Original articles

Risk predictors of paroxysmal atrial fibrillation following aortic valve replacement

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Key words:
Aortic valve replacement; Atrial fibrillation; Postoperative arrhythmias.

Background. **Atrial fibrillation (AF) is the most frequently encountered arrhythmic complication associated with cardiac surgery. The aim of this paper was to identify the clinical predictors of AF occurrence following aortic valve replacement.**

Methods. **Three hundred and two patients were included in this study and divided into two groups according to the absence (SR group, 243 patients, mean age 55.6 ± 15 years) or the evidence (AF group, 59 patients, mean age 63.8 ± 11 years) of post-aortic valve replacement AF. Sixty-five perioperative variables (37 preoperative, 8 intraoperative and 20 postoperative) were considered.**

Results. **Post-aortic valve replacement paroxysmal AF occurred in 59 out of 302 patients (19%). At univariate analysis, post-aortic valve replacement AF was associated with advanced age, left atrial enlargement, preoperative episodes of paroxysmal AF, the use of a warm blood cardioplegic solution and normothermia, administration of inotropic agents, prolonged assisted ventilation but also with postoperative acidosis, electrolyte imbalance and atrioventricular and intraventricular conduction disorders. Stepwise forward multivariate logistic regression analysis identified age (p = 0.002, odds ratio-OR 1.04), left atrial enlargement (p = 0.004, OR 2.6), a prior history of paroxysmal AF (p = 0.0003, OR 10.9), and postoperative electrolyte imbalance (p = 0.01, OR 2.3) as independent correlates of AF, whereas the use of hypothermia appeared to be a protective factor (p = 0.0004, OR 0.26).**

Conclusions. **According to our findings, post-aortic valve replacement AF seems to be associated with well-defined anatomical and electrical substrates generated by advanced age, increased left atrial dimensions, and a possible electrical remodeling consequent to prior repetitive episodes of paroxysmal AF. On these grounds, external factors such as postoperative electrolyte imbalance might enhance atrial ectopic activity and trigger postoperative sustained tachyarrhythmias, while the use of hypothermia might allow for better protection of the atrial myocardium against intraoperative ischemia.**

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Introduction

Atrial fibrillation (AF) is the most frequently encountered postoperative arrhythmia following cardiac surgery. It has been reported that this complication occurs in up to one third of patients submitted to coronary artery bypass grafting (CABG) surgery[1-18].

Despite the fact that it is often considered as a benign and self-limited event, postoperative AF may not only favor the onset of dreadful complications such as systemic embolization, hemodynamic instability and in-hospital mortality[1-3,11], but also significantly increase the length and costs of hospitalization[8,19]. However, most of the data regarding the occurrence of AF following cardiac surgery derives from studies involving patients submitted to CABG[1-20]. Conversely, at present little is known about the occurrence of AF in patients submitted to aortic valve replacement[21,22].

The aim of our study was thus to identify the clinical predictors of postoperative AF, including all the preoperative, intraoperative and postoperative variables that might be associated with its occurrence, in a cohort of patients who underwent aortic valve replacement.

Methods

Study population selection. Three hundred and two consecutive patients who underwent aortic valve replacement at our Institution (Department of Cardiothoracic and

Respiratory Sciences, Second University of Naples, Italy) between September 1998 and December 1999 were included in the study. The underlying aortic diseases were: aortic stenosis in 120 patients (60% degenerative calcification; 30% calcification of the bicuspid valve; 10% other); aortic regurgitation in 88 patients (42% aortic root dilatation; 33% rheumatic disease; 15% bicuspid valve; 10% other); combined aortic stenosis and regurgitation in 94 patients. The exclusion criteria were the presence of preoperative chronic AF, preoperative pacemaker implantation and intraoperative or postoperative death occurring during the in-hospital stay. On the other hand, patients who underwent associated interventions such as CABG (20 patients) and mitral and/or tricuspid valve surgery (68 patients) were deliberately included in order to test the contribution of combined procedures in increasing the atrial susceptibility to arrhythmias.

