

# Can perioperative C-reactive protein and interleukin-6 levels predict atrial fibrillation after coronary artery bypass surgery?

Shervin Ziabakhsh-Tabari, MD, FCTS.

## ABSTRACT

**الأهداف:** لفحص العلاقة بين السيتوكينات المحفزة للإلتهاب مثل الانترلوكتين6 (IL6) والبروتين التفاعلي (CRP)، وعلاقتها بالارتجاج الأذيني (AF) بعد تركيب مجازة الشريان التاجي (CABG).

**الطريقة:** شملت الدراسة 54 مريضاً يعانون من أمراض في الشريان التاجي، تعرضوا لعملية اختيارية تم فيها تركيب مجازة للشريان التاجي (CABG)، بمستشفى جامعة مازانداران - إيران، وتم إدراجهم في دراستنا هذه في عام 2007م. تمت مراقبة معدل ضربات القلب والإيقاع باستمرار بعد العملية الجراحية لمدة خمسة أيام. كما تم الحصول على عينات فحص سكر الصيام من جميع المرضى من أجل فحص البروتين التفاعلي (CRP) والانترلوكتين6 (IL6) في اليوم قبل العملية واليوم الثاني بعد العملية في وحدة العناية المركزة.

**النتائج:** من بين 54 مريضاً، 11 مريضاً (20.4%) أصيبوا بالارتجاج الأذيني (AF) بعد عملية تركيب المجازة (CSBG). بلغ متوسط العمر للمرضى الذين يعانون من الارتجاج الأذيني (51.45±10.74)، بالمقارنة مع المرضى الذين لديهم إيقاع الجيب (57.28±9.04) ( $p=0.072$ ). وقت شلل القلب، ووقت التعليق، ووقت الضخ كان أعلى لدى المجموعة المصابة بالارتجاج الأذيني (AF)، ولكن لم يكن هنالك اختلافاً ملحوظاً بين المجموعتين. كانت مستويات البروتين التفاعلي (CRP) والانترلوكتين6 (IL6) أعلى لدى المرضى الذين يعانون من الارتجاج الأذيني (AF). ارتفعت مستويات البروتين التفاعلي (CRP) والانترلوكتين6 (IL6) بعد إجراء عملية تركيب مجازة للشريان التاجي (CABG) لدى جميع المرضى ولكنها ازدادت لدى مجموعة الارتجاج الأذيني (AF).

**خاتمة:** كان هنالك علاقة ملحوظة بين الانترلوكتين6 (IL6) قبل العملية والارتجاج الأذيني (AF)، ولكن لم تكن هنالك علاقة بين البروتين التفاعلي (CRP) والارتجاج الأذيني (AF). بناء عليه، قد تساعد المعالجة بالجلوكوكورتيكويز على خفض مستويات الانترلوكتين6 (IL6) بشكل ملحوظ، وبالتالي قد يساهم في خفض احتمالات حدوث الارتجاج الأذيني (AF) بعد عملية تركيب مجازة الشريان التاجي (CSBG).

**Objectives:** To examine the relationship between proinflammatory cytokines, such as interleukin-6 (IL-6) and C-reactive protein (CRP) and atrial fibrillation after (on-pump coronary artery bypass grafting (CABG).

**Methods:** Fifty-four patients with coronary artery disease undergoing elective CABG at the Mazandaran

Medical University, Mazandaran, Iran were enrolled in our prospective study in the year 2007. Postoperatively, heart rate and rhythm were continuously monitored for 5 days. Fasting blood samples were taken from all patients to examine quantities of CRP and IL6 the day before surgery and on the second postoperative day in the intensive care unit.

**Results:** From 54 patients, 11 patients (20.4%) developed atrial fibrillation (AF) after CABG. The median age of patients with AF was 51.45 ± 10.74 compared with 57.28 ± 9.04 for patients with sinus rhythm ( $p=0.072$ ). Cardioplegic time, cross clamp time, and pump time were higher in the AF group, but there was no significant difference between the 2 groups. Preoperative CRP and IL6 levels were higher in patients with AF. The CRP and IL6 increased after CABG in all patients, but it increased more in the AF group.

**Conclusion:** There was a significant relationship between preoperative IL6 and AF in patients who underwent on-pump CABG, but there was no relationship between CRP and AF. Therefore, administration of glucocorticoids, which significantly reduce plasma levels of IL6 can reduce the incidence of AF after on-pump CABG.

