statins protect against PAF in patients with stable coronary artery disease,[15] and that they can help prevent a recurrence of atrial fibrillation after successful cardioversion.[16] Statins have also been associated with a reduced recurrence of ventricular tachycardia in patients implanted with an automatic defibrillator.[24] In a recent study, Amar et al[25] found that treatment with statins before non-cardiac thoracic surgery protected against the appearance of PAF independent of baseline plasma CRP concentrations, similar to that seen in the present study. In addition, Patti et al[23] reported findings very similar to those of the present work in a study involving similar patients; these authors recorded a significant reduction in PAF in patients randomized to receive atorvastatin from 7 days before surgery compared to those who received a placebo.

In a non-surgical population of over 500 elderly patients, Aviles et al[26] found a relationship between the baseline plasma CRP concentration and the risk of developing atrial fibrillation. The present results, however, are not able to confirm prior observations regarding the predictive value of the baseline plasma CRP concentration on PAF.[8] With respect to coronary surgery, inflammation alone does not appear to explain the development of this arrhythmia. Therefore, mechanisms additional to the anti-inflammatory action of statins must be at work in their affording protection against PAF. In the context of their different pleiotropic effects, they may help prevent PAF by improving myocardial ischemia (particularly atrial ischemia), by improving ion currents across the myocyte membrane via their effects on autonomic modulation,[27,28] or by inhibiting extracellular matrix remodeling.[22] The lack of a relationship between inflammation, CRP concentration, and coronary surgery may also explain the lack of an association between CPB and PAF (CPB is known to be associated with an increased systemic inflammatory response). It is likely that surgery with or without CPB is associated with mechanisms that favor the development of PAF, such as the opening of the pericardium, the manipulation of the heart, coronary ischemia, or local inflammation processes.[29]

In contrast to that reported by Wazni et al,[9] who found a relationship between the concentration of baseline brain natriuretic peptide and PAF, no association was found in the present study between baseline plasma NT-proBNP and the risk of developing this arrhythmia. The NT-proBNP concentration is a biological variable that correlates with the increase in intraventricular pressure and volume. Its lack of correlation with PAF agrees with the known lack of association between the latter and such pre-surgery variables as the left ventricular ejection fraction, NYHA functional class, or high blood pressure (all of which are associated with higher circulating NT-proBNP concentrations). However, it cannot be ruled out that an increase in post-operative NT-proBNP may have some predictive value with respect to the development of PAF, since an increase would reflect surgery-induced myocardial stress.

Limitations

The main limitations of this study are its small sample size and its non-randomized nature; associations can be explored but no causality identified. Neither the effect of statin dose nor the duration of statin treatment was analyzed; this should be investigated in future studies. Further, this work only took into account the prognostic value of baseline indicator concentrations; the study of post-surgery concentrations might provide interesting information. Finally, continuous ECG monitoring beyond that performed in the intensive care unit might have detected subclinical episodes of PAF.

CONCLUSIONS

PAF continues to be a common complication of coronary surgery. Pre-operative treatment with statins, however, may protect against its appearance. Neither the pre-surgery plasma concentrations of CRP and NT-proBNP, nor the use of CPB, appear to be associated with the development of PAF.

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