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Perioperative cardiovascular system failure in South Asians undergoing cardiopulmonary bypass is associated with prolonged inflammation and increased Toll-like receptor signaling in inflammatory monocytes

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ABSTRACT

Background: South Asian ethnicity is an independent risk factor for mortality after coronary artery bypass. We tested the hypothesis that this risk results from a greater inflammatory response to cardiopulmonary bypass (CPB).

Methods: This was a single-site prospective cohort study. We compared the inflammatory response to CPB in 20 Caucasians and 17 South Asians undergoing isolated coronary artery bypass grafting surgery.

Results: Plasma levels of proinflammatory cytokines (interleukin [IL]-6, IL-8, IL-12, interferon gamma, and tumor necrosis factor) and anti-inflammatory mediators (IL-10 and soluble TNF receptor I) were measured. The Toll-like receptor (TLR) signaling pathway was examined in peripheral blood monocytes by flow cytometry, measuring surface expression of TLR2, TLR4, and coreceptor CD14 and activation of downstream messenger molecules (interleukin-1 receptor-associated kinase 4, nuclear factor kappa from B cells (NF-κB), c-Jun amino-terminal kinase, p38 mitogen-activated protein kinase, and Protein Kinase B). South

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Asians had persistently higher plasma levels of IL-6 and exhibited increased TLR signaling through the p38 mitogen-activated protein kinase and Protein Kinase B pathways in inflammatory monocytes after CPB. This increased inflammatory response was paralleled clinically by a higher sequential organ failure assessment score (5.1 ± 1.4 *versus* 1.5 ± 1.6, $P = 0.027$) and prolonged cardiovascular system failure (23.5% *versus* 0%) 48 h after CPB.
Conclusions: South Asians develop an exacerbated systemic inflammatory response after CPB, which may contribute to the higher morbidity and mortality associated with coronary artery bypass in this population. These patients may benefit from targeted anti-inflammatory therapies designed to mitigate the adverse consequences resulting from this response.

1. Introduction

South Asian ethnicity is associated with an increased risk of cardiovascular disease and its complications [1]. In a retrospective study of South Asians (persons originating from India, Pakistan, Bangladesh, and Sri Lanka) and white patients, morbidity and mortality after coronary artery bypass grafting (CABG) surgery were increased in patients of South Asian ethnicity [2]. Analysis of patients propensity-matched for known risk factors revealed increased prevalence of low output syndrome, myocardial infarction (MI), and sternal wound infection in South Asian patients. Logistic regression analysis demonstrated that South Asian ethnicity was an independent predictor of mortality after CABG surgery, conferring a 3.1-fold increased risk. The pathophysiological mechanism underlying the difference in outcome after CABG surgery between these ethnic groups has not been elucidated.

Cardiopulmonary bypass (CPB) is thought to mediate many of the adverse effects associated with cardiac surgery [3]. This is attributed to the induction of a systemic inflammatory response, involving both the humoral and cellular arms of the innate immune system [4]. CPB has been shown to produce alterations in signaling through the Toll-like family of receptors (TLRs), particularly TLR2 and TLR4, which regulate the activation of monocytes and other leukocytes [5,6]. The result is a systemic release of cytokines, chemokines, metalloproteinases, and reactive oxygen species, which perpetuate the inflammatory response and mediate end-organ damage. Among the proinflammatory cytokines, interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)-α have been the most extensively studied in the context of CPB [7]. Anti-inflammatory cytokines, such as IL-10, are also induced by CPB [7].

We hypothesized that South Asians have a greater inflammatory response to CPB and that this increased response might contribute to the increased morbidity and mortality observed in these patients. We designed a prospective observational study to examine the cytokine and cellular inflammatory response elicited by CPB in South Asian and Caucasian patients and correlate these experimental findings with clinical outcomes in the early postoperative period. This study extends our current understanding of the inflammatory response elicited by CPB by characterizing the response in an ethnic group not studied previously and examining, for the first time, the role of the innate immune system at the cellular level in human subjects.

2. Materials and methods

2.1. Study population

Between 2008 and 2010, we screened 35 Caucasians and 26 South Asians. Ethnicity was self-reported. Patients were eligible to participate if they were of South Asian or Caucasian ethnicity; age 19–85 y; able to provide informed consent; and scheduled for elective isolated CABG with CPB. Patients were excluded if they had severe congestive heart failure (New York Heart Association [NYHA] class IV) preoperatively; previous sternotomy; previous coronary revascularization (open or percutaneous); need for emergent revascularization; need for hemodialysis, or estimated glomerular filtration rate (eGFR) < 45 mL/min; preoperative use of corticosteroids, nonsteroidal anti-inflammatory drug, or other immunosuppressive drug; and preexisting inflammatory disease or hematologic disorder. A total of 20 Caucasians and 17 South Asians were included in the study. Reasons for exclusion are presented in Figure 1. The study was approved by the Research and Ethics Board at St. Michael's Hospital.

2.2. Surgical intervention and conduct of cardiopulmonary bypass

Anesthesia was narcotic-based. All patients underwent isolated CABG through a median sternotomy approach. A small adult cardiopulmonary bypass circuit with Carmeda coating tip-to-tip was used, consisting of a right atrial venous cannula, a Stöckert S5 roller pump (Stöckert Instrumente GmbH,

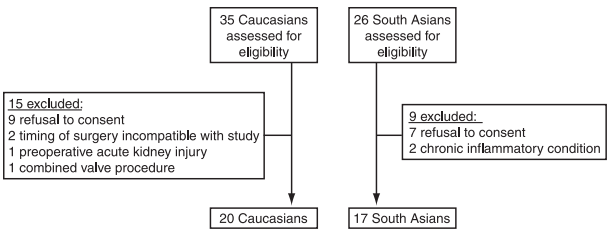

Fig. 1 – Study profile.