The −174G/C Interleukin-6 Polymorphism Influences Postoperative Interleukin-6 Levels and Postoperative Atrial Fibrillation. Is Atrial Fibrillation an Inflammatory Complication?

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Background—It has been suggested that inflammation can have a role in the development of atrial arrhythmias after cardiac surgery and that a genetic predisposition to develop postoperative complications exists. This study was conceived to verify if a potential genetic modulator of the systemic inflammatory reaction to cardiopulmonary bypass (the −174 G/C polymorphism of the promoter of the Interleukin-6 gene) has a role in the pathogenesis of postoperative atrial fibrillation (AF).

Patients and Results—In 110 primary isolated coronary artery bypass patients the −174G/C Interleukin-6 promoter gene variant was determined. Interleukin-6, fibrinogen and C-reactive protein plasma levels were determined preoperatively, 24, 48, and 72 hours after surgery and at discharge. Heart rate and rhythm were continuously monitored for the first 36 to 48 hours; daily 12-lead electrocardiograms were performed thereafter until discharge. GG, CT, and CC genotypes were found in 62, 38, and 10 patients, respectively. Multivariate analysis (which included genotype, age, sex, and classical risk factors for AF) identified the GG genotype as the only independent predictor of postoperative AF. The latter occurred in 33.9% of GG versus 10.4% of non-GG patients (hazard ratio 3.25, 95%CI 1.23 to 8.62). AF patients had higher blood levels of Interleukin-6 and fibrinogen after surgery ($P<0.001$ for difference between the area under the curve).

Conclusion—The −174G/C Interleukin-6 promoter gene variant appears to modulate the inflammatory response to surgery and to influence the development of postoperative AF. These data suggest an inflammatory component of postoperative atrial arrhythmias and a genetic predisposition to this complication. **(*Circulation*. 2003;108[suppl II]:II-195-II-199.)**

Key Words: aortocoronary bypass ■ atrial fibrillation ■ genetics

Atrial arrhythmias, and in particular atrial fibrillation (AF), are common after cardiac operations and have important clinical and economic implications. The reported incidence of postoperative AF ranges from 5 to 70% and is associated with significant morbidity[1] and considerable increase of in-hospital stay and costs.[2]

Although several studies have analyzed the risk factor for postoperative AF and its possible preventive strategies, the exact pathophysiology of this complication has not yet been elucidated.

Recently, data derived from the histological analysis of atrial specimens from patients affected by lone AF refractory to conventional treatment have suggested that atrial myocarditis can play a causal role in the determination of this arrhythmia[3] and observations performed in cardiac surgery series seemed to testify an inflammatory component of postoperative AF.[4]

Our group has previously shown how the −174 G/C polymorphism of the promoter of the Interleukin-6 gene determines postoperative Interleukin-6 levels;[5] the present study was conceived to elucidate if this genetic polymorphism (one of the possible modulators of the systemic inflammatory reaction to cardio-pulmonary bypass) has a role in the determination of postoperative atrial arrhythmias after on-pump primary isolated coronary artery bypass surgery.

Patients and Methods

Patient Population

From January 1998 to May 1999 a prospective study on the systemic and inflammatory reaction to cardiopulmonary bypass (CPB) was

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conducted at the Department of Cardiac Surgery of the Catholic University of Rome (*Fibrinolisi ed Infiammazione nella Fase Acuta: FIFA study*); part of the results of this study have been published elsewhere.[5,6] During this period all patients scheduled to undergo isolated elective coronary artery bypass grafting (CABG) at our Institution were screened for inclusion. Exclusion criteria were: associated cardiac or noncardiac surgical procedures, age >80 years, single-vessel disease, emergent or urgent revascularization, left ventricular ejection fraction <0.30, carotid artery disease, previous cerebrovascular accident, chronic dialysis, hepatic failure, respiratory or renal insufficiency (defined respectively as a preoperative creatinine level ≥2.0 mg/dL and a preoperative $pO_2 \leq 60$ mm Hg or $PCO_2 > 50$ mm Hg on room air and/or a preoperative FEV1<1.25 l or <75% of the normal value), hemorrhagic conditions, active infection and chronic anti-inflammatory and antifibrinolytic therapy.

The study received Ethical Committee approval and all included patients gave their consent to participate. A total of 113 cases were included; as for 3 patients information on the postoperative rhythm were considered incomplete, 110 of these cases were included in the present analysis.