For each patient a complete preoperative echocardiographic evaluation had been performed using an Acuson XP10 ultrasound system (Mountain View, CA, USA). The left atrial M-mode derived antero-posterior diameter was assessed in the parasternal long-axis view. The cut-off points for left atrial enlargement were obtained from a control group of 50 healthy subjects (25 men and 25 women), comparable in demographic characteristics to the patients of the present study. These normal subjects were divided into sex-specific left atrial quartiles. The mean value of the left atrial dimensions for the highest quartile (men: x = 43.7 mm, mean height 175.3 ± 2 cm; women: x = 38.7 mm, mean height 165.3 ± 4 cm) was chosen to be the cut-off point for left atrial enlargement. This value is also confirmed by previous reports[23].

Data were collected at the time of hospital discharge. A relevant schedule containing all the 37 preoperative, 8 intraoperative and 20 postoperative variables considered (Tables I-III) was filled in. In particular, preoperative episodes of paroxysmal AF were verified by accurate anamnesis and electrocardiographic evidence.

Table I. Preoperative variables.

	SR group (n=243)	AF group (n=59)	p
Age (years)	55.6 ± 15	63.8 ± 11	< 0.001
Age > 70 years (%)	20	30	NS
Male sex (%)	61.4	62.7	NS
Height (cm)	172.3 ± 4	172.4 ± 2	NS
Body mass index (kg/m^2)	26.3 ± 4	26.1 ± 4	NS
Body surface area (m^2)	1.74 ± 0.2	1.71 ± 0.2	NS
Prior MI (%)	3.6	6.8	NS
Prior PTCA (%)	0.5	0	NS
Prior CABG (%)	0	1.7	NS
COPD (%)	8.7	17.3	NS
Hypertension (%)	28.5	25	NS
Diabetes (%)	15.3	13.5	NS
Coronary heart disease (%)	7	5.8	NS
Aortic stenosis (%)	40.6	40.7	NS
Aortic regurgitation (%)	28.9	28.8	NS
Aortic stenosis + regurgitation (%)	30.4	30.5	NS
Associated valve disease (%)	21.5	30.8	NS
Other cardiac disease (%)	15.7	19.2	NS
LVEF < 30% (%)	5.5	2	NS
NYHA class	2.4 ± 0.6	2.3 ± 0.6	NS
Bioprosthesis (%)	2.1	5	NS
Left atrial enlargement (%)	54.4	75	0.017
Pulmonary hypertension (%)	4	9.4	NS
Preoperative anemia (%)	2.8	5.5	NS
Preoperative electrolyte disorder (%)	2.2	1.7	NS
Syncope (%)	5.4	7.3	NS
Premature ventricular beats (%)	7.1	6.8	NS
Preoperative paroxysmal AF (%)	1.5	11.9	0.001
Preoperative cardiac arrest (%)	0	0	NS
Atrioventricular conduction abnormalities (%)	3.1	5.1	NS
Intraventricular conduction abnormalities (%)	19.9	22	NS
Preoperative calcium antagonists (%)	7	7.7	NS
Preoperative beta-blockers (%)	3.5	11.5	NS
Preoperative digitalis (%)	37	44.2	NS
Preoperative amiodarone (%)	3.5	9.6	NS
Preoperative ACE-inhibitors (%)	38.5	44.2	NS
Preoperative nitrates (%)	19.5	26.9	NS

AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; SR = sinus rhythm.

Table II. Intraoperative variables.

	SR group	AF group	p
Bypass time (min)	89.5 ± 38	94.9 ± 30	NS
Ischemia time (min)	59.5 ± 22	63.1 ± 19	NS
IABP (%)	0	1.70	NS
Hypothermia (%)	87	71	0.005
Blood cardioplegia (%)	13	27	0.019
St. Thomas cardioplegia (%)	87	73	0.019
Intraoperative acidosis (%)	10	10.3	NS
Intraoperative transfusion (%)	8	10.2	NS

IABP = intra-aortic balloon pump. Other abbreviations as in table I.

