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Interleukin 6 production during cardiac surgery correlates with increasing age

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ABSTRACT

Background: Cardiac surgery produces a proinflammatory response characterized by cytokine production. Proinflammatory cytokines such as interleukin 6 (IL-6) may contribute to morbidity and mortality after cardiopulmonary bypass (CPB). Elderly patients undergoing CPB are at increased risk of morbidity and mortality. We hypothesized that patients aged >70 y produce more IL-6 during CPB.

Methods: Twenty-three patients (ages 23–80) undergoing cardiac surgery had blood sampled from the ascending aorta and coronary sinus on initial cannulation for bypass, at 30 min of aortic cross-clamp time, on release of the aortic cross–clamp, and at 20 min after reperfusion. Group 1 patients ($n = 8$) were aged <60 y, group 2 patients ($n = 7$) were aged between 60 and 70 y, and group 3 patients ($n = 8$) were aged >70 y. Plasma levels of tumor necrosis factor-alpha, IL-1, and IL-6 were analyzed.

Results: The three groups did not differ with respect to preoperative ejection fraction, New York Heart Association classification, mean aortic cross-clamp time, or mean CPB time. IL-6 levels rose throughout myocardial ischemia and reperfusion in all three age groups. The increase in IL-6 during ischemia and reperfusion in the age group >70 was greater than the increase in younger patients. IL-6 was similar in the coronary sinus and the ascending aorta.

Conclusions: These data suggest that patients aged >70 y undergoing cardiac operations generate more IL-6 during CPB. The increased circulating IL-6 in elderly patients may incite a proinflammatory state that could subsequently underlie the associated higher mortality and morbidity of these procedures in elderly patients.

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1. Introduction

Cardiovascular disease remains as the leading cause of death in the United States and western populations. As the segment of the population aged ≥65 y continues to expand as the most rapidly growing subset of our population, the impact of cardiovascular disease and health most directly affects this group of individuals. Indeed, of the over 6 million cardiovascular

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procedures performed during 2005 in the United States, over 50% were carried out in patients aged >65 y [1]. The challenges of providing surgical therapy for coronary artery disease and valvular heart disease in older patients are increasing.

Increasing patient age has been identified as an important risk factor predicting worse outcomes following cardiac surgery in contemporary risk models [2]. Indeed, when one examines the operative risk of patients over 80 undergoing coronary artery bypass (CAB) surgery, the operative mortality exceeds that of a cohort aged 50–79 by greater than twofold [3]. Morbidities such as stroke, renal failure, and respiratory failure are also similarly increased in elders undergoing cardiac surgical operations. At present, mechanisms responsible for these observed worsened outcomes in elders undergoing cardiac surgical procedures remain unknown and poorly characterized.

A proinflammatory state characterized by cytokine release during cardiopulmonary bypass (CPB) is well described [4,5]. An increase in circulating levels of tumor necrosis factor-alpha (TNF-α); interleukins (ILs) 1, 6, and 8; as well as several other cytokines occurs with CPB during cardiac surgical operations. Similarly, but seemingly unrelated, many common problems in elder adults such as lethargy, confusion, and catabolism of muscle can also be induced by these cytokines—and in particular IL-6 [6]. Although much effort has been directed toward modulating the heightened inflammatory response associated with the release of these cytokines during CPB, cytokine production during CPB as an age-related phenomenon has been poorly characterized. This heightened proinflammatory cytokine production during cardiac surgical procedures with CPB could explain or contribute to the observed poorer outcomes of elderly patients who require cardiac surgical procedures. The present study was undertaken to better characterize the cytokine expression of patients undergoing elective cardiac surgical operations (CAB and valvular operations) as a function of deciles of age.

2. Patients and methods

2.1. Patients

Twenty-three patients undergoing elective cardiac surgical procedures at the University of Colorado Hospital or the Denver VA Medical Center were studied. The study was approved by the Colorado Multiple Institutional Review Board. All patients gave informed consent for blood and tissue sampling. Inclusion criteria for the study were patients undergoing elective cardiac surgical operations—either CAB surgery, mitral or aortic valvular surgery, and combined coronary/mitral or aortic valvular operations. Exclusion criteria were reoperation, infection the week before surgery, immunosuppression, emergent operations, and operations involving the great vessels. We separated each group of patients by their age based on previous research demonstrating differences in outcomes after cardiac surgery in certain age groups [7]: group 1 was patients aged <60 y ($n = 8$), group 2 was patients aged between 60 and 70 y ($n = 7$), and group 3 was patients aged >70 y ($n = 8$).

2.2. Technique of CPB

The extracorporeal circuit consisted of a hollow-fiber membrane oxygenator, an extracorporeal line set, and a roller pump (Medtronic, Minneapolis, MN). Heparin (3-mg/kg body weight) was given centrally before cannulation of the aorta. Core body temperature was reduced to 32°C, and a nonpulsatile flow of 2.4 L/min/m^2 was maintained. Myocardial protection was delivered as antegrade and retrograde cold blood cardioplegia (4°C). Myocardial temperature was monitored with a septal myocardial temperature probe and was maintained at <10°C.

2.3. Blood samples and cytokine analysis

Paired blood samples were simultaneously taken from the ascending aortic vent and the coronary sinus cannula at the following four time points: (1) after initial cannulation, before initiation of CPB; (2) 30 min after aortic cross-clamping; (3) on release of aortic cross-clamp (start of myocardial reperfusion); and (4) 20 min after aortic cross-clamp release—immediately before termination of CPB. The blood was collected in heparin-coated tubes and kept on ice.

The blood samples were processed within 2 h after collection. Centrifugation was carried out at 3000 rpm/min for 15 min, and the plasma was frozen and stored at −70° for assays of TNF, IL-1, IL-6, IL-8, and monocyte chemoattractant protein 1 (MCP-1). The levels of plasma cytokines were measured using enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN). The detection limits of these assays were <10 pg/mL.

2.4. Tissue samples and immunostaining

A small piece of right atrium was removed at the following two time points: (1) on initial cannulation, before initiation of CPB, and (2) 20 min after aortic cross-clamp release—immediately before termination of CPB. Tissue samples were embedded in tissue-freezing media (optimal cutting temperature compound), snap-frozen in isopentane chilled on dry ice, and stored at −70°C for cryosectioning and immunostaining.

Immunohistochemical staining was applied to detect IL-6 in the myocardium. Tissue sections (5-μm thick) were cut with a cryostat (Frigocut 2800; Reichert-Jung, Mannheim, Germany) and dried at room temperature for 2 h. Sections were fixed in 4% paraformaldehyde and then washed with phosphate-buffered saline (PBS). To quench endogenous peroxidase activity, sections were treated for 10 min with 3% hydrogen peroxide. To block nonspecific binding sites, sections were incubated for 30 min with 10% normal goat serum in PBS. Sections were then incubated for 90 min with a rabbit polyclonal antibody against human IL-6, 5 μg/mL in PBS containing 1% bovine serum albumin (BSA). After three washes with PBS, sections were incubated for 45 min with biotinylated goat anti–rabbit immunoglobulin G (1:50 dilution with PBS containing 1% BSA). Subsequently, sections were incubated with ABC reagent (avidin and biotinylated peroxidase). After thorough washes with PBS, color development was carried out with 3,3'-diaminobenzidine (DAB) substrate. Sections were

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