direction is expected to have a major impact on our future practice.

**REFERENCES**


**Pulmonary Injury After Cardiopulmonary Bypass**

It has been known since the early experience with cardiac surgery using cardiopulmonary bypass that significant pulmonary injury may follow these operations and can cause significant mortality and morbidity. The pulmonary injury, colloquially referred to as “pump lung,” was recognized early on to be a problem of increased microvascular permeability, since the pulmonary edema and hypoxemia with increased alveolar-arterial oxygen gradient occurred in the presence of relatively low directly measured left atrial pressure, a value that was then rarely available to the clinician except early after cardiac surgery. It has since become clear that the clinical features and pathophysiology of pulmonary injury associated with cardiopulmonary bypass is nearly identical to ARDS associated with other etiologies. Indeed, the lung injury is only a part of a systemic inflammatory response syndrome (SIRS) that is probably activated to a variable degree in all patients undergoing cardiopulmonary bypass and perhaps even those undergoing major operations without bypass.

The SIRS after bypass as well as the pulmonary injury that is a major part of this syndrome has been the subject of recent comprehensive reviews in CHEST and other journals. The clinical features of this syndrome include pulmonary injury with increased pulmonary vascular resistance; increased alveolar-arterial oxygen gradient with a pulmonary edema pattern shown on chest radiography; as well as decreased peripheral vascular resistance, with increased cardiac output, tachycardia, fever, and a tendency for hemoconcentration. The transient neuropsychologic dysfunction variably observed after bypass has also been in part attributed to the inflammatory response it elicits. Most patients have this syndrome resolve in the first 24 h after bypass and have no serious consequences. When patient weights are followed accurately, patients are typically 3% to 8% over their preoperative dry weight on the first postoperative day. Early correction of this state of fluid retention, caused in large part by the inflammatory response after bypass, is important to achieving early recovery after operation and, in particular, in preventing significant delayed pulmonary complications.

Unfortunately, a few patients will have a less-benign course. The incidence of more significant pulmonary injury after cardiopulmonary bypass has varied considerably and clearly depends on one’s definition and threshold for this diagnosis. The reported incidence of ARDS has varied from about 0.5 to 1.7%, but the incidence of a lesser degree of early
postoperative pulmonary dysfunction, defined as a Pao2/fraction of inspired oxygen ratio of ≤ 150 mm Hg and chest radiography consistent with pulmonary edema on arrival in the ICU, was 12% in a study by Rady et al from the Cleveland Clinic. In the small group of patients in whom ARDS occurs, the mortality has been reported to be in the 40 to 60% range or higher, with many of these being due to progression to multiorgan failure.3

The pathophysiology of the SIRS and, in particular, the pulmonary injury associated with it has been studied extensively both in laboratory models and clinical studies. Clearly, what separates procedures utilizing cardiopulmonary bypass from other situations in which similar injury may occur is the extensive exposure of blood to the foreign surfaces, and abnormal conditions that result during cardiopulmonary bypass.5 Organ injury from ischemia and reperfusion and particularly gut mucosal injury from occult splanchnic ischemia leading to endotoxin release may also contribute to the problem.8 All of these cause activation of complement, and release of thromboxane and pro-inflammatory cytokines, particularly interleukin (IL)-6 and IL-8 and tumor necrosis factor (TNF)-α.1 Inflammatory cells, particularly leukocytes, are activated and in turn become sequestered in various organs (particularly the lungs) and cause an inflammatory response and tissue injury. In this issue of CHEST (see page 31), Massoudy et al studied the role of the lung itself in the release of the proinflammatory cytokines, IL-6, IL-8, and TNF-α. By measuring levels in the right atrial as well as the right superior pulmonary vein blood, they showed a significant percent increase in the levels of IL-6 and IL-8, but not TNF-α, on the pulmonary venous side. They also showed that there was a decrease in the counts of activated leukocytes across the lung consistent with sequestration and presumably from adherence of these inflammatory cells to the pulmonary vascular endothelium. They did not correlate these variables with pulmonary function measured early postoperatively, which may have added clinical relevance to this study.

A problem with this study that the authors have recognized is that during cardiopulmonary bypass, after release of the aortic cross-clamp and resumption of cardiac mechanical activity, the amount of blood flow through the lungs by way of the pulmonary arterial circulation is highly variable (5 to 20% of normal as stated in their article) and is dependent on the effectiveness of venous drainage from the right heart. Indeed, if venous drainage is highly effective and the right heart is nearly completely decompressed on full cardiopulmonary bypass, the majority of pulmonary blood flow could still be coming from the bronchial circulation. The authors stated they have measured simultaneously drawn blood from the right atrium and radial artery and have determined there were no differences in the same inflammatory variables, indicating no detectable activation across the cardiopulmonary bypass circuit. If bronchial arterial and right atrial blood levels are indeed not different, this would validate their qualitative conclusion that the lungs are the site of inflammatory mediator release, but leave us without the ability to quantitate this without knowing pulmonary blood flow.