Table III. Postoperative variables.

	SR group	AF group	p
Inotropic agents	39.5	61.8	0.005
Ventilation > 24 hours	4.6	14	0.028
Postoperative acidosis	19.3	42.6	< 0.001
Postoperative electrolyte disorders	21.5	39.6	0.009
Total CK > 1000 IU	13.5	16.4	NS
CK-MB > normal range	8.4	9.3	NS
Postoperative blood transfusion	19.5	27.6	NS
Return to operating room	0.5	0	NS
Postoperative cardiac arrest	2	0	NS
Cerebral implications	1.5	5.1	NS
Pulmonary complications	1.5	0	NS
Cardiac implications	2	19.6	NS
Renal complications	0	3.4	NS
Postoperative adjunctive AV conduction abnormalities	8.1	15.5	0.027
Postoperative pacemaker	3	2	NS
Postoperative adjunctive IV conduction abnormalities	5.1	2	0.017
Postoperative calcium antagonists	6.1	10	NS
Preoperative beta-blockers	4.7	30	NS
Preoperative nitrates	12.1		NS
Preoperative ACE-inhibitors	37.2		NS

Values are expressed as percentages. AV = atrioventricular; CK = creatine kinase; IV = intraventricular. Other abbreviations as in table I.

Operative techniques. Cardiopulmonary bypass with moderate hemodilution (hematocrits 20-28%), flow rates of 22-24 l/min/m^2 and a mean pressure of 50-70 mmHg was used. Warm blood cardioplegia and hyperkalemic cold crystalloid cardioplegia were alternatively used. When the latter was chosen, core-cooling up to 28°C was performed in order to achieve hypothermia. In both cases, a volume of the solution equivalent to 10 ml/kg was administered through the antegrade route at a rate of 200-250 ml/min. If necessary, a further half dose of the cardioplegic solution was administered every 20 or 30 min, depending on the type of cardioplegia adopted (respectively warm blood or cold crystalloid). Finally, a left ventricular vent was only rarely used.

Postoperative protocols. Patients were weaned off the ventilator as soon as it appeared that they were hemodynamically stable, presented with no major bleeding, were normothermic and conscious. Potassium and magnesium supplements were provided as necessary to maintain the electrolyte balance within the normal range. Electrolyte disorders were defined as serum potassium levels < 3.5 mEq/l, serum magnesium levels < 2.0 mEq/l or serum calcium levels < 4 mEq/l. For each patient the heart rate, ECG lead II, central venous pressure, arterial pressure and acid-base balance were continuously monitored during their stay in the intensive care unit. Intraoperative and postoperative acidosis were identified in case of an arterial pH < 7.36. Until the day of discharge, 12-lead ECGs were routinely obtained once or, if necessary, more times daily to confirm any rhythm disturbance, ischemic incident, atrioventricular (first, second or third-degree atrioventricular blocks) or intraventricular (left or right bundle branch blocks) conduction disturbances. Inotropic support with dobutamine was provided to several patients in order to achieve, in the intensive care unit, stable hemodynamic conditions more rapidly. Further inotropic agents were then added only if the ventricular contractility was found to be frankly impaired and if dobutamine alone did not prove to be sufficient for the maintenance of an adequate ejection fraction.

Statistical analysis. Statistical analysis was performed using the SPSS statistical package for windows, release 8.0 (Chicago, IL, USA). The correlation of all preoperative, intraoperative and postoperative factors with the occurrence of postoperative AF was analyzed using the Student's t-test and χ^2 test. In particular, the Student's t-test was used to identify significant differences in numerical variables, while categorical variables were analyzed using the χ^2 test. Differences were considered statistically significant when $p < 0.05$. Stepwise forward multiple logistic analyses were performed to weigh the independent effects of potential predictors on the dependent variable. Univariate factors exhibiting a p value < 0.05 were included in the multivariate logistic regression analysis. Differences were considered statistically significant for p values < 0.05.

