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Off-pump Coronary Artery Bypass Does Not Influence Biomarkers of Brain Injury, But Does Exacerbate the Systemic Inflammatory Response

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Abstract

Background: The protective effects of off-pump (OPCAB) compared to conventional (CCAB) coronary artery bypass graft surgery on neurological injury and inflammation has been controversial. We evaluated pre- and post-operative levels of the brain injury marker, S100β, and markers of inflammation, Interleukin-6 (IL-6) and high sensitivity C-reactive protein (hs-CRP) in a prospective randomized controlled trial.

Methods: A sub-group sample of the randomized controlled trial of 50 consecutive randomized patients (n=27 CCAB, n=23 OPCAB) was utilized for the present biomarker analysis. Each patient had blood drawn before and after surgery. Analysis of variance and Kruskal-Wallis were used to assess significant differences in biomarkers.

Results: There was no difference in post-procedure S100β (p=0.1) or change in S100β from baseline (p=0.9). Hs-CRP and IL-6 were higher in the OPCAB arm post-procedure (P_{CRP}=0.001; P_{IL-6}=0.053) and change from baseline (P_{CRP}=0.003; P_{IL-6}=0.001).

Conclusion: OPCAB did not result in preventing neurological injury over CCAB; however, OPCAB had significantly more inflammation than CCAB following the procedure.

Keywords: Cardiopulmonary bypass (CPB); Biomarkers; On-pump; Off-pump; CABG surgery; Neurocognitive deficits

Abbreviations: OPCAB: off-pump; CCABG: Conventional Coronary Artery Bypass Graft Surgery; IL-6: Interleukin-6; hs-CRP: High Sensitivity C-Reactive Protein

Introduction

Coronary artery bypass grafting (CABG) is one of the most intensely studied of all surgical procedures. Since 1987 when the predecessor to the Centers for Medicare and Medicaid (Healthcare Financing Administration) published surgical mortality rates to the public, surgeons have made great inroads in improving both processes of care as well as clinical outcomes [1]. One such development has been the use of off-pump (OPCAB) relative to the more common "conventional" CABG procedure utilizing a cardiopulmonary bypass circuit.

As mortality rates for CABG have precipitously dropped to near 2%, greater attention has been paid to more subtle yet still important injuries, such as the systemic inflammatory response (SIRS) as well as neurologic injury [2,3]. Great interest has been paid to the use of serum biomarkers as a mechanism for detecting both SIRS as well as neurologic injury. By leveraging the innate properties of individual biomarkers, investigators may identify acute injuries in the setting of CABG that otherwise might not be revealed by otherwise evaluating traditional clinical outcomes.

We sought to assess the impact of OPCAB, relative to its CCAB counterpart, in terms of both SIRS as well as neurologic injury, in the setting of a randomized trial. By doing so, we hope to shed light on the impact of different surgical revascularization strategies on subtle yet important clinical areas.

Materials and Methods

Method of conducting CCAB and OPCAB

Methods for conducting the randomized controlled trial study have been previously reported [4]. Non-emergent patients between the ages of 40-89 years undergoing first-time isolated CABG were candidates for this trial. Patients found to have a heavily diseased aorta, deep intra-myocardial left anterior descending artery, pre-operative inotropic support or intra-aortic balloon pump were not eligible for randomization. In total, 102 patients were randomized to CCAB, and 99 to OPCAB between January 2001 and January 2004.

The Genzyme OPCAB Elite (Genzime Surgical, Fall River, MA) or Medtronic Octopus system (Medtronic, Minneapolis, MN) was used to stabilize the target vessels for patients undergoing OPCAB. During the trial time period, cell salvage of blood was not conducted.

Data collection

A sub-group sample of the original randomized controlled trial of 50 patients (n=27 CCAB, n=23 OPCAB) was utilized for the present biomarker analysis, which consisted of the last 50 consecutive patients. Each patient had blood drawn before and within 48 hours after surgery. The decision to draw samples was determined once the study was already underway, and was dependent on adequate funding being ascertained.

