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Volatile anesthetic attenuates phagocyte function and worsens bacterial loads in wounds

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ABSTRACT

Background: Previously we have shown that volatile anesthetic isoflurane attenuated neutrophil recruitment and phagocytosis in mouse sepsis and skin inflammation models. The objectives of this study were to test *ex vivo* function of neutrophils in patients who underwent cardiac catheterization under volatile anesthesia *versus* intravenous anesthesia (IA), and also to assess the effect of anesthesia on surgical site infections (SSIs) using mouse model to understand the clinical relevance of anesthesia-induced immunomodulation.

Methods: Whole blood from patients who underwent cardiac catheterization procedures either by volatile anesthesia or IA was collected and subjected to phagocytosis assay and a lipopolysaccharide-induced tumor necrosis factor-α assay. Mouse SSI with *Staphylococcus aureus* USA300 was created, and the effect of isoflurane and propofol exposure (short or long exposure) on bacterial loads was tested.

Results: Neutrophil phagocytosis was significantly attenuated after the induction of volatile anesthesia in patients, but not by IA. Monocyte phagocytosis was not affected by the anesthesia regimen. Bacterial loads following SSIs were significantly higher in mice receiving long, but not short, isoflurane exposure. Propofol exposure did not affect bacterial loads.

Discussion: Neutrophil phagocytosis can be affected by the type of anesthesia, and preclinical model of SSIs showed potential clinical relevance. The effects of anesthesia regimen on SSIs in patients needs to be studied extensively in the future.

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Introduction

Phagocytes are cells that ingest harmful particles and bacteria to protect the host and include an array of innate immune cells such as neutrophils, monocytes, macrophages, and dendritic cells. These professional phagocytes express surface receptors that assist clearance of a wide range of microbial pathogens and their products, including toll-like receptors (TLRs), Fc receptors, and C3b receptors.[1,2] Phagocytes are also important sources of pro- and anti-inflammatory cytokines, which help to regulate the host immune response. Thus, phagocytes are considered to be the front-line defense cells.[3]

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Because perioperative infections, such as surgical site infections (SSIs) result in significant morbidity, mortality, and financial burdens,[4-7] it is of great interest to understand the factors that potentially affect the behavior of these professional phagocytes in the perioperative setting, thereby mitigating the risk of infection.

The effect of anesthetics on the immune system was described more than a century ago when Graham reported that ether anesthesia significantly inhibited leukocyte phagocytosis of streptococci.[8] This observational study did not lead to subsequent investigations by others for a long time, but recently there is a renewed interest in understanding the effect of anesthetics on immune cells.[9-11] Ether is no longer used in clinical practice, but its derivatives isoflurane and sevoflurane are the main volatile anesthetics (VAs) in clinical use. We previously showed that isoflurane exposure attenuated the recruitment and phagocytic capacity of neutrophils in mouse experimental abdominal sepsis and skin inflammation models.[12,13] Neutrophils are initial responders in surgical procedures during which anesthesia is provided, and their adequate function is critical to control SSIs.[14] However, studies that directly examine the effect of different anesthetics on phagocytes, including neutrophils, in surgical patients are limited. Therefore, the objective of this study was to test if VAs would affect phagocyte function in patients. Because anesthesia for younger pediatric patients are often induced and maintained by VAs, we studied *ex vivo* phagocyte function in these patients under VA-based anesthesia. We also included an intravenous anesthesia (IA) group as a comparator. An additional study objective was to assess the clinical relevance of anesthesia-induced immunomodulation by using a clinically relevant mouse SSI model.

Materials and methods

Study design and sample collection

In this study, we compared the effect of volatile anesthesia and IA on neutrophil function in patients who underwent routine cardiac catheterization procedures between November 2014 and January 2017. The study was approved by the Institutional Review Board at Boston Children's Hospital, and written informed consent was obtained from all patients. The study was registered in ClinicalTrials.gov (NCT02207842) and carried out in accordance with Declaration of Helsinki. We included patients greater than or equal to 1 y of age for the study because the maturation of phagocytes may take up to 1 y of age.[15,16] We excluded patients with noncardiac comorbidities such as known underlying hematological disorders, known oncological disorders, or cyanotic heart disease. In addition, we excluded patients who did not require preoperative laboratory testing or preoperative intravenous catheter insertion.

From electronic medical records, we obtained the age, weight, primary diagnosis, procedure, comorbidities, list of regular medications, preoperative complete blood count with differential (if available), American Society of Anesthesiologist physical status, and medications administered intraoperatively. The function of phagocytes for each patient was assessed at two different time points. The initial time point was at the preoperative blood draw or for some patients at the preoperative intravenous line insertion. The secondary time point was 1 h after the induction of anesthesia. As parameters of phagocyte function, we measured phagocytosis and lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF)-α production. In addition, the activation level of phagocytes at the time of blood collection was probed by testing CD18 and m24 expression levels. The method for each assay is described in the following. For the VA group, patients underwent mask induction with sevoflurane. Once induced, anesthesia was maintained with sevoflurane (end-tidal concentration of 1.0%-2.5%) or isoflurane (end-tidal concentration of 0.3%-1.1%). For the IA group, an intravenous catheter was placed preoperatively. Anesthesia was induced and maintained with propofol infusion. One hour after anesthesia, blood was collected in heparin-containing tubes. At the time of intraoperative blood collection, none of patients had received catheter intervention by cardiologists yet. Assays were initiated within 30 min of sample collection.

Phagocytosis assay

Phagocytosis assay was performed using Phagotest (Glycotope Biotechnology; Berlin, Germany) per the company protocol with minor modification. Phagotest is a widely used phagocytosis assay for clinical samples.[17-19] Briefly, 50 μL of heparinized whole blood was incubated with 2.5 μL of opsonized and fluorescein isothiocyanate (FITC)-labelled *Escherichia coli* (*E coli*) at 37°C for 5 min. Negative controls were kept on ice. After quenching, samples were centrifuged and washed. After blood erythrocytes were lysed with FACS lysis solution (BD Biosciences; Billerica, MA), samples were subjected to flow cytometry analysis. Granulocytes and monocyte population were gated by forward and side scatter analysis. Phagocytosis percentage was defined as [the number of FITC positive granulocytes (or monocytes)/the number of granulocytes (or monocytes)] $\times$ 100 (%).

Ex vivo *TNF-α production assay*

The capacity of the subjects' phagocytes to respond to a challenge was also tested by using an *ex vivo* TNF-α production assay as previously described.[20] Monocytes are the primary producers of TNF-α. Briefly, 50 μL of whole blood collected in a heparinized tube was incubated with 500 pg/mL of LPS (O111:B4, purified by phenol extraction; Sigma–Aldrich, St. Louis, MO) and incubated for 4 h at 37°C. After centrifugation, the plasma was subjected to TNF-α measurements using a human TNF-α ELISA kit (R&D systems; Minneapolis, MN) per the company protocol.

CD18 and m24 expression on neutrophils

After Fc blocking, whole blood was incubated with anti-human CD18-phycoerythrin antibody (Biolegend; San Diego, CA) and anti-human m24-FITC antibody (kindly provided by Professor Nancy Hogg, London Research Institute). After blood erythrocytes were lysed with FACS lysis solution, samples were subjected to flow cytometry analysis. Granulocytes and monocyte populations were gated from forward and side scatter analysis.

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