Low Circulating Levels of Growth Differentiation Factor-15 Before Coronary Artery Bypass Surgery May Predict Postoperative Atrial Fibrillation

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Objectives: **To assess the role of growth differentiation factor-15 (GDF-15) as a potential new predictor of postoperative atrial fibrillation (POAF) after off-pump (OFP) and on-pump (ONP) coronary artery bypass graft (CABG) surgery.**

Design: **Prospective, single-center, observational study.**

Setting: **University teaching hospital.**

Participants: **The first 50 patients planned for OFP surgery and the first 50 patients planned for ONP surgery among patients referred for CABG with the following exclusion criteria: age <18 or >80 years, previous atrial fibrillation/flutter, previous treatment with amiodarone, previous cardiac surgery, and emergency surgery.**

Interventions: **Included patients were equipped with long-duration (7 days) Holter-ECG monitoring.**

Measurements and Main Results: **POAF was defined as an AF episode lasting >30 seconds. All patients underwent preoperative echocardiography to assess left ventricular ejection fraction and left atrial diameter. GDF-15 levels were assessed after induction of anesthesia and 12 hours after arrival at the intensive care unit. Among the 100 patients, 34 (34%) developed POAF. In Cox multivariate regression analysis, the EuroSCORE, left atrial diameter >45 mm, and low GDF-15 levels at induction were associated independently with the onset of POAF. In contrast, preoperative NT-proBNP levels did not predict POAF. The use of ONP surgery was not associated with a higher incidence of POAF, even though baseline and follow-up characteristics in ONP and OFP patients were identical.**

Conclusions: **In patients with no history of AF, a low plasma level of GDF-15 before CABG surgery was a strong independent predictor of POAF. Moreover, preoperative plasma GDF-15 levels added an incremental predictive value to classic risk factors of POAF.**

KEY WORDS: atrial fibrillation, biochemistry, coronary artery bypass grafts, cardiopulmonary bypass, off-pump surgery

POSTOPERATIVE ATRIAL FIBRILLATION (POAF) has a high prevalence, affecting 20% to 45% of CABG surgery patients within 7 days of the procedure.[1,2] POAF increases the duration of hospitalization and healthcare costs, and has been associated with an increased incidence of postoperative stroke, the need for a permanent pacemaker, and early and late mortality.[3]

Male sex, valvular heart disease, left atrial enlargement, obesity, previous cardiac surgery, chronic lung disease, discontinuation of beta-blockers or ACE inhibitors, AF history, pericarditis, and inflammation are predictive factors for POAF, but advanced age has the strongest and most consistent correlation.[3,4] The identification of these risk factors has led to modifications in several intraoperative practices.

Because there are many interconnected factors involved in the pathophysiology of POAF, it is difficult to identify the contribution of each to the resulting condition. Therefore, the huge release of inflammation markers triggered by CABG cardiac surgery may not fully explain the occurrence of POAF,[5] and there is still a critical need for preoperative clinical predictors.

Growth differentiation factor-15 (GDF-15) is a stress-responsive member of the transforming growth factor-β superfamily that originally was cloned as a macrophage-inhibitory cytokine.[6] Increased expression of this cytokine can be induced by myocardial stretch, left atrial pressure overload (11), and experimental cardiomyopathy as well as oxidative stress, inflammatory cytokines, and ischemia/reperfusion,[7] suggesting that the plasma levels of this cytokine are related not only to myocardial dysfunction but also to circulatory stress. This biomarker thus seems particularly relevant in the setting of cardiac surgery, in which almost all these mechanisms are involved.

A recent study has shown that preoperative plasma levels of GDF-15 were useful to improve the risk stratification of the EuroSCORE in 1,458 cardiac surgery patients and an independent predictive factor of postoperative mortality in these patients.[8] In a recently published study, the plasma GDF-15 level was associated with nonvalvular, nonpostoperative paroxysmal AF.[9]

In this observational study, the objective was to assess the role of GDF-15 as a potential new marker of POAF after off-pump (OFP) and on-pump (ONP) coronary artery bypass graft (CABG) surgery.

MATERIAL AND METHODS

Study Design

The independent ethics committee of the University Hospital of Dijon approved the study protocol, and written informed consent was obtained from the patients or their legal representatives. The study was designed as a prospective observational study. All investigations were conducted in accordance with the principles outlined in the Declaration of Helsinki.

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Dr. O. Bouchot and Dr. C. Guenancia contributed equally to this work. This work was supported by the University Hospital of Dijon and by grants from Conseil Régional de Bourgogne.

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1053-0770/2601-0001$36.00/0

http://dx.doi.org/10.1053/j.jvca.2015.01.023

Selection of Patients

All of the patients operated on by 2 surgeons for CABG surgery at the University Hospital of Dijon from September 2011 to March 2013 were screened for participation in this prospective, observational study. The exclusion criteria were age <18 years or >80 years, previous atrial fibrillation/flutter, previous treatment with amiodarone, previous cardiac surgery, and emergency surgery. This observational study was designed to recruit the first 50 patients planned for on-pump surgery and the first 50 patients planned for off-pump surgery among patients meeting the inclusion criteria. The surgical strategy (ONP *v* OFP) was decided by the medical and surgical team according to the anatomy of the coronary arteries.

