Neutrophil CD11b Upregulation During Cardiopulmonary Bypass is Associated With Postoperative Renal Injury

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Background. **Renal injury remains a persistent complication of cardiopulmonary bypass (CPB) that, when sufficient to require dialysis, increases mortality eight-fold. The high prevalence of renal failure in sepsis and adult respiratory distress syndrome has been linked to the systemic inflammatory response associated with those disorders. We hypothesized that components of the inflammatory response to CPB may similarly contribute to post-CPB acute renal injury.**

Methods. **Markers of leukocyte and platelet activation peri-CPB were measured in 75 patients undergoing cardiac operation with CPB and were correlated with acute renal injury, defined as an increase (≥ 50%) in peak serum creatinine post-CPB.**

Results. **Eleven patients sustained post-CPB acute renal injury. This subset of patients demonstrated significantly greater increases in neutrophil CD11b density ($p = 0.01$), as well as higher total neutrophil counts ($p = 0.045$), compared with patients with preserved renal function. Hemodynamic instability sufficient to require postoperative hemodynamic support also predicted an increased risk of acute renal injury. However, neutrophil CD11b upregulation did not correlate with this or any other clinical variables associated with renal risk, suggesting that this marker of the neutrophil inflammatory response may independently predict renal injury. By contrast other inflammatory markers, neutrophil myeloperoxidase levels, monocyte CD11b, base line C-reactive protein, and platelet CD62P expression did not differ between the two patient groups.**

Conclusions. **Upregulation of the neutrophil adhesion receptor CD11b and high circulating neutrophil numbers are associated with acute renal injury after CPB, suggesting a contribution by activated neutrophils to the pathophysiology of this complication.**

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Acute renal insufficiency (ARI) is a frequent complication of cardiac operations using cardiopulmonary bypass (CPB). ARI occurs in 8% to 20% of these patients depending on the diagnostic criteria used, and 1% to 5% of patients require postoperative dialysis [1–6]. Progression to dialysis-dependent renal failure is associated with an eightfold increased risk of mortality after CPB, which is independent of comorbid conditions [7], making prevention of CPB-induced renal injury a high priority for strategies to improve the safety of CPB.

The known preoperative factors associated with an increased risk of post-CPB renal injury are largely preexisting patient variables that provide limited options for therapeutic intervention intended to minimize renal injury. Attempts to improve intraoperative conditions by varying temperature [8] or perfusion pressure [9] during CPB, as well as pharmacologic interventions aimed at improving renal blood flow [10], have met with little success, prompting some surgeons to advocate off-pump operations whenever possible for patients at high risk for having ARI develop [11]. Nonetheless, CPB continues to be essential for certain surgical procedures.

Progress in renal protection during CPB is likely to hinge on a better understanding of the pathophysiology of CPB-induced renal injury. The role of hypoperfusion in producing renal damage is clearly established; however, the possible importance of factors known to promote renal injury in other settings (eg, vascular damage mediated by hematopoietic cells) [12] has been less well explored. Activated leukocytes and platelets are components of the systemic inflammatory response syndrome that accompanies sepsis and acute respiratory distress syndrome [13]. These cellular mediators likely contribute to the multiorgan failure associated with these disorders, which is itself, a strong predictor of mortality in this situation [14]. CPB is likewise characterized by a systemic inflammatory response syndrome [15], albeit one which is typically more moderate in terms of time and scope. However, individual patients vary widely in the degree of platelet and leukocyte activation provoked by CPB [16].

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We hypothesized that patients demonstrating a greater degree of circulating hematopoietic cell activation in response to CPB might be at greater risk for CPB-induced renal injury.

Patients and Methods

Patient Selection and Conduct of CPB

After the Human Investigation Committee approval and informed consent, 75 adults undergoing elective CPB at Yale-New Haven Hospital who were enrolled in the Multicenter Study of Perioperative Ischemia (McSPI) Research Group's prospective study of post-CPB outcomes were studied. As previously described [17, 18], all patients underwent CPB using a standardized membrane oxygenator, roller pump, aortic filter [2], mannitol-containing prime [8], and cardiotomy suction setup. None of the patients had a recent major infection.