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Biomarker analysis

These tubes were stored at -80°C until the end of the trial and then transported on dry ice to the Laboratory for Clinical and Biochemical Research in Colchester, VT for biomarker measurement. Samples were thawed once for measurement. Serum levels of S100β were measured by ELIZA using the two-site immunoassays by Sangtec 100 ELISA from DiaSorin AB (Bromma, Sweden). IL-6 and C-reactive protein were measured using the BNII nephelometer from Dade Behring (Deerfield, IL) utilizing a particle enhanced immunonepholometric assay.

Table 1: Patient and Disease Characteristics.

	CCAB	OPCAB	p-value*
Number of procedures by group	27	23	
Patient age, years (%)			
<60	40.7	30.4	0.45
60-69	37.0	39.1	0.88
70-79	22.2	30.4	0.51
Female (%)	7.4	17.4	0.28
Body mass index (%)			
<31	66.7	69.6	0.83
31-36 (obese)	29.6	26.1	0.78
37+ (severely obese)	3.7	4.4	0.91
Estimated IQ			
WRAT-3 Reading	-0.3±0.8	-0.5±0.9	0.46
Patient Comorbidities			
Vascular Disease (%)	14.8	17.4	0.80
Diabetes (%)	25.9	43.5	0.19
Preoperative renal failure or creatinine ≥2 (%)	3.7	0.0	0.54
COPD (%)	7.4	4.4	0.65
Cardiac History, Function, and Anatomy			
Ejection Fraction (%)			
<40	7.7	0.0	0.58
40-49	7.7	4.8	
50-59	23.1	23.8	
≥60	61.5	71.4	
Number of diseased vessels			
2	40.7	30.4	0.45
3	48.2	60.9	0.37
Coronary artery stenosis (%)			
Left main ≥50%	14.8	17.4	0.80
LAD ≥70%	74.1	91.3	0.11
RCA ≥70%	77.8	69.6	0.51
CX ≥70%	66.7	78.3	0.36
PDA ≥70%	3.7	0.0	0.54
Procedural Data			
Urgent (%)	63.0	56.5	0.64
Number of distal anastomoses	3.4±1.0	3.3±0.9	0.75
Number of distals/number diseased vessels	1.5±0.6	1.4±0.4	0.99
IMA Used (%)	100.0	95.7	0.99
Cross-overs (n)	0	2	

*p for chi-square test, Wlcoxon rank-sum test and t-test.
Percents or mean±standard deviation
CCAB: conventional coronary artery bypass, OPCAB: off-pump coronary artery bypass; WRAT=3: Wide Range Achievement Test, 3rd Edition; COPD: chronic obstructive pulmonary disease; CX: left circumflex coronary artery; LAD: left anterior descending coronary artery; PDA: posterior descending coronary artery; RCA: right coronary artery; IMA: internal mammary artery

Statistical analysis

All analyses were performed using the STATA 9.0 program (Stata Corporation, College Station, TX). Significant differences in all biomarkers were tested with analysis of variance and Kruskal-Wallis.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written. This study was approved by the Institutional Review Board of Eastern Maine Medical Center and written informed consent was obtained from all participants.

Results

Table 1 displays patient and disease characteristics for the 50 patients represented in the study. Almost twenty-six percent of the CCAB and forty-three percent of the OPCAB patient's suffered from diabetes. Forty-eight percent and sixty percent of the CCAB and OPCAB patients respectively had three-vessel disease. The mean age of patients across the study was comparable.

Median S100β levels were significantly lower among OPCAB [0.06 (IQR: 0.08-0.12)] vs. CCAB [0.12 (IQR: 0.09-0.16], p=0.01. Median post-operative values did not differ between the groups: OPCAB [0.21 (IQR: 0.18-0.35)], p=0.1 vs. CCAB [0.26 (IQR: 0.20-0.49)], Figure 1. The groups had similar computed median changes between the pre versus post-operative setting: OPCAB [0.16 (IQR: 0.13-0.23)] and CCAB [0.15 (IQR: 0.04-0.37)], p=0.9.

