Postoperative Atrial Fibrillation Is Associated with High On-Aspirin Platelet Reactivity

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Background. **Atrial fibrillation (AF) contributes to a prothrombotic state through platelet activation. It is unclear whether increased platelet aggregability in patients with AF is caused by the underlying cardiovascular condition rather than the arrhythmia per se. We investigated the effect of postoperative atrial fibrillation (POAF) on platelet reactivity after coronary artery bypass grafting (CABG).**

Methods. **This study is a post hoc analysis from a randomized controlled trial (ClinicalTrials.gov: NCT01159639) based on patients undergoing elective primary CABG. Patients were dichotomized according to POAF. Postoperative platelet function testing with arachidonic acid as the platelet agonist (ASPI test) was used to define high on-aspirin platelet reactivity (HAPR). ΔASPI presented the difference between pre- and postoperative ASPI test values. To account for the isolated effect of POAF on platelet reactivity, a propensity score analysis was applied.**

Results. **Overall incidence of POAF was 23% (92 of 398 patients). HAPR was detected in 54% (214 of 398) of patients. HAPR was more prevalent among patients with POAF when compared with patients without POAF (64.1% versus 50.7%; odds ratio [OR], 1.74; 95% confidence interval [CI], 1.08–2.82; $p = 0.023$). The propensity score model produced a subcohort of patients that was well balanced for comorbidities. When compared with the matched group without POAF, the POAF group maintained its prevalence for HAPR (64.1% versus 45.7%; OR, 2.13; 95% CI, 1.18–3.85; $p = 0.012$) and had greater ΔASPI values (15.0 [IQR, 0.0–36.0] vs 8.0 [IQR, −5.5–19.5]; $p = 0.030$).**

Conclusions. **The main finding of our study indicates there is added platelet activation in patients with POAF after CABG before and after controlling for pathologic conditions through propensity matching. The present study does not prove a causal association between POAF and HAPR.**

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Despite all the prophylactic measures, postoperative atrial fibrillation (POAF) still occurs in about 15% to 30% of patients who undergo coronary artery bypass grafting (CABG) [1–4]. It is associated with increased risk-adjusted mortality, hospital costs, and readmission rates [4] as well as late mortality [1, 2]. Proper and timely treatment may reduce the risk of stroke and mortality associated with POAF.

There is a strong correlation between atrial fibrillation (AF) and thromboembolic sequelae. The precise mechanism behind the increased thromboembolic risk has not been fully elucidated. Abnormalities in cardiac blood flow combined with endothelial disturbances are partly responsible for the hypercoagulable state in AF. Other possible mechanisms that have been proposed include inflammatory response reaction [5] and neuroendocrine activation [6]. Increased expression of platelet activation markers has been shown to be associated with AF [7, 8].

There is excess platelet activation in patients with AF compared with healthy controls [7], although no significant difference in sinus rhythm between patients with AF and controls has been established [7]. What remains unclear is whether the underlying AF-associated cardiovascular conditions, rather than the arrhythmia per se, cause the platelet activation noted in those patients. The aim of the present study was to determine whether an increase in platelet reactivity might be associated with AF after CABG. We hypothesized that an increase of on-aspirin platelet reactivity in patients with new-onset POAF is associated with the arrhythmia per se, regardless of the cardiovascular conditions associated with AF. Data available from a randomized study (NCT01159639) were used for this post hoc analysis. Although patients who formed the basis for this analysis did have underlying AF-associated cardiovascular conditions, pathologic conditions were controlled for through propensity matching to explain the additional effect of the

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ADP = adenosine diphosphate
AF = atrial fibrillation
ASPI = arachidonic acid-induced
AUC = area under the curve
CABG = coronary artery bypass grafting
CI = confidence interval
HAPR = high on-aspirin platelet reactivity
IQR = interquartile range
MACCE = major adverse cardiac and cardiovascular events
OR = odds ratio
PFT = platelet function testing
POAF = postoperative atrial fibrillation
POD = postoperative day
Δ = delta

arrhythmia. The disease control group was formed of individuals without POAF from the matched patient subcohort.