Renal Evaluation

Serum creatinine was measured in samples drawn preoperatively, at the time of intensive care unit arrival, on postoperative days 1 and 2, and thereafter when clinically indicated. One patient was excluded because of preoperative renal failure (base line creatinine > 3) [7] leaving 74 patients who completed the study. Similar to prior studies, acute CPB-associated renal injury was defined as a postoperative creatinine peak that was greater than or equal to 150% of the base line preoperative value [5].

Platelet and Leukocyte Activation

Blood samples were drawn into fixative (1% paraformaldehyde final concentration): (1) at the start of the operation, (2) immediately before aortic cross-clamping, (3) 10 minutes after aortic cross-clamp release, (4) on arrival in the intensive care unit, and (5) in the morning on postoperative day 1. Platelet and leukocyte activation were examined by flow cytometry as previously reported [16] using monoclonal antibodies to CD62P and CD11b, respectively. Blood samples from the same time points were prepared for serum and plasma and immediately frozen for later measurement of (1) quantitative C-reactive protein (CRP) levels using the Beckman IMMAGE (high sensitivity) CRP immunochemistry reagent (Beckman-Coulter, Fullerton, CA) and (2) myeloperoxidase levels (MPO) using the Bioxytech MPO-enzyme immuno-assay of OXIS International (Portland, OR), both according to the manufacturer's instructions. An additional blood sample (1 mL) was drawn into ethylenediaminetetraacetic acid (5 mmol/L final concentration) at the same follow-up time points as for leukocyte and platelet activation and additionally at 48 and 72 hours post-CPB; a complete blood count and leukocyte differential were measured in these samples using an automated counter (STKS; Coulter Electronics, Hialeah, FL).

Statistics

The two patient groups (those demonstrating acute post-CPB renal injury and those with preserved renal function) were compared by preoperative renal risk factors as follows: for continuous variables (ie, base line creatinine, age, bypass time, cross-clamp time), the groups were examined using the Mann–Whitney *U* test, for binary variables, the populations were compared by Fischer's exact test. For variables that changed over time (leukocyte and platelet activation markers), the two renal function populations were compared by analysis of variance (ANOVA); correlation coefficients were calculated between continuous variables using the Spearman correlation. The above statistics were performed using Graphpad Prism (San Diego, CA) software. For multiple logistic regression analysis, an acute postoperative creatinine increase to greater than or equal to 150% of base line, which was used as the dependent variable. The following variables were evaluated using SigmaStat software (SPSS, Chicago, IL) with continuous variables categorized as follows to avoid having to assume linear associations with outcome [7]: age greater than 70, elevated base line creatinine (> 1.2, the upper limit of normal at our institution), previous coronary artery bypass graft, New York Heart Association class IV congestive heart failure, diabetes mellitus, concurrent peripheral vascular disease, coronary artery bypass graft plus valve operation, myocardial infarction in previous 10 days, pump time more than 110 minutes, pre-bypass inotropic agents or intraaortic balloon pump, post-bypass inotropic agents and intraaortic balloon pump, and peak polymorphonuclear (PMN) CD11b more than 2.5 times base line. In addition, multiple logistic regression analysis was repeated with high peak MPO levels (> 600 ng/mL) as the dependent variable.

Results

Patient Demographics

No patients received long-acting antiplatelet drugs (ie, GP (glycoprotein) IIb/IIIa or adenosine diphosphate receptor antagonists with the exception of aspirin) within 1 week of elective operation. All short-acting platelet-active agents were stopped at least 24 hours before the operation. Only 2 of 74 patients received aprotinin intraoperatively.