*Saudi Med J 2008; Vol. 29 (10): 1429-1431*

*From the Department of Cardiac Surgery, Fatemeh Zahra Hospital of Sari, University of Medical Sciences, Mazandaran, Iran.*

*Received 7th April 2008. Accepted 1st July 2008.*

*Address correspondence and reprint request to: Dr. Shervin Ziabakhsh-Tabari, Assistant Professor of Cardiac Surgery, Fatemeh Zahra Hospital of Sari, University of Medical Sciences, Mazandaran, Iran. Tel. +98 (151) 2200480. E-mail: Shervin\_Zia@yahoo.com*

Atrial fibrillation (AF) is the most frequent arrhythmic complication after coronary artery bypass grafting (CABG) that occurs in 10-65% of these patients, depending on patients profile, type of surgery, method of arrhythmia surveillance, and definition of arrhythmia.<sup>1,2</sup> Although it is usually a self limiting arrhythmia, it has been associated with prolonged hospital stay, postoperative stroke, congestive heart failure and increased mortality, often resulting in limited quality of life.<sup>3-5</sup> Although several risk factors for postoperative AF have been elucidated, the mechanism by which AF develops is not completely understood.<sup>3</sup> Anderson et al<sup>6</sup> showed that C-reactive protein (CRP), an inflammatory marker, is associated with occurrence of AF.<sup>6</sup> Gaudino et al<sup>7</sup> demonstrated the interleukin-6 (IL6) gene polymorphism influences the occurrence of AF after CABG. It has been suggested that inflammation participates in the pathogenesis of postoperative AF in patients with CABG. In this study, we examined the relationship between proinflammatory cytokines, such as IL-6 and CRP, and AF after on-pump CABG.

**Methods:** Fifty-four patients with coronary artery disease undergoing elective CABG at Fatemeh Zahra Hospital, Mazandaran, Iran, in 2007, were enrolled in our prospective study. The institutional ethics committee approved the study, and written informed consent was obtained from all cases. All patients were in normal sinus rhythm at the time they underwent surgery. None of the patients had preoperative AF or recent infection, as documented by the lack of fever and positive blood or tissue culture, renal or hepatic failure, malignancy, collagen, or acute immune disease, and recent surgery. No patients were received corticosteroid before, during, or after surgery. All patients underwent surgery with the same surgeon and same method (on-pump CABG). Postoperatively, heart rate and rhythm were continuously monitored for 5 days. Atrial fibrillation was defined as an irregular narrow complex between 100 and 160 bpm and presence of F-wave on the electrocardiogram and the confirmatory diagnosis of AF by the cardiologist. Patients with AF were treated with amiodarone after correction of electrolyte and acid-base imbalance. Fasting blood samples were taken from all patients to examine quantities of CRP and IL6 the day before surgery and the second postoperative day in the intensive care unit. High sensitivity CRP was measured by nephelometry method and IL6 by enzyme linked immunosorbent assay (ELISA). The CRP levels were divided in 2 groups (normal and abnormal) with a cut off point of 3.8 mg/L, and IL6 with level of 4.5 mg/L. Other variables assessed included age, gender, history of documented diabetes (fasting blood sugar  $\geq 126$  or randomized blood sugar  $>200$ ) or use

of anti diabetic agents, hypertension (systolic blood pressure [BP]  $\geq 140$  mm Hg and diastolic BP  $\geq 90$  mm Hg) or use of anti hypertensive drugs, hyperlipidemia, occurrence of myocardial infarction in the previous 6 months, family history of early coronary artery disease (history of cardiovascular death, myocardial infarction, coronary revascularization at  $<65$  years old in first-degree relatives), and some variables on operation, such as cross-clamp time, use of balloon pump, intubation time, and drain remaining time.

Baseline information is summarized as mean  $\pm$  SD for continuous variables and as frequencies for discrete variables. Comparison between groups was performed by T-test for continuous variables and with chi-square test for discrete variables (multivariable logistic regression were carried out for independent predictive variables of postoperative AF). A  $p < 0.05$  was statically significant. All analysis was carried out with SPSS Microsoft.