Operative Technique

All surgical procedures were performed in standard fashion by the same surgical team through median sternotomy, and using CPB. As the FIFA study had as secondary endpoint the study of the effect of CPB temperature on postoperative inflammatory activation and fibrinolysis during CPB the nasopharingeal temperature was kept at 37°C in 53 cases and at 26°C in 57 according to a randomized sequence; of note, as reported elsewhere, no effect of CPB temperature on postoperative inflammation and hemostasis could be demonstrated.[6] Myocardial protection was always accomplished by anterograde isothermic intermittent blood cardioplegia.

Interleukin-6 Promoter Polymorphism Analysis

For genetic analysis blood was drawn immediately before surgery; samples were collected in CTAD and centrifuged without delay at 3000 *g* at 4°C for 20 minutes; cellular pellets were then kept at −20°C. DNA was extracted by standard techniques; −174 G/C IL-6 promoter genotyping was performed following a methodology previously described.[7]

Postoperative Evaluations

To avoid investigators-related biases, all the physicians involved in patients' care were blinded to the results of the genetic and biochemical analyses.

The in-hospital clinical course of all patients, including major and minor postoperative complications were prospectively recorded.

C reactive protein, Interleukin-6, fibrinogen and others inflammatory and coagulative markers were determined preoperatively, 24, 48, and 72 hours after surgery and at hospital discharge following a methodology previously described[5,6]

Postoperative Arrhythmias Evaluation

In the postoperative period heart rate and rhythm were continuously monitored for the first 36 to 48 hours and daily 12-lead electrocardiograms were performed from the first postoperative day until discharge and in case of clinical suspicion of arrhythmia.

Postoperative 24-hours Holter evaluation was available for 68 of the 110 cases. ECG and Holter examination were performed independently by two observers. Discordances were resolved by common re-evaluation.

Statistical Analysis

Analyses were carried out using the SAS statistical package, version 8.1.[8] Chi-square or Fisher-exact tests were used to compare discrete parameters. To remove skewness, logarithms were applied to data when appropriate, although untransformed data are shown. Continuous variables (presented as means±SD) were compared by parametric (or nonparametric, when data remained skewed) univariate analysis of variance, and by multivariate analysis of variance, using general linear models (GLM procedure for SAS). Association between genotype and incidence of AF was measured by using hazard ratio (HR) obtained from multivariate regression analysis (PHREG procedure for SAS), including the recognized risk factors for postoperative AF: model a) age, gender, and history of dyslipidemia or hypertension or myocardial infarction; model b) age, gender, type of diseased coronary vessels, major complications; model c) age, gender, stay in hospital, and in intensive care unit. A full model including all the covariates was avoided because of the small number of events.

For each patient the area under the curve of C reactive protein, Interleukin-6 and fibrinogen at 24, 48, and 72 hours and at predischarge was calculated by using the Simpson method with the trapezium division areas: "[T*(Y24 hour/2)+Y48 hour+Y(72 hour)+Y (predischarge)/2)]" where "T" is the time value and "Y" is the examined parameter value of Interleukin-6, fibrinogen and C-Reactive protein.

For statistical analysis cases of postoperative sinus bradycardia and atrio-ventricular block were separated from atrial tachi-arrhythmias (flutter and fibrillation) and considered in the "*Without atrial arrhythmias*" group in the univariate and multivariate analysis.

Statistical significance was defined by a two-tailed $P<0.05$.

Results

The main pre- and intraoperative features of the 110 cases as a all and according to genotype are reported in Table 1; genetic analysis revealed GG genotype in 62 patients, GC in 38, and CC in 10, a distribution which did not differ significantly from that predicted by the Hardy-Weinberg equilibrium law ($P=0.29$). Allele frequencies were 0.73 (95% CI: 0.68 to 0.79) for G and 0.27 (95% CI: 0.21 to 0.32) for C.

The randomization to normothermia versus hypothermia result in equal distribution for the −174G/C polymorphism: the prevalence of the GG genotype was 28/62 and 25/48 ($P=0.35$), respectively, in the group with normothermia and hypothermia.

There were 2 in hospital deaths because of myocardial infarction and pulmonary embolism; 5 patients developed a postoperative myocardial infarction and 2 of them had to be reoperated for graft malfunction. No perioperative stroke occurred, 1 patient developed renal and 2 respiratory insufficiency. Mean stay in the intensive care unit was 2.0±2.7 days and mean in-hospital stay after surgery was 6.1±3.2 days.