Data Collection

Exhaustive clinical data were collected at admission, and the following variables were recorded: age, sex, cardiovascular risk factors, cardiovascular and pulmonary diseases, previous regular medication, and preoperative echocardiographic parameters. Medications administered during the hospital stay (but not the doses) were recorded. Previous renal failure was defined as preoperative estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 using the MDRD formula.[10]

Echocardiography

All of the patients underwent preoperative transthoracic echocardiography (TTE). The left ventricular ejection fraction (LVEF) was calculated using the Simpson method on the apical four-chamber and apical two-chamber views. LVEF was dichotomized at 45% for more clinical relevance. LA anteroposterior diameter was calculated in the parasternal long-axis view, using the M-mode technique, measuring from the trailing edge of the anterior LA wall to the leading edge of the posterior LA wall. For clinical relevance, LA diameter was dichotomized at 45 mm following classic cut-off values.[11]

Anesthesia and Heart Surgery Procedure

Patients were premedicated with midazolam orally plus hydroxyzine 90 minutes before anesthesia. Routine cardiac medications were continued until the morning of the surgery, except for clopidogrel, which was stopped at least 5 days earlier. Before the induction of anesthesia, a complete hemodynamic monitoring system was set up in the operating room. Anesthesia was induced with intravenous midazolam (0.02 mg/kg), sufentanil (0.2 to 0.5 mg/kg/h), and propofol (1.5 to 2.5 mg/kg). After verifying that manual ventilation was satisfactory, cisatracurium dibesylate (0.06 mg/kg/h) was injected. Patients were intubated orally and ventilated with F_IO_2: 0.4. Anesthesia was maintained with sufentanil and cisatracurium as required and inhaled desflurane.

Surgical Technique

Surgical management was standardized. After median sternotomy and graft harvesting (left and right internal mammary arteries $\pm$ saphenous graft), the patient received heparin (1.5 mg/kg in the off-pump group versus 3 mg/kg in the on-pump group).

On-pump surgery was performed according to the following protocol: aortic and cavoatrial cannulation, and cardiopulmonary bypass (CBP) was started. Myocardial protection was induced and maintained by warm blood anterograde cardioplegia. Normal body temperature (36°C) was used. Depending on the patients' grafts and characteristics of the target vessels, the right internal mammary artery or the saphenous vein and/or the left internal mammary artery (LIMA) were used for the grafts. All arterial grafts were treated with papaverine to avoid vasospasm. After completion of the CABG (from 1 to 6 CABGs in the patients studied), CPB was discontinued and protamine was given (1:1) for heparin reversal.

Off-pump surgery was performed according to the following protocol: cardiac stabilization and displacement was obtained using Cor vasc OPCAB (Coroneo, Montréal, Canada). Anastomoses were constructed using temporary occlusion, with thermoreversible LeGoo gel (SANOFI, Paris, France).[12] The LIMA was investigated primarily and anastomosed to the LAD. The right internal thoracic artery was used pediculised or with the Y graft technique on the LIMA and the distal part was anastomosed to the ramus intermedius.

After closure of the sternum, the patients were transferred to the postoperative intensive care unit (ICU) and, finally, to the surgery ward.

Diagnosis of POAF

All patients underwent Holter ECG monitoring (Spider Flash, Sorin Group France) started immediately after inclusion. The Holter ECG device was programmed to record every arrhythmic event for 7 days. The device was consistent with routine use in the ICU, because only 3 electrodes were required, thus providing a 2-lead recording, and was easily removable if necessary for patient care or to perform imaging exams. The Holter ECG monitor was removed after 7 days of recording, or at death (whichever occurred first). An experienced cardiologist who was blinded to the patient's clinical data analyzed the Holter ECG recordings. If the diagnosis was uncertain, a second cardiologist, blinded to the first results, also analyzed the tracings. No cases of discordance between the 2 analyses occurred.

AF was diagnosed according to the guidelines of the European Society of Cardiology for the interpretation of Holter ECG recordings (ie, any arrhythmia that presents the ECG characteristics of AF; namely, "the surface ECG shows 'absolutely' irregular RR intervals, there are no distinct P waves on the surface ECG, and the atrial cycle length [when visible], ie, the interval between 2 atrial activations, is usually variable and <200 ms [>300 bpm]") and lasting at least 30 seconds on a rhythm strip, should be considered AF.[9] Silent AF was defined as the occurrence of AF on the Holter ECG recording, regardless of the duration or number of episodes, and in the absence of any mention of AF in the medical file during the first 7 days of the hospital stay (ie, AF not diagnosed by the ICU physicians). In contrast, symptomatic AF was defined as any AF diagnosed by a physician during the hospital stay.

When AF was diagnosed on the Holter ECG recording, the following data were collected: date and time of the first