There was no significant difference in median Hs-CRP levels at baseline: OPCAB [3.58 (IQR: 1.83- 6.50)] vs. CCAB [4.33 (IQR: 1.06-10.7)], p=0.09, Figure 2). Patients undergoing OPCAB had significantly higher median post-operative Hs-CRP levels: OPCAB [123 (IQR: 79-173)] vs. CCAB [43 (IQR: 28-95)], p=0.001. Patients undergoing OPCAB had higher computed median changes between the pre versus post-operative setting: OPCAB [115 (IQR: 76-165)] vs. CCAB [35 (IQR: 20-87)], p=0.003.

Median IL-6 concentrations were similar at baseline: OPCAB [4.62 (IQR: 3.01- 6.09)] vs. CCAB [5.27 (IQR: 2.82-20.08], p=0.7, Figure 3). Patients undergoing OPCAB had median post-operative IL=6 concentrations: OPCAB [121 (IQR: 67-123)] vs. CCAB [60 (IQR: 41-123], p=0.053. Patients undergoing OPCAB had higher computed median changes between the pre versus post-operative setting: OPCAB [114 (IQR: 70-118)] vs.CCAB [49 (IQR: 30-86], p=0.001).

There were no deaths at the time of discharge for patients undergoing either OPCAB or CCAB. In addition, no patient developed a cerebral vascular accident. Two CCAB patients developed low cardiac output failure and one OPCAB patient returned to the operating room for bleeding.

Discussion

We report on the peri-operative changes in inflammatory and neurological biomarkers in the setting of a randomized controlled trial of on- versus off-pump CABG surgery. We found no difference in the neurological marker, S100β between the on- and off-pump randomized arms. However, we did identify statistically significant differences in changes in both inflammatory markers, IL-6 and hs-CRP.

We conducted a single-center single-blinded randomized controlled trial of 201 patients randomized to CCAB or OPCAB

[4]. During the last quarter of the trial (N=50) baseline and 24-hour post-operative serum samples were obtained from each patient and analyzed for inflammatory and neurological markers. One limitation of this study is that the biomarker cohort of the SCARECROW trial represents one quarter of the trial, however we found no difference in patient and disease characteristics between the first three quarters of the trial the later biomarker cohort. All patients in the biomarker cohort were consecutively enrolled and therefore should not bias our patient selection. Second, our findings stem from a single-blinded study; while the patient and laboratory was blinded to the treatment, it was impossible to blind the surgeon or surgical team to the treatment allocation. Nonetheless, the surgical protocols were adhered to, and thus it is unlikely that surgical practice altered the biomarker findings.

Biomarkers of cerebral damage

Investigators have explored the use of biomarkers for detecting new brain injuries [5]. This work has been complicated by extracerebral sources of these markers as well as limitations in the diagnostic properties of the assays [6]. Nonetheless, great interest remains in utilizing these markers as a means for both assessing acute injuries, as well as linking processes of care with an intermediate endpoint (i.e. the levels of a biomarker) [5,7,8].

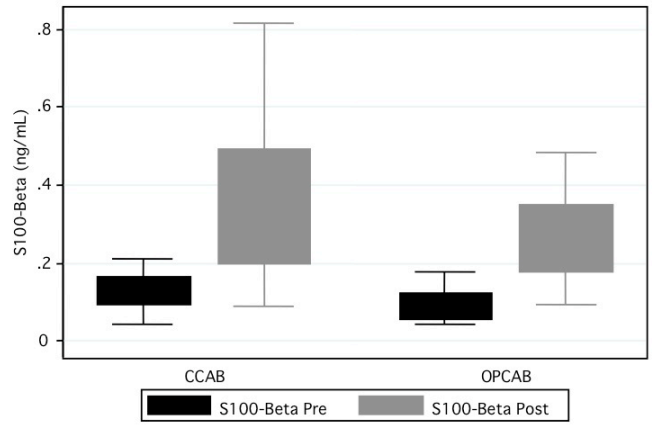

Figure 1: Box plot for pre- (black) and post-operative (gray) S-100B levels stratified by CCAB (left) and OPCAB (right). There was no difference in post-procedure S-100B (p=0.1) or change in S-100B from baseline (p=0.9).