Postoperative atrial tachi-arrhythmias developed in 26 of the 110 patients (23.6%); in 24 of these cases AF was the only documented rhythm, whereas atrial flutter interposed to periods of fibrillation was documented in one patient and atrial flutter alone in one other. The mean duration of the arrhythmia was 12 hours (range 2 to 70). In 23 cases therapy with amiodarone and digitalis was able to convert AF to normal sinus rhythm, in two patients pharmacological measures were ineffective and electrical cardioversion was necessary to regain sinus rhythm and in a single case the arrhythmia was refractory to both treatments and the patient was discharged to the rehabilitation facility in AF.

Of the considered pre-, intra-, and postoperative factors only hypertension and GG genotype of the Interleukin-6 promoter polymorphism were correlated with the development of postoperative atrial arrhythmias at univariate analysis (Table 2).

TABLE 1. Pre- and Intraoperative Characteristics of the Patients According to IL-6 Promoter Polymorphism

	All (N=110)	GG (N=62)	CG+CC (N=48)
Age (years)	61±8	61±9	61±8
Males	102	59	43
Current smokers	43	23	20
Hypercholesterolemia	28	15	13
Hypertension	69	39	30
Diabetes	23	13	10
Preoperative serum creatinine (mg/dL)	1.1±0.4	1.1±0.6	1.1±0.1
Previous myocardial infarction	57	31	26
Previous heart failure	5	4	1
Preoperative use of antiarrhythmic drugs	10	6	4
Diseased vessels			
3	80	46	34
2	20	10	10
≥1+left main	10	6	4
LVEF			
>0.50	81	45	36
0.30–0.50	29	17	12
Number of distal anastomoses			
2	21	10	11
3	55	32	23
4	29	16	13
5	5	4	1
Bypass conduits			
LIMA+GSV(s)	90	49	41
GSV(s)	16	10	6
LIMA+RIMA or LRA	4	3	1
CPB time (min)	74±20	76±21	71±18
Aortic clamp time (min)	61±17	64±17	58±18
Normothermic CPB	53	28	25

Statistical analysis revealed lack of difference between the GG and GC+CC groups for all the considered variables (CPB, cardiopulmonary bypass; LIMA, left internal mammary artery; LRA, left radial artery; LVEF, left ventricular ejection fraction; RIMA, right internal mammary artery; GSV, great saphenous vein).

TABLE 2. Pre- and Intra-operative Characteristics of the Patients According to Development of Post-operative Atrial Fibrillation

	Without AA (N=84)	With AA (N=26)
Age (years)	62±9	60±9
Males	77 (92%)	25 (96%)
Hypercholesterolemia	19 (23%)	9 (35%)
Hypertension	48 (57%)	21 (81%)*
Previous myocardial infarction	43 (53%)	14 (54%)
Diseased LAD	83 (99%)	25 (96%)
Diseased CX	75 (89%)	21 (81%)
Diseased RCA	75 (89%)	24 (92%)
Diseased LM	5 (5%)	5 (19%)
Target coronary vessels		
1) LAD+CX	20 (24%)	4 (15%)
2) LAD+RCA	14 (17%)	4 (15%)
3) LAD+CX+RCA	45 (55%)	17 (65%)
4) LAD+D/AL	1 (1%)	1 (4%)
5) Diag+CX/RCA	2 (2%)	0 (0%)
Any major complications	28 (33%)	7 (27%)
Mean intensive care unit stay (days)	2.4±4.2	1.6±1.1
Mean postoperative stay (days)	5.9±3.3	6.0±1.8
Mean CPB time (min)	74±21	75±18
Mean aortic clamp time (min)	61±18	63±15

*Fisher exact test: $P=0.037$.

AA, atrial arrhythmias; CPB, cardio-pulmonary bypass; CX, circumflex artery; Diag, diagonal branch; LAD, left anterior descending artery; RCA, right coronary artery; LM, left main).