Results

Post-aortic valve replacement paroxysmal AF occurred in 59 out of 302 patients (19%). Of these, 8 out of 59 (13.5%) were discharged in spite of persisting AF. All the patients were divided into two groups according to the absence (SR group, 243 patients, mean age 55.6 ± 15 years) or the evidence (AF group, 59 patients, mean age 63.8 ± 11 years) of post-aortic valve replacement AF.

Table I shows the preoperative baseline characteristics for each group. Patients with AF were significantly older and presented more frequently with left atrial enlargement and prior episodes of paroxysmal AF.

As for the intraoperative variables, normothermia and the administration of a warm blood cardioplegic solution were more frequent in the AF group (Table II).

With regard to the postoperative variables, the use of inotropic agents and prolonged assisted ventilation and the occurrence of postoperative acidosis, electrolyte imbalance and finally atrioventricular and intraventricular conduction disorders were more frequent in the AF group (Table III).

Stepwise forward logistic regression analysis including only preoperative variables identified age (odds ratio-OR 1.04, $p < 0.005$), left atrial enlargement (OR 2.3, $p < 0.005$), and a history of prior episodes of paroxysmal AF (OR 9.9, $p < 0.0005$) to be independent correlates for AF. In an additive multivariate logistic regression model which also included intraoperative and postoperative variables, advanced age, left atrial enlargement, a history of prior episodes of paroxysmal AF, the use of hypothermia and the development of postoperative electrolyte imbalance were the only independent predictors of postoperative AF. The OR and the p value for each multivariate predictor are shown in table IV.

Table IV. Multivariate predictors of post-aortic valve replacement atrial fibrillation (AF) in a stepwise forward multivariate logistic regression analysis which included all the perioperative variables.

	p	OR	95% CI
Age	0.002	1.04	1.01-1.07
Left atrial enlargement	0.004	2.6	1.4-5.2
Preoperative paroxysmal AF	0.0003	10.9	3.1-15.8
Hypothermia	0.0004	0.26	0.12-0.55
Postoperative electrolyte disorders	0.01	2.3	1.2-4.4

CI = confidence interval; OR = odds ratio.

Discussion

Recent data demonstrated that AF is generated by multiple wavelets that wander around anatomical obstacles and/or areas of functional conduction block, resulting in a continuous random alternation of depolarizations and repolarizations of contiguous regions[24-26]. Many studies addressed the point why the arrhythmia is so frequently encountered after CABG surgery and consequently identified several features that turned out to be important risk predictors of postoperative AF at multivariate analyses[4-18]. Age, male sex, a post-surgical hyperadrenergic condition caused by preoperative beta-blocker withdrawal, together with the presence of delayed intra-atrial conduction, left atrial enlargement, preoperative paroxysmal episodes of AF and atrial ischemia have been recognized as key factors playing a major role in predicting the occurrence of post-CABG AF[4-18]. Surprisingly, only a few reports searched for the variables associated with the onset of an AF crisis following aortic valve replacement[11,18,21,22]. Advanced age, atrial ischemia, electrical alterations due to action potential modifications, left atrial enlargement, prolonged respirator use and the administration of inotropic agents appeared to be the only independent predictors of post-aortic valve replacement AF.

In our study, we deliberately included most of the factors that had been separately considered in the previous studies, in order to comprise a satisfactory number of perioperative variables (65 variables in all) that might exert a possible influence on atrial arrhythmogenesis after aortic valve replacement. In particular, even patients who underwent associated interventions such as CABG (6.6%) and mitral and/or tricuspid valve surgery (22.5%) were enrolled to test the contribution of combined procedures in increasing the atrial susceptibility to arrhythmias.

