Mast cell activation and arterial hypotension during proximal aortic repair requiring hypothermic circulatory arrest

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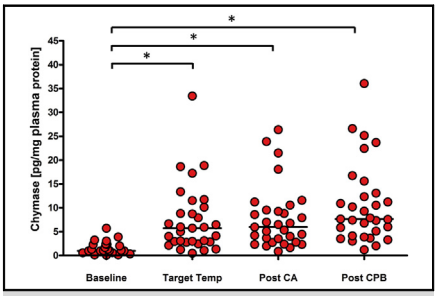
ABSTRACT

Objective: Aortic surgeries requiring hypothermic circulatory arrest evoke systemic inflammatory responses that often manifest as vasoplegia and hypotension. Because mast cells can rapidly release vasoactive and proinflammatory effectors, we investigated their role in intraoperative hypotension.

Methods: We studied 31 patients undergoing proximal aortic repair with hypothermic circulatory arrest between June 2013 and April 2015 at Duke University Medical Center. Plasma samples were obtained at different intraoperative time points to quantify chymase, interleukin-6, interleukin-8, tumor necrosis factor alpha, and white blood cell CD11b expression. Hypotension was defined as the area (minutes × millimeters mercury) below a mean arterial pressure of 55 mm Hg. Biomarker responses and their association with intraoperative hypotension were analyzed by 2-sample *t* test and Wilcoxon rank sum test. Multivariable logistic regression analysis was used to examine the association between clinical variables and elevated chymase levels.

Results: Mast cell-specific chymase increased from a median 0.97 pg/mg (interquartile range [IQR], 0.01-1.84 pg/mg) plasma protein at baseline to 5.74 pg/mg (IQR, 2.91-9.48 pg/mg) plasma protein after instituting cardiopulmonary bypass, 6.16 pg/mg (IQR, 3.60-9.41 pg/mg) plasma protein after completing circulatory arrest, and 7.64 pg/mg (IQR, 4.63-12.71 pg/mg) plasma protein after weaning from cardiopulmonary bypass (each P value $< .0001$ vs baseline). Chymase was the only biomarker associated with hypotension during ($P = .0255$) and after ($P = .0221$) cardiopulmonary bypass. Increased temperatures at circulatory arrest and low presurgical hemoglobin levels were independent predictors of increased chymase responses.

Conclusions: Mast cell activation occurs in cardiac surgery requiring cardiopulmonary bypass and hypothermic circulatory arrest and is associated with intraoperative hypotension. (J Thorac Cardiovasc Surg 2016;■:1-9)



Significant release of mast cell-specific chymase during proximal aortic repair surgery.

Central Message

Mast cell activation during proximal aortic repair with hypothermic circulatory arrest is associated with hemodynamic instability.

Perspective

In patients undergoing proximal aortic repair with hypothermic circulatory arrest, we provide the first evidence that mast cell activation is an important mechanism propagating inflammatory and vasomotor disturbances. Well-tolerated drugs exist to stabilize mast cells and could provide a novel therapeutic opportunity to reduce adverse systemic responses in cardiac surgery.

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Episodes of intraoperative hypotension have been linked to adverse outcomes such as end-organ injury and mortality.[1] In cardiac surgery, complex vasomotor disturbances lead to hypotension through generalized vasoplegia and threaten adequate organ perfusion through endothelial leakage and associated tissue edema (reviewed elsewhere[2]). In fact, up

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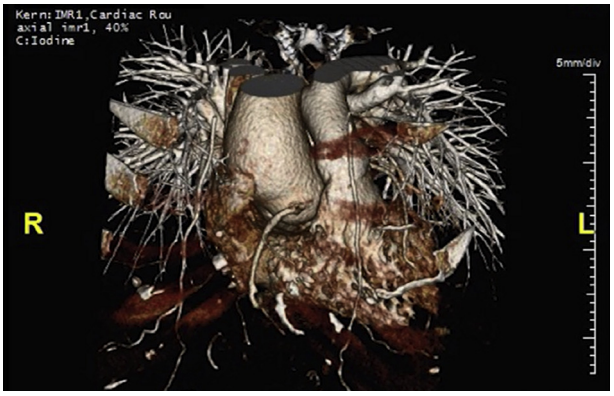
Abbreviations and Acronyms

Δ chymase	= delta baseline chymase
CPB	= cardiopulmonary bypass
HCA	= hypothermic circulatory arrest
IL	= interleukin
I/R	= ischemia/reperfusion
LT	= leukotriene
MAP	= mean arterial pressure
MC	= mast cell
TNFα	= tumor necrosis factor alpha

to 25% of cardiac surgery patients develop a vasoplegic syndrome, a form of distributive shock that is linked to increased length of stay and mortality.[3,4] But even in less dramatic manifestations, prolonged periods spent outside a still poorly defined optimal perfusion range affect postoperative outcomes.[5,6] Currently, the factors that cause such hemodynamic shifts during cardiac surgery are not well understood, impeding substantial advancement of patient care beyond supportive measures.