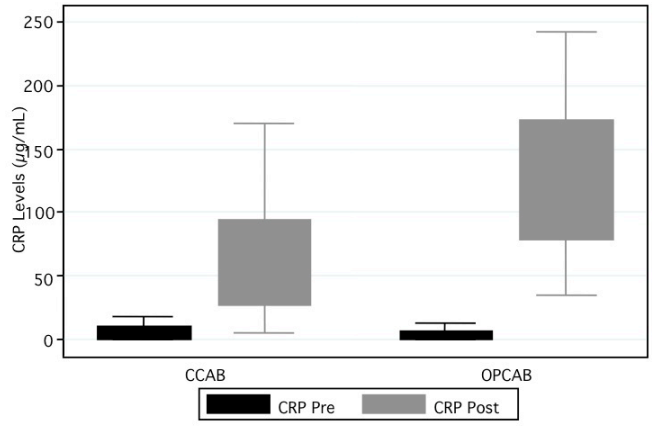

Figure 2: Box plot for pre- (black) and post-operative (gray) hs-CRP levels stratified by CCAB (left) and OPCAB (right). Hs-CRP was significantly higher in the OPCAB arm post-procedure (p=0.001) and change in from baseline (p=0.003).

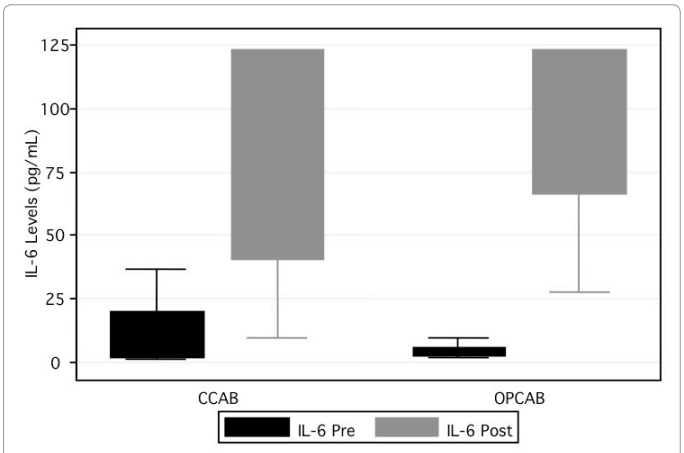

Figure 3: Box plot for pre- (black) and post-operative (gray) IL-6 levels stratified by CCAB (left) and OPCAB (right). IL-6 was higher in the OPCAB arm post-procedure (p=0.053) and significantly higher in the change from baseline (p=0.001).

In the present study, we found no apparent difference in the change in S100β values (post vs. pre-operative). Previous randomized trials comparing CCAB and OPCAB have found similar yet inconsistent results. A review of the literature on the topic sheds light on the inconsistency in the timing of serum draws and management of extracerebral sources of S100β [6]. For instance, Ascione et al. [5] found S100β levels to be 2.4 ($CI_{95\%}$ 1.8 – 3.2) times higher among patients undergoing CCAB relative to OPCAB. Ascione attributed these elevations in the CCAB arm to microemboli, as detected through transcranial Doppler. Comparison of our findings to those of Ascione are hampered by a difference in the timing of serum draws, with Ascione's group drawing 1 hour after surgery, while ours was drawn within 48 hours of surgery. Lloyd et al. [9] originally showed a significant increase in S100β levels in the CCAB group at 30-minutes, but this difference was diminished at 4 hours. Kobayashi et al., (2005) evaluated S100β at the time of admission to the intensive care unit and demonstrated S100β levels were significantly lower in the OPCAB versus CCAB group (0.20+/-0.11 versus 0.34+/-0.22 (ng/mL), p<0.001) [10]. Diegeler et al. [11] reported significantly lower S-100β levels in OPCAB patients compared to CCAB: 0.13 (0.04 to 1.01) versus 3.76 (0.13 to 11.2) microg/L, p< 0.0001. However, Diegelers randomized trial demonstrated cognitive impairment in 90% of CCAB patients and none in the OPCAB, albeit these findings may be attributed to its limited sample size (n=40). Mazzei et al. [12] in a randomized trial comparing minimal extracorporeal circulation to off-pump reported a non-significant reduction in S100β in the OPCAB group, whereas Bonacchi et al. [13] reported a statistically significant reduction in S100β among patients undergoing OPCAB compared to CCAB (0.5+/-0.11 versus 1.38+/-0.4 (microg/l), p<0.001). While patients undergoing CCAB may have higher exposure to microemboli, patients undergoing OPCAB may be exposed to an increased burden of hypotention or cerebral hypoperfusion during the construction of the posterior distal anastomoses [14,15].