The randomization to normothermia versus hypothermia result in equal incidence of postoperative atrial fibrillation (AF): the incidence of AF was 20% and 28% ($P=0.32$), respectively, in the group with normothermia and hypothermia

Multivariate analysis identified GG genotype as the only independent predictor of postoperative atrial arrhythmias, which occurred in 33.9% of GG patients versus 10.4% of no-GG patients (HR=3.25; 95% confidence interval: 1.23 to 8.62; Table 3). The HR remains practically the same in multivariate analyses including different types of covariates: model a) age, gender, and history of dyslipidemia or hypertension or myocardial infarction: (Likelihood Ratio=12.6, df=6, $P=0.0498$; c-statistic=0.75): HR=3.20 (1.20 to 8.55); model b) age, gender, type of diseased coronary vessels, major complications (Likelihood Ratio=12.2, df=13, $P=0.51$; c-statistic=0.75): HR=3.18 (1.16 to 8.75); model c) age, gender, stay in hospital, and in intensive care unit (Likelihood Ratio=7.7, df=5, $P=0.17$; c-statistic=0.68): HR=2.96 (1.09 to 8.06). Neither of the covariates showed statistical significant association with the incidence of atrial fibrillation. In addition, as it is expected from the results reported in the previous 2 steps, the inclusion of the variable "normothermia versus hypothermia" in all the multivariate analyses did not change the association between the −174G/C polymorphism and AF (data not shown).

The area under the curve of Interleukin-6 and fibrinogen was significantly higher in GG versus non-GG cases and in AF versus non-AF patients AF ($P<0.001$ for both; see Figures 1 and 2), whereas postoperative C-Reactive protein level did not significantly differ between cases with and without postoperative atrial arrhythmias ($P=0.11$).

TABLE 3. Incidence of Postoperative Atrial Fibrillation According to IL-6 Promoter Polymorphism

Genotype	Without AA (N=84)	With AA (N=26)	Hazard Ratio (95% CI)
non-GG (N=48)	43 (89.6%)	5 (10.4%)	Reference
GG (N=62)	41 (66.1%)	21 (33.9%)*	3.25 (1.23 to 8.62)

*Fisher exact test: $P=0.0060$.

AA, atrial arrhythmias.

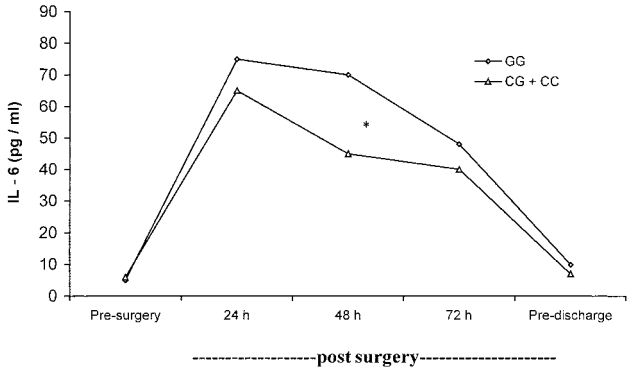

Figure 1. Plasma concentration of IL-6 according to genotype (*=$P<0.001$ for difference between areas under the curve).

Discussion

Postoperative AF is frequent after CABG procedures and represents one of the most common complications of surgical myocardial revascularization. The reported incidence of AF after CABG varies considerably in relation to the study methodology and statistical power, with a range as large as 5 to 70%;[9,10] however, basing on a meta-analysis of 24 controlled randomized trials an incidence of around 26% with a 95% CI of 24.7 to 29.1 can be estimated.[11]

The economic and clinical implications of postoperative AF are considerable. Clinically AF plays a major role in the determination of postoperative neurological events[1] and can be associated with hemodynamic deterioration. Even when AF does not lead to further clinical events, its occurrence lengthens the hospitalization of CABG patients of a mean of 4.9 days with an additional cost estimated at around US $10 000 per case in 1996.[2]

Although in the last 2 decades the pathophisiology of postoperative AF has been the object of intensive investigation, its exact determinants remain unclear.

What is certain is that the incidence in CABG patients by far exceeds the prevalence in the general population and in patients with nonoperated coronary artery disease or after noncardiac surgery procedures.[12,13]

Many pre- and postoperative factors have been suggested to increase the incidence of postoperative AF: age, gender, hypertension, withdrawal of β-blocker drugs therapy, right coronary artery stenosis, respiratory complications, need for intra-aortic balloon support, and excessive bleeding have all been associated with AF in published reports.[2,14–18] The large number and the heterogeneity of these factors is probably the best testimonial of the poor understanding of the mechanisms and pathophisiology of this arrhythmia.