Eleven of 74 patients experienced a significant decrease in renal function, manifested by a peak in plasma creatinine concentration that was greater than or equal to 150% of their base line in the early post-CPB period. None of these patients required dialysis, either acutely or for long-term management. In this relatively small study, the only demographic variable that predicted ARI by multiple logistic regression analysis (Table 1) was the postoperative need for hemodynamic support (odds ratio, 26.1; 95% confidence interval, 1.1 to 607; $p = 0.042$).

Table 1. Risk Factors for Cardiopulmonary Bypass-Induced Renal Injury by Multiple Logistic Regression Analysis

			Confidence Interval	
	p Value	Odds Ratio	Lower 5%	Upper 95%
Age > 70 years	0.882	1.2	0.12	11.4
↑ Baseline Creatinine (> 1.2 mg/dL)	0.265	0.26	0.02	2.8
Previous cardiac operation	0.527	0.27	0.005	15.4
NYHA Class IV CHF	0.974	<0.001		(+inf)
Diabetes Mellitus	0.285	3.2	0.39	25.8
Peripheral Vascular Disease	0.215	4.6	0.41	52.7
Combined CABG + valve	0.087	0.06	0.002	1.5
MI within 10 days of operation	0.468	2.2	0.27	17.6
↑ Bypass time (> 110 minutes)	0.736	1.5	0.13	17.2
Inotropic drugs or IABP pre-CPB	0.545	2.9	0.09	98.2
Inotropic drugs or IABP post-CPB	0.042	26.1	1.13	607
PMN CD11b > 2.5 × baseline	0.031	62.6	1.4	2,704

CABG = coronary artery bypass grafting; IABP = intra-aortic balloon pump; NYHA Class IV CHF = New York Heart Association class IV congestive heart failure.

Leukocyte Activation and Renal Injury

As previously reported for CPB [16], neutrophils manifested significant upregulation in their surface expression of CD11b, which reached a peak just before cross-clamp release and remained increased during the period immediately after reperfusion of the arrested heart. Patients (n = 11) manifesting ARI experienced a significantly greater increase in neutrophil CD11b expression (Fig 1) ($p = 0.01$; ANOVA). Similarly, the peak PMN CD11b increase correlated with the percentage change in creatinine ($p = 0.036$; $r = 0.24$; Spearman correlation). Peak PMN CD11b also predicted ARI by multiple logistic regression analysis (Table 1) (odds ratio, 62.6; 95% confidence interval, 1.4 to 2,704; $p = 0.031$). However, the population of patients manifesting postoperative need for hemodynamic support did not have significantly greater PMN CD11b increases compared with their more stable counterparts ($p = 0.60$; Mann–Whitney *U* test). Similarly the patient populations exhibiting (1) the need for post-CPB inotropic support and (2) peak PMN CD11b levels more than 2.5 times baseline were compared by Fischer's exact test ($p = 0.598$), which similarly confirmed no significant relationship between these two groups. For the two patients who received aprotinin, one manifested a peak CD11b more than 2.5 times baseline, whereas the other did not, and neither exhibited ARI. Patients with ARI also had significantly greater absolute PMN counts than patients with preserved renal function (Fig 2) ($p = 0.045$; ANOVA).