**Results.** From 54 patients, 24 (44.4%) were women, 11 (20.4%) had a history of smoking, 14 (25.9%) had hypertension, 7 (13%) had previous MI, 14 (25.9%) had diabetes mellitus. Eleven patients (20.4%) developed AF after CABG. The median age of patients with AF was  $51.45 \pm 10.74$  compared with  $57.28 \pm 9.04$  for patients with sinus rhythm ( $p=0.072$ ). Patients in the AF group were more likely to be female. There were no significant differences in cholesterol, age, low-density lipoprotein, high-density lipoprotein, smoking, hypertension, diabetes mellitus and prior myocardial infarction between the 2 groups. Cardioplegic time, cross clamp time, and pump time were higher in the AF group, but there were no significant differences between the 2 groups. Preoperative CRP and IL6 levels were higher in patients with AF. There was a statically significant relationship between the preoperative IL6 and postoperative AF ( $3.95 \pm 1.02$  versus  $1.24 \pm 0.8$ ,  $p=0.02$ ), but there was not between preoperative CRP and postoperative AF ( $10.42 \pm 9.58$  versus  $8.4 \pm 4.9$ ,  $p=0.12$ ). The CRP and IL6 increased after CABG in all patients, but it increased more in the AF group. There was a significant relationship between preoperative IL6 and AF ( $65.4 \pm 21.01$  versus  $38.2 \pm 32$ ,  $p=0.004$ ), but there was not between CRP and postoperative AF ( $68.24 \pm 34.11$  versus  $60.6 \pm 44.62$ ,  $p=0.23$ ). There was no relationship between pre and postoperative levels of CRP and IL6.

**Discussion.** This study examined the relationship between pre and postoperative levels of CRP and IL6, and AF. Agreeing with other studies<sup>5</sup> that reported the incidence of AF after CABG as 10-65%, our incidence of AF was 20.4%. Agreeing with the previous results,<sup>3</sup>

we had no significant difference in CRP levels between the groups, although CRP levels were higher in the AF group. Agreeing with other literature,<sup>7</sup> the IL6 level elevated after surgery and was higher in patients with postoperative AF. It remains unclear why CRP and IL6 levels are elevated in AF. The role of inflammation in the pathogenesis of AF has not been clearly defined. Histological changes, such as inflammatory infiltrates, myocyte necrosis, and fibrosis has been reported in the atrial biopsy specimens of patients with AF.<sup>7</sup> The CRP and IL6 in AF might not only mark atrial inflammation, but also play an active role in pathophysiology. Conversely, they might be a consequence rather than a cause of AF-related pathophysiology. Studies<sup>3</sup> showed that administration of glucocorticoids, which significantly reduce plasma levels of IL6, could reduce the incidence of AF after on-pump CABG. In this study, we did not find any correlation between CRP and IL6 levels, which might have been caused by a difference in rate of clearance. A longitudinal study is necessary to confirm our hypothesis that inflammation has a role in development of AF. If so, new therapeutic strategies, such as anti-inflammatory drugs may be effective for prevention and treatment of AF.

## References

1. Ishida K, Kimura F, Imamaki M, Ishida A, Shimura H, Kohno H, et al. Relations of inflammatory cytokines to atrial fibrillation after off-pump coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2006; 29: 501-505.
2. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998; 82: 2-9.
3. Conway DS, Buggins P, Hughes E, Lip GY. Prognostic significance of raised plasma levels of interleukin-6 and C-reactive protein in atrial fibrillation. *Am Heart J* 2004; 148: 462-466.
4. Watanabe E, Arakawa T, Uchiyama T, Kodama I, Hishida H. High-sensitivity C-reactive protein is predictive of successful cardioversion for atrial fibrillation and maintenance of sinus rhythm after conversion. *Int J Cardiol* 2006; 108: 346-353.
5. Lauer MS, Eagle KA, Buckley MJ, DeSanctis RW. Atrial fibrillation following coronary artery bypass surgery. *Prog Cardiovasc Dis* 1989; 31: 367-378.
6. Anderson JL, Allen Maycock CA, Lappé DL, Crandall BG, Horne BD, Bair TL, et al. Frequency of elevation of C-reactive protein in atrial fibrillation. *Am J Cardiol* 2004; 94: 1255-1259.
7. Gaudino M, Andreotti F, Zamparelli R, Di Castelnuovo A, Nasso G, Burzotta F, et al. The -174G/C interleukin-6 polymorphism influences postoperative interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? *Circulation* 2003; 108 (Suppl 1): 195-199.

## Ethical Consent

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.