Biomarkers of the systemic inflammatory response

IL-6 and hs-CRP are inter-related through the inflammatory cascade. The inflammatory hierarchy begins with tumor necrosis factor

(TNF)-α as a primary pro-inflammatory cytokine, which induces the production of interleukin (IL)-6, a messenger cytokine, which in turn induces acute-phase reactants, such as hs-CRP, fibrinogen and serum amyloid A proteins to be produced in the liver [16,17]. The measurement of both IL-6 and hs-CRP is important to capture both the cytokine inflammatory response as well as the end-product, or acute-phase reactant inflammatory response. It has been suggested that the factors contributing to both OPCAB and CCAB inflammation include surgical traiuma, endotoxemia, and ischemia [18]. CCAB patients have been thought to be susceptible to a heightened inflammatory response through blood contact with the cardiopulmonary bypass circuits [18], however coating circuits and other foreign contact points with blood have helped to ameliorate this effect. For OPCAB patients, ischemia through manipulation of the heart through the use of stabilization devices and inversion and torqueing of the heart resulting in ischemia and hypotension could be responsible for activating inflammatory mediators [15].

Wan et al. [19] reported significant higher elevations in IL-6 in CCAB patients immediately after surgery compared to OPCAB, but this difference was diminished at 4-hours post-operatively. Wippermann et al. [20] reported IL-6 levels at 24-hours post-operatively to be lower in the CCAB group (18.8+/-13.1 pg/dl) compared to the OPCAB (31.6+/-26.2 pg/dl) supporting our findings that CCAB can support less inflammatory response than OPCAB. Nesher et al. [21] demonstrated including IL-6 was significantly lower in the OPCAB compared with CCAB: 32 +/- 35 versus 230 +/- 30 (pg/mL), $p<0.05$. Immer et al. [22] in an observational cohort were able to demonstrate a reduction in inflammatory markers (including IL-6) using minimal extracorporeal circulation compared to conventional methods. Formica et al. [23] reported concentrations in IL-6 were more elevated among patients randomized to OPCAB as opposed to a miniaturized circuit, but they found no difference in TNF-α.

Rasmussen et al. [24] and Parolari [25] and Wehlin [26] reported no difference in IL-6 or hs-CRP following randomization to CCAB or OPCAB. Chowdhury et al. [27] demonstrated a significant increase in hs-CRP among CCAB in the on-pump group compared to the off-pump surgical arm, but questioned the diagnostic ability of hs-CRP for myocardial damage. Paulitsch et al. [28] reported no difference in hs-CRP between on- and off-pump groups.

In summary, in a prospective randomized trial comparing OPCAB to CCAB we found no difference in S100β, a marker of brain injury, or change in S100β from baseline after the procedure, confirming our previous findings suggesting that CABG surgery with the use of cardiopulmonary bypass does not significantly cause neurological dysfunction or deficits. However, patients undergoing OPCAB had significantly more inflammation as measured by IL-6 and hs-CRP than patients undergoing CCAB.

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