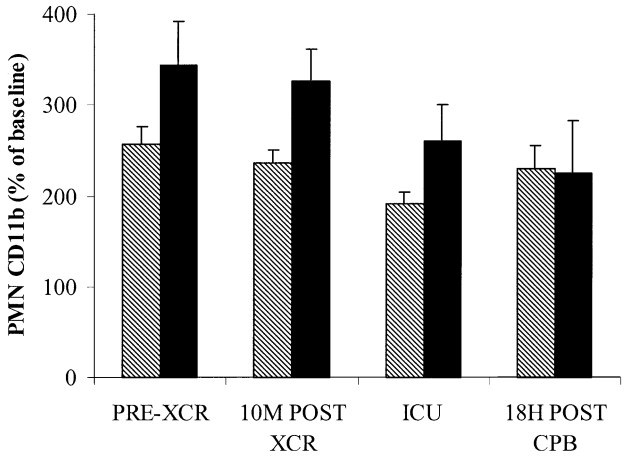

*Fig 1. Polymorphonuclear (*PMN*) CD11b expression during and after cardiopulmonary bypass (*CPB*). Surface expression of PMN CD11b was measured preoperatively for baseline values just before aortic cross-clamp release (*PRE-XCR*), 10 minutes after cross-clamp release (*10M POST XCR*), on intensive care unit arrival (*ICU*), and 18 hours after CPB (*18H POST CPB*). The mean ± standard error of the mean PMN CD11b levels for these time points are displayed, expressed as a percentage of the preoperative value.* Hatched bars *represent patients whose peak postoperative creatinine remained less than 150% of their baseline.* Solid bars *represent acute renal insufficiency patients whose peak postoperative creatinine increased to greater than or equal to 150% of their baseline. Acute renal insufficiency patients demonstrated significantly greater PMN CD11b levels than did patients with more preserved renal function (*p = *0.01; analysis of variance).*

Plasma levels of PMN MPO also increased significantly during CPB. Peak MPO levels did not correlate with peak CD11b levels ($p = 0.48$; Spearman correlation) nor did patients manifesting acute post-CPB renal injury demonstrate higher MPO levels (Fig 3) ($p = 0.65$; ANOVA) than those with preserved renal function. Multiple regression analysis was repeated using peak MPO levels as the dependent variable to look for factors associated with higher MPO levels. Elevated baseline MPO level, New York Heart Association class IV congestive heart failure, and myocardial infarction 1 to 10 days preoperatively were significantly associated with elevated peak MPO levels ($p = 0.001$, $p = 0.03$, and $p = 0.015$, respectively). By contrast, multiple regression analysis using peak CD11b as the dependent variable did not demonstrate an association with any of the preoperative clinical variables.

Monocyte CD11b expression also increased before cross-clamp release, reaching a peak after cross-clamp

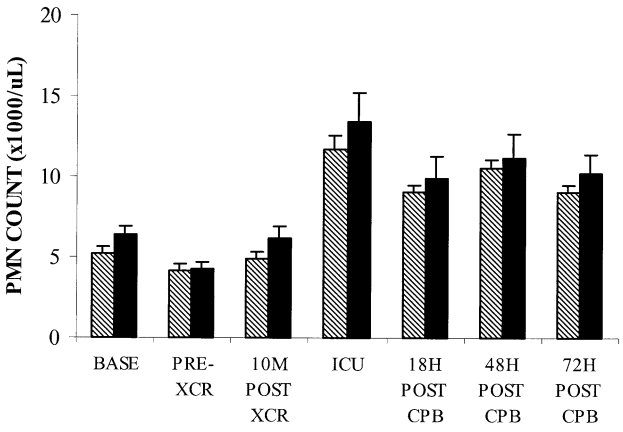

Fig 2. Polymorphonuclear (PMN) *counts during and after cardiopulmonary bypass* (CPB). *Absolute numbers of PMN were measured at the time points noted in Figure 1 and additionally at 48 hours after CPB* (48H POST CPB) *and 72 hours after CPB* (72H POST CPB). *The mean ± standard error of the mean for each time point is displayed.* Hatched bars *represent patients whose peak postoperative creatinine remained less than 150% of their baseline.* Solid bars *represent patients whose peak postoperative creatinine increased to greater than or equal to 150% of their baseline. Acute renal insufficiency patients demonstrated significantly greater absolute numbers of PMN than did patients with more preserved renal function* (p = *0.045; analysis of variance).* (10M POST XCR = *10 minutes after cross-clamp release;* 18H POST CPB = *18 hours after cardiopulmonary bypass;* ICU = *intensive care unit arrival;* PRE-XCR = *just before aortic cross-clamp release.)*