At univariate analyses, post-aortic valve replacement AF was associated with advanced age, left atrial enlargement, preoperative episodes of paroxysmal AF, the use of a warm blood cardioplegic solution, the administration of inotropic agents, prolonged assisted venti-

lation and finally to postoperative acidosis, electrolyte imbalance and atrioventricular and intraventricular conduction disorders. Of note is the fact that concomitant surgical procedures did not have any impact on the development of AF. In addition, only advanced age, preoperative paroxysmal episodes of AF, left atrial enlargement and postoperative electrolyte imbalance were independent predictors of the occurrence of post-aortic valve replacement AF at multivariate analysis, while the use of intraoperative hypothermia appeared to be an independent protective factor (Fig. 1).

Our findings are consistent with previous observations made in patients undergoing CABG surgery and incurring postoperative AF[4-18]. In fact, AF seems to require a well-defined preexisting electro-anatomical substrate consisting of atrial aging, increased left atrial dimensions and previous episodes of AF. Atrial aging and enlargement are accompanied by important architectural and structural changes such as the replacement of atrial myocytes by fibrous and/or adipose tissue that might alter the intra-atrial electrical impulse transmission, generating several areas of conduction block. Furthermore, through a complex electrophysiological remodeling of both atria that finally leads to a progressive and spatially inhomogeneous shortening of the atrial relative and effective refractory periods, preoperative repetitive episodes of paroxysmal AF may predispose to further atrial tachyarrhythmias[22]. As a result, an ectopic impulse might encounter contiguous regions with a different refractoriness and therefore be propagated at different conduction velocities. If this phenomenon takes place at a microscopic level, it may generate multiple wavelets that could trigger and maintain the fibrillation process. In addition, external factors such as postoperative electrolyte imbalance might act on this fertile background triggering postoperative sustained tachyarrhythmias. On the other hand, the use of hypothermia might provide improved atrial myocardial protection against intraoperative ischemia, thus reducing atrial ectopic activity and consequently the incidence of postoperative AF.

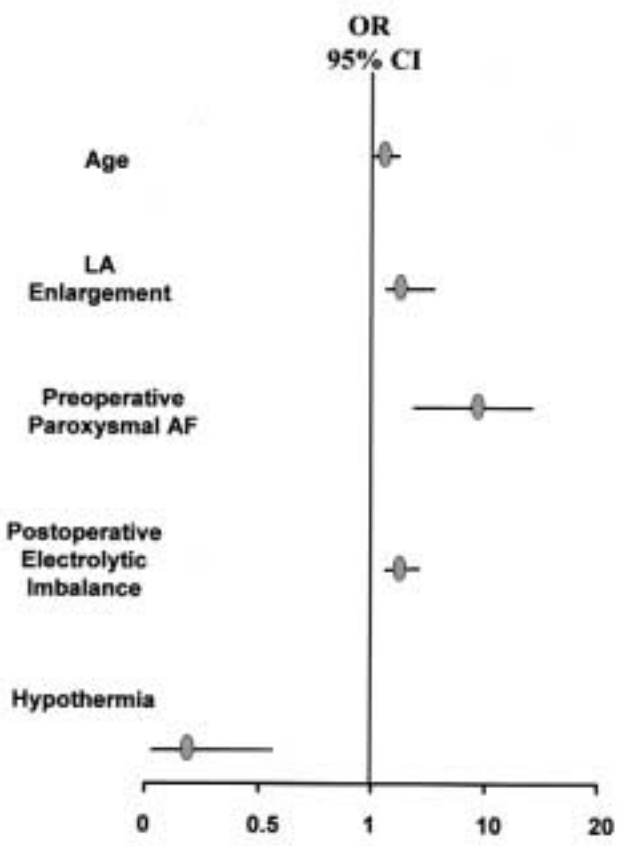

Figure 1. *Multivariate predictors of the occurrence of post-aortic valve replacement atrial fibrillation (AF) in a multivariate logistic model which included all the perioperative variables. CI = confidence interval; LA = left atrial; OR = odds ratio.*

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