Another factor the authors recognized that may have affected their results is their routine use of aprotinin, which has been shown to decrease the inflammatory response to bypass by decreasing complement activation as well as decreasing neutrophil expression of several adhesion molecules, including CD11b.1,9 Since aprotinin is reserved for use in cardiac reoperations in most centers, the authors may have underestimated the potential extent of neutrophil activation and sequestration within the lungs in most patients having bypass, since aprotinin is not routinely used.

The data from their study do support the idea that the lung is the site of proinflammatory cytokine production in the period between the release of the aortic cross-clamp and discontinuation of cardiopulmonary bypass. During this early period of reperfusion after release of the aortic cross-clamp, the lungs, like the heart, may be involved in an ischemia/reperfusion injury pattern. This may be the major inciting factor that causes release from the lung of inflammatory mediators as measured in the pulmonary venous blood and mirror the efflux of similar mediators from the heart that occurs early after cardiac reperfusion.1 It is unfortunate, however, that they did not extend their measurements to the period early after discontinuation of cardiopulmonary bypass, particularly when protamine is being administered. Protamine and the heparin protamine complex have been shown to activate complement by the classical pathway and to cause leukosequestration in the lungs.1

Although there have been numerous studies investigating interventions to blunt the inflammatory response and decrease lung injury after bypass, we are still far from having an immediately available intervention that will eliminate this problem. The list of such interventions that have been variably effective in decreasing the inappropriate inflammatory response has included the use of heparin-coated bypass circuits; leukocyte filtration; ultrafiltration early after bypass; and various pharmacologic agents, including aprotinin, steroids, direct inhibitors of inflammatory mediators, metalloprotease inhibitors, and, most recently, nitroprusside.1,3,4,9—11 With the incidence of hard end points such as clear
ARDS or death being so low with current techniques, well-planned randomized clinical trials will have to either be very large, perhaps prohibitively large, to show efficacy using a new intervention. If we are to make progress in eliminating this problem, it may have to be accepted that softer end points, such as inflammatory mediator levels coupled with postoperative clinical variables such as alveolar-arterial oxygen gradient, pulmonary and peripheral vascular resistance, and degree of fluid retention, be used to determine efficacy. The variable morbidity from the inflammatory response to bypass has been a major motivation for the increasing trend to perform coronary artery bypass grafting without bypass. This disadvantage of bypass would be considerably less compelling and our outcomes further improved for operations using cardiopulmonary bypass, were we to have an effective, preventive regimen to eliminate the SIRS and pulmonary injury that is associated with it.

Vincent R. Conti, MD, FCCP
Galveston, TX

Dr. Conti is Professor and Chief, Division of Cardiothoracic Surgery, Department of Surgery, The University of Texas Medical Branch.

Correspondence to: Vincent R. Conti, MD, FCCP, The University of Texas Medical Branch, 301 University Blvd, Galveston, TX 77555-0528; e-mail: vconti@utmb.edu

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Sleep Apnea

A Global Perspective

Recently, two well-designed studies by researchers from the University of Wisconsin1 and the Sleep Heart Health Study Group2 documented that untreated obstructive sleep apnea (OSA) increases the risk for hypertension in American adults. In both studies, the risk for hypertension increased in a dose-response association with the frequency of obstructive respiratory events during the night, independently of confounding factors such as age, gender, and weight. It is expected that these and other studies evaluating large patient cohorts will determine whether this increased risk for hypertension results in added morbidity and mortality from ischemic heart disease and other cardiovascular diseases. It may well be that the increased risk of cardiovascular disease sequelae from OSA will warrant widespread efforts at early detection and treatment, much as is the current clinical practice for hyperlipidemia.

Sleep apnea is typically characterized as a disease of obese, middle-aged men.3,4 This stereotype is a result of older studies completed in the United States, Europe, and Australia that found that 60 to 90% of all OSA patients are obese,5 as defined by a body mass index (BMI) of ≥ 28 kg/m². A landmark study by Young et al6 determined that 2 to 4% of Wisconsin factory workers had OSA, and that the risk for OSA increased in close association with measures of truncal obesity, such as neck size. The study by Ip et al in this issue of CHEST (see page 62) indicates that OSA may occur with a similar prevalence in a cohort of nonobese subjects, as the mean BMI for this study cohort was only 23.9 kg/m². Of great importance is the fact that the study cohort was 784 Chinese office workers in Hong Kong.

There are a paucity of data characterizing the epidemiology of OSA in populations other than middle-aged or older white men, and few studies have focused on young adults, women, or patients of African or Asian descent. Recent investigations on the epidemiology of ischemic heart disease indicate that the clinical recognition and management of this disease varies markedly in cohorts of women7 or of nonwhite patients, compared with that of white men.8 The scenario may be much the same for the epidemiology of OSA.