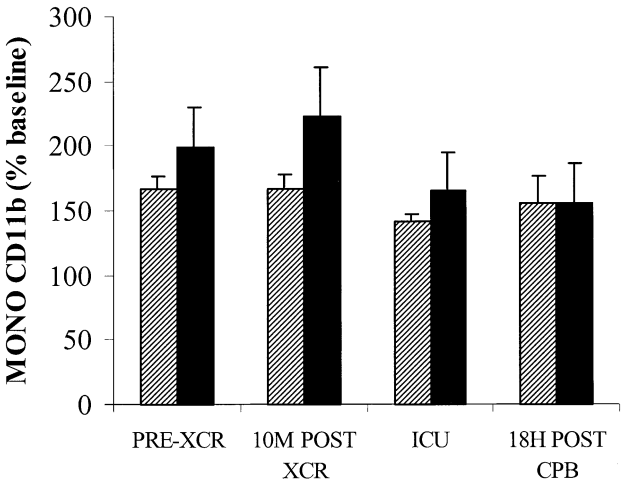

Fig 4. Monocyte (MONO) CD11b expression during and after cardiopulmonary bypass (CPB). *Surface expression of monocyte CD11b (mean ± standard error of the mean) was measured perioperatively at the time points noted in Figure 1. Monocyte CD11b levels are expressed as a percentage of the baseline value.* Hatched bars *represent patients whose peak postoperative creatinine remained less than 150% of their baseline.* Solid bars *represent patients whose peak postoperative creatinine increased to greater than or equal to 150% of their baseline. Acute renal insufficiency patients did not differ significantly from patients with preserved renal function* (p = *0.09; analysis of variance).* (10M Post XCR = *10 minutes after cross-clamp release;* 18H POST CPB = *18 hours after cardiopulmonary bypass;* ICU = *intensive care unit arrival;* PRE-XCR = *preoperative cross-clamp release.)*

release and myocardial reperfusion, and remaining elevated into the postoperative period (Fig 4). Those patients with ARI showed a trend toward higher monocyte CD11b levels compared with patients with preserved function, but this did not reach statistical significance (p = 0.09; ANOVA). The absolute number of circulating monocytes was indistinguishable in the two patient groups (p = 0.62; ANOVA).

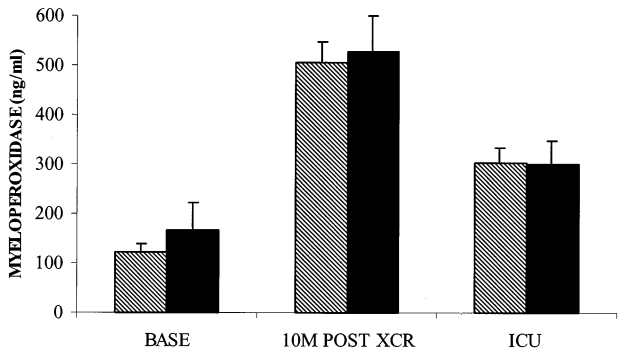

Fig 3. Myeloperoxidase levels during and after cardiopulmonary bypass. Plasma levels of myeloperoxidase levels (mean ± standard error of the mean) were measured preoperatively (BASE), *10 minutes after cross-clamp release* (10M POST XCR), *and on intensive care unit arrival* (ICU). Hatched bars *represent patients whose peak postoperative creatinine remained less than 150% of their baseline.* Solid bars *represent patients whose peak postoperative creatinine increased to greater than or equal to 150% of their baseline. Acute renal insufficiency patients did not differ significantly from patients with preserved renal function* (p = *0.65; analysis of variance).*

Platelet Activation, C-Reactive Protein and Renal Injury

Platelet activation on CPB was also compared in the two patient groups. CD62P is mobilized from the α-granule of the resting platelet to the surface membrane upon activation. As previously noted [16], CPB caused significant activation of circulating platelets, peaking at the time of cross-clamp release and remaining increased into the early postoperative period. Unlike PMN activation, patients experiencing greater CPB-induced renal injury did not demonstrate a difference in platelet activation compared with patients with preserved renal function (p = 0.32; ANOVA).