We have recently shown in a rat model that mast cells (MCs) play an important role in early inflammatory and tissue injury responses following deep hypothermic circulatory arrest.[7] As evidenced by their pivotal role in asthma and anaphylaxis, MCs can rapidly launch local and systemic inflammatory responses through release of potent mediators from preformed stores. These effectors can dramatically change vasomotor function (eg, heparin, histamine, and prostaglandins), endothelial integrity (eg, proteases, prostaglandins, and vascular endothelial growth factor), and can activate further inflammatory components (eg, chemokines and cytokines) (reviewed elsewhere[8]). This identifies MCs as crucial regulators of vascular integrity, tone, and function and as a potent factor in the propagation of systemic inflammation.

Establishing significant MC activation in cardiac surgery constitutes a first step toward establishing a possible causative role of MCs in the development of hemodynamic disturbances and systemic inflammatory activation. Here, we present the first study that specifically addresses the activation pattern of MCs during aortic surgery by measuring intraoperative plasma chymase levels, an MC-specific protease stored in intracellular vesicles and rapidly released upon MC stimulation. Based on our experimental data[7] and the pronounced inflammatory responses regularly observed, we targeted our study to patients undergoing proximal aortic repair necessitating hypothermic circulatory arrest (HCA) (see Videos 1-3 for representative procedure). Furthermore, as a first exploration into the clinical relevance, we characterized the perioperative setting in which MC responses occur and examined their association to intraoperative hypotension.

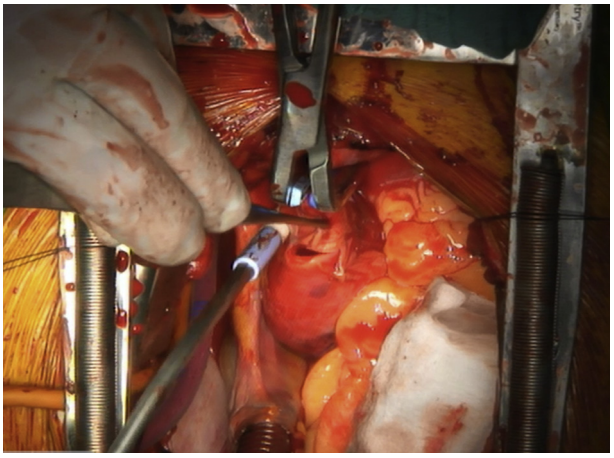


VIDEO 1. An example of proximal aortic repair surgery requiring hypothermic circulatory arrest at the Duke University Medical center. Part 1: Case presentation, cannulations including right axillary cannulation and crossclamp. Video available at: http://www.jtcvs.org.

METHODS

Patient Selection and Data Collection

As part of our ongoing research effort, we conducted a pilot study to define inflammatory responses and cognitive outcomes in patients undergoing proximal aortic arch surgery and requiring HCA between June 2013 and April 2015 at the Duke University Medical Center. The Institutional Review Board for Clinical Investigations at Duke University Medical Center approved this study and informed consent was obtained preoperatively from all patients. We included all patients aged $\geq$ 40 years except those with a history of symptomatic cerebrovascular disease and substantial residual deficit, alcoholism, psychiatric illness, renal failure (creatinine > 2.0 mg/dL), or those with less than a seventh-grade education, or unable to complete neuropsychological testing or cranial magnetic resonance imaging. Patient data were extracted from the electronic health record software (Epic, Verona, Wis) and included patient demographic characteristics, procedure type, preoperative medications, pre- and



VIDEO 2. An example of proximal aortic repair surgery requiring hypothermic circulatory arrest at the Duke University Medical center. Part 2: Moderate hypothermic circulatory arrest with antegrade cerebral perfusion, transverse aortic arch reconstruction (Hemi-Arch), and preparation of the aortic root for reconstruction. Video available at: http://www.jtcvs.org.