Recently a large prospective randomized series demonstrated a significantly lower incidence of AF after off pump coronary artery surgery compared with traditional CABG,[19] suggesting the hypothesis that the use of the cardiopulmonary bypass and the consequent systemic inflammatory reaction[20] can play a major role in determining postoperative atrial arrhythmias (although this finding is still debated on the basis of the conflicting results reported by others studies).[21–23]

The observation of a link between postoperative complement activation and atrial arrhythmias in CABG patients[4] and the evidence derived from the analysis of atrial specimens from patients with isolated AF that atrial myocarditis can constitute the histological background of this arrhythmia,[3] led further support to an "inflammatory" theory of the pathophysiology of postoperative AF.

In our investigation the −174 C/G polymorphism of the promoter of the Interleukin-6 gene (one of the potential genetic modulators of the systemic inflammatory reaction to CPB) was significantly associated with postoperative Interleukin-6 levels and the development of AF and at multivariate analysis resulted the only independent predictor of postoperative atrial arrhythmias.

The evident correlation between the polymorphism of the promoter of the Interleukin-6 gene, the Interleukin-6 levels and the development of postoperative AF are strong arguments in favor of an inflammatory component of the development of atrial arrhythmias after cardiac surgery. The lack of association between postoperative AF and C-reactive protein is easily explainable on the basis of the different kinetic of this inflammatory protein after cardiac operations[24]

Recently Chew and associates have showed how the ϵ4 polymorphism of another gene known to be involved in the mediation of the inflammatory and tissue repair reactions (the gene for the Apolipoprotein E) is associated with postoperative renal dysfunction in cardiac surgery patients, suggesting for the first time the possibility of a genetic modulation of postoperative clinical outcome.[25] Our data lead further support to this theory showing that the postoperative inflammatory activation that follows cardiac surgery is genetically modulated by the −174 G/C polymorphism of the promoter of the Interleukin-6 gene and the magnitude of the inflammatory systemic reaction to CPB influence the development of postoperative complications and, in particular, of AF.

These results must be viewed in light of the limitations of our study. The present analysis is a post-hoc comparison of data collected in a prospective randomized investigation[6] and the relatively small number of patients enrolled can limit the statistical power of the study. The failure to identify as predictors of postoperative AF some variables that have been linked with this arrhythmia in other series can in fact be the expression of the reduced statistical power of our series. However, the fact that, despite the reduced power, we were able to clearly define a relationship between the Interleukin-6

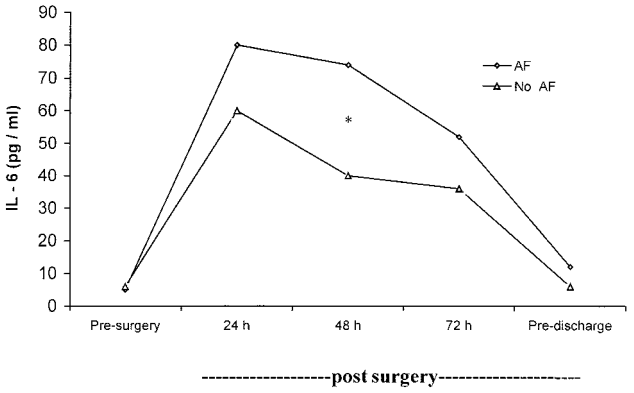

Figure 2. Plasma concentration of IL-6 in patients with and without atrial fibrillation (AF) (*=$P<0.001$ for difference between areas under the curve).

gene promoter polymorphism and the occurrence of postoperative AF can be viewed as the demonstration of the important role of this polymorphism in the determination of atrial arrhythmias after coronary artery surgery.

A further limit of our protocol lies in the fact that continuous telemetry was used only for the first 72 hours after surgery and from this time on patients were submitted to surface ECG every day and in case of clinical suspicion of arrhythmia. This methodology can have resulted in the missing of some episode of transient asymptomatic atrial arrhythmia. However, it seems unlikely that these episodes can have had a significant incidence in patients who did not developed persistent or symptomatic atrial arrhythmia during their all postoperative course (and that have been classified in the *"without atrial arrhythmias"* group in the univariate and multivariate analysis) and, thus, their confounding effect is likely to have been minimal.

In conclusion, our findings demonstrate a close relation between the −174G/C Interleukin-6 promoter gene variant, the inflammatory response to surgery and the development of postoperative AF. These data open new perspectives on a possible inflammatory determinant of postoperative AF after CABG and suggest a genetic modulation of the postoperative course and outcome after cardiac surgery.

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