CRP was measured in the serum samples drawn at base line to gauge the inflammatory state of patients presenting for the operation and then compared in the two patient groups with differing renal response to CPB. The patients whose creatinine increased to greater than or equal to 150% of baseline had preoperative CRP levels that were not significantly different from those of patients with more preserved renal function (p = 0.53; Mann–Whitney U test). The baseline CRP also did not predict patients who had the greatest increases in PMN CD11b (p = 0.50; Spearman correlation).

Comment

This study examined markers of leukocyte and platelet activation in patients after CPB. We demonstrated that patients who had acute post-CPB renal injury, compared with patients who had preserved renal function, had increased expression of the neutrophil adhesion receptor CD11b, together with a higher total PMN count. By contrast other inflammatory markers including plasma MPO levels (released from PMN azurophilic granules), monocyte CD11b levels, total monocyte numbers, the percentage of circulating CD62P+ platelets, and baseline CRP levels did not differ between the two groups. There was also no correlation of other preoperative clinical variables with PMN CD11b upregulation.

The etiology of CPB-induced renal injury is multifactorial [2, 3, 5, 6]. Preoperative patient characteristics that can potentially diminish renal reserve (age, concurrent diabetes, basal creatinine) clearly aggravate the risk of renal insult. The peri-CPB variables most frequently linked to renal injury are the duration of bypass and poor postoperative cardiac output [4], suggesting that renal ischemia during or after CPB plays a prominent, although by no means invariant, role in this pathophysiology. In the present study the need for post-CPB hemodynamic support was associated with an increased risk of renal injury, suggesting that hypoperfusion was a likely contributor to ARI.

The obligate blood-biomaterial contact occurring during CPB produces a systemic inflammatory response [15] that varies appreciably from patient to patient, both in terms of degree of activation and the cell types most profoundly affected. As we and others have previously noted [16, 19], CPB causes PMN to increase their surface expression of CD11b, the β2-integrin whose activation-induced changes permit leukocyte adhesion to endothelial cells and PMN vascular egress. Whether these circulating CD11b-upregulated PMN leukocytes are capable of contributing to renal damage during CPB, particularly after an ischemic insult, has not been previously examined. However, activated PMN have been linked to ischemic renal injury in other clinical settings [12, 13]. Syndromes characterized by a systemic inflammatory response (including sepsis and the adult respiratory distress syndrome) are frequently complicated by renal injury even in the absence of overt hypotension [14], suggesting that subtle intrarenal ischemia may be potentiated by the presence of coexisting inflammatory pathologies. Animal ischemia/reperfusion models have explored the ways that circulating inflammatory mediators exacerbate primary ischemic insults. Linas and colleagues [20] used an isolated kidney subjected to mild-to-moderate ischemia to demonstrate that subsequent reperfusion with *activated* PMN converts an otherwise recoverable renal insult into irreversible renal injury. Thus, episodes of renal hypoperfusion and/or ischemia insufficient to independently cause renal injury, can produce significant damage if the kidneys are subsequently exposed to primed PMN leukocytes. Furthermore, in whole animal studies of ischemia/reperfusion, PMN blockade with agents targeting PMN CD11b-endothelial cell intercellular adhesion molecule adhesion can rescue renal function [21]. Additional support for this hypothesis comes from human studies demonstrating that acute renal failure patients will more often recover renal function if dialysis is performed with more biocompatible membranes, presumably by inducing a lesser systemic inflammatory response [22].

