Increased Inflammation in Pericardial Fluid Persists 48 Hours After Cardiac Surgery

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Cardiac surgery causes direct trauma to cardiac tissue, breaches the pericardium, and disrupts the normal composition of the fluid largely produced from the myocardial interstitium and epicardial and visceral pericardium. This leaves the heart exposed to pericardial fluid (PCF) and mediastinal contents comprising inflammatory cells and their products that now bathe the heart. This can potentially have adverse effects on the thin-walled atria leading to postoperative atrial fibrillation (AF).[1] After cardiac surgery, the pericardium remains open, and chest drains are routinely placed to prevent fluid accumulation around the heart. Here, we describe the concentration and trajectory of blood proinflammatory factors in the PCF after cardiac surgery over time. The study protocol was approved by the University of Alabama at Birmingham. Institutional Review Board approval and informed consent were obtained from all patients.

PCF (n=19) was collected immediately after pericardiotomy (time 0) and from the pericardial drains at times 4, 12, 24, and 48 hours after surgery. The patient population (mean age, 60±3 years) included 26.3% women and 26.3% blacks undergoing cardiac surgery (coronary artery bypass graft, n=14; coronary artery bypass graft+valve procedure, n=3; valve procedure alone, n=2). Patients with ventricular assist devices, AF surgery, thoracic aorta surgery, and AF within 6 months prior were excluded. All participants who had valve replacement (with or without coronary artery bypass graft) underwent on-pump surgeries. Of the patients undergoing coronary artery bypass graft only, 7 underwent on-pump and 7 underwent off-pump surgeries. Blood samples were collected in parallel with PCF.

ELISA analysis[2] revealed that neutrophil products (myeloperoxidase and neutrophil-gelatinase–associated lipocalin), neutrophil chemotactic factors (C-X-C motif chemokine ligand 6 and interleukin-8), and cardiac inflammatory factors (tumor necrosis factor-α and oncostatin M) were manyfold higher in PCF than in blood over the 4- to 48-hour time course after cardiac surgery (Figure A). Matrix metallopeptidase-9 (MMP-9), a major product of neutrophils, was significantly higher in blood than in PCF at time 0, but quickly rose in PCF to 2.6-, 2.3-, and 2.7-fold higher than in blood at 4, 12, and 24 hours, respectively. Mast cell chymase activity was increased at 4, 12, and 24 hours in comparison with time 0, whereas MMP-9 activity, which is activated by chymase, was significantly higher than time 0 throughout the 48 hours postsurgery (Figure B).

Seven of the 19 patients (37%) had postoperative AF. There was no relationship between AF and PCF proinflammatory proteins at baseline. PCF troponin I levels were significantly higher at 48 hours among those who had postoperative AF (0.22±0.05 μg/mL) than those who did not (0.09±0.07 μg/mL, t=3.125, P=0.01).

Troponin I (Figure A, second row, right graph) was markedly elevated in PCF over blood values at 4, 12, 24, and 48 hours after surgery. As opposed to the other PCF constituents that can come from multiple sources, troponin I is solely produced by cardiac myocytes. The persistent 3-fold elevation of troponin as

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