Patients and Methods

The present study is a post hoc analysis from a randomized controlled trial (NCT01159639). It is a retrospective analysis of prospectively collected data from a single-center randomized trial. Details of the study design, eligibility, and exclusion criteria have been published previously [9]. Briefly, adult patients scheduled to undergo elective primary CABG were eligible for the randomized study. On postoperative day (POD) 4, patients underwent platelet function testing (PFT). Patients found to have high on-aspirin platelet reactivity (HAPR) on POD4 were randomized to either 75 mg of clopidogrel and 300 mg of aspirin or 300 mg of aspirin. Patients who had adequate platelet reactivity (no HAPR) were excluded from the randomized analysis but were included in the follow-up. Results comparing the incidence of major adverse cardiac and cerebrovascular events (MACCE) at 6 months have already been published [10]. An exploratory analysis from the randomized trial showing 6-month MACCE outcomes comparing patients with no HAPR to patients with HAPR who were receiving aspirin only have been published more recently [11]. For the purpose of this analysis, both patients with HAPR and those without HAPR were included and dichotomized to either the POAF group or the no POAF group.

Patients

All patients were treated with equal antiplatelet therapy during the first 4 days after operation (aspirin 300 mg/d). The only additional exclusion criterion in this analysis not accounted for in the original randomized trial is a history of previous AF. A flowchart of the study is shown in Fig 1. The POAF status in this analysis represents all patients who had a recorded episode of AF lasting for 10 minutes or more. Most of these patients were converted to sinus rhythm with medication. The POAF status was established regardless of medical or spontaneous conversion.

Perioperative Management

Perioperative management as previously described [9] consisted of our standard hospital protocol for patients undergoing elective CABG. Preoperative antiplatelet therapy, 100 mg of aspirin, was continued up to the day of operation. Clopidogrel in the preoperative period was discontinued 4 to 5 days before the procedure. Patients receiving preoperative β-blockers were given their normal dose on the morning of the operation. Angiotensin-converting enzyme (ACE) inhibitors were discontinued on the day of admission, usually 2 days before the procedure. The anesthetic, intraoperative, and early postoperative protocols were described in the randomized trial [9].

Detection, Prophylaxis, and Management of AF

Patients were continuously monitored with telemetry (Nihon Kohden WEP-4208; Nihon Kohden, Tokyo, Japan) until POD5. Routine initiation of β-blocker therapy started on POD1 or once inotropic support had been suspended, with daily dosing escalation. Postoperative medication typically included a β-blocker, a hydroxymethylglutaryl-CoA reductase inhibitor, a proton pump inhibitor for peptic ulcer prophylaxis, and a diuretic agent. An ACE inhibitor usually was not instituted before discharge. Atypical opioid analgesics (eg, tramadol) were used for pain relief. Nonsteroidal antiinflammatory drugs were generally not administered in the early postoperative period. Magnesium and potassium supplements were administered to maintain high-normal levels. POAF was treated with amiodarone.

Platelet Function Testing

Blood samples for PFT were obtained using venipuncture on the morning before the operation (POD0) and on POD4. Blood was collected in 4-mL heparin-coated (lithium heparin 68 IU) plastic tubes. The test was performed 30 minutes after blood sampling. Multiple electrode aggregometry (Multiplate analyzer; Roche Diagnostics Int, Ltd, Mannheim, Germany) was used. Platelet aggregation, as evaluated by multiple-electrode aggregometry, accounts for the variability in sensor wire impedances [12]. Increase in impedance is expressed in arbitrary area under the curve (AUC) units. Arachidonic acid (0.5 mM) and adenosine diphosphate (ADP, 6.4 μM) were used as platelet agonists for conducting the ASPI and ADP tests, respectively. The blood samples were incubated for 3 minutes, and platelet aggregation was measured 6 minutes after stimulation with a platelet agonist. The ASPI test evaluates cyclooxygenase-1–dependent platelet aggregation in response to aspirin. The cutoff point for HAPR of patients receiving aspirin was defined as an ASPI test value exceeding 30 AUC [13]. This definition was verified using data from another source [14]. Change in PFT measurements for each patient is presented as delta (Δ); ΔASPI = ASPI POD4 – ASPI POD0 and ΔADP = ADP POD4 – ADP POD0. The phenomenon of "aspirin resistance," a term