In the present study, regression analysis linked worse renal outcome with greater hemodynamic instability after separation from CPB. PMN CD11b peaked before separation from CPB, however, and independent of renal outcome, hemodynamic instability did not correlate with higher PMN CD11b levels, implying that PMN CD11b upregulation is not simply another manifestation of tissue hypoperfusion. It is possible that the enhanced PMN reactivity seen in patients with acute post-CPB renal injury could be a consequence of the preoperative inflammatory risk factors that also predisposed these patients to post-CPB renal dysfunction. However, given that (a) the pre-CPB CRP was identical in the two patient groups with differing renal outcome and that (b) peak PMN CD11b did not correlate with the baseline CRP, it is more likely that the PMN CD11b upregulation represents a specific response to CPB and/or cardiac operation, rather than the consequence of a comorbid process/disease predating CPB.

The failure of plasma MPO to correlate with PMN CD11b upregulation highlights the distinct functions subserved by these activation markers and their corresponding differential regulation [23]. Intracellular CD11b is located on the membrane of PMN secretory vesicles, and mobilization of these vesicles fuses their membrane with the surface membrane, thereby priming the cell for migration into tissues. This is a very rapid and nonspecific marker of PMN activation. Both soluble inflammatory mediators and PMN contact with activated endothelium cause CD11b upregulation. By contrast, MPO is contained in PMN azurophilic granules along with other hydrolytic and bactericidal proteins [24]. These enzymes have the potential to cause significant autologous tissue injury, and in the hierarchy of PMN activation responses, azurophilic granule release is largely reserved for special microbicidal responses [25]. Accordingly, PMN CD11b and MPO do not correlate with each other in a number of settings where generalized PMN activation is prominent [26, 27]. By contrast, high baseline MPO levels and a myocardial infarction in the 10 days before CPB were significant predictors of higher peak MPO levels, suggesting that this inflammatory marker may be particularly sensitive to pre-CPB cardiac status.

The role of monocytes in the pathophysiology of ischemic renal damage has not been extensively studied. In acute renal injury associated with glomerulonephritis and hypertensive injury, monocytes and "primed" monocytes in particular have been implicated in promoting the local inflammatory activity of mesangial cells [28]. In the present study, renal injury patients demonstrated a trend toward greater monocyte activation that was not statistically significant. Activated monocytes may con-

tribute to renal injury or may simply reflect the overall greater systemic inflammatory response to CPB in this patient subset. Similarly, increased platelet CD62P expression was not associated with renal injury, suggesting that greater activation of cellular coagulation did not play a major role in ARI. Previously published outcome studies on CPB patient populations found that PMN CD11b upregulation was not a risk factor for either neurocognitive decline or acute myocardial injury [17, 18]. Instead, a genetic polymorphism predisposing to platelet hypercoagulability was linked to these particular organ injuries. These studies, together with the present investigation, suggest that post-CPB injury in a given organ is not simply the manifestation of a generalized inflammatory response. Instead, the combination of specific component(s) of the CPB inflammatory response, amplified by genetic and/or environmental factors (such as hypoperfusion), or both, cause damage to that particular organ.

Multiple factors during CPB are capable of producing PMN and monocyte activation, including complement activation [29], cardiotomy suction [30], and byproducts of the contact activation pathway [15, 31]. In this relatively small study, none of the variables previously identified as renal injury risk factors [1–4] were linked to increased PMN CD11b. The prevalence of renal injury produced by CPB has changed little over the past 10 years [5], and with aging of the population presenting for CPB this complication may increase in the future. Strategies for minimizing renal ischemia by manipulation of perfusion pressure [9], pharmacologically augmenting renal vasodilatation [10], and minimizing cellular metabolism [8] so far have been disappointingly unproductive. The finding here and in other studies [12, 20, 32] that renal injury may be aggravated by priming systemic PMN for adhesion opens up new options for improving the reperfusion aspect of the ischemia/reperfusion equation. Interventions might include oxygenators of even greater biocompatibility [33], blunting PMN activation directly or by targeting intermediate mediators (such as activated complement components), or blocking activated PMN adhesion. Such reductions in the PMN inflammatory response to CPB might reduce the renal injury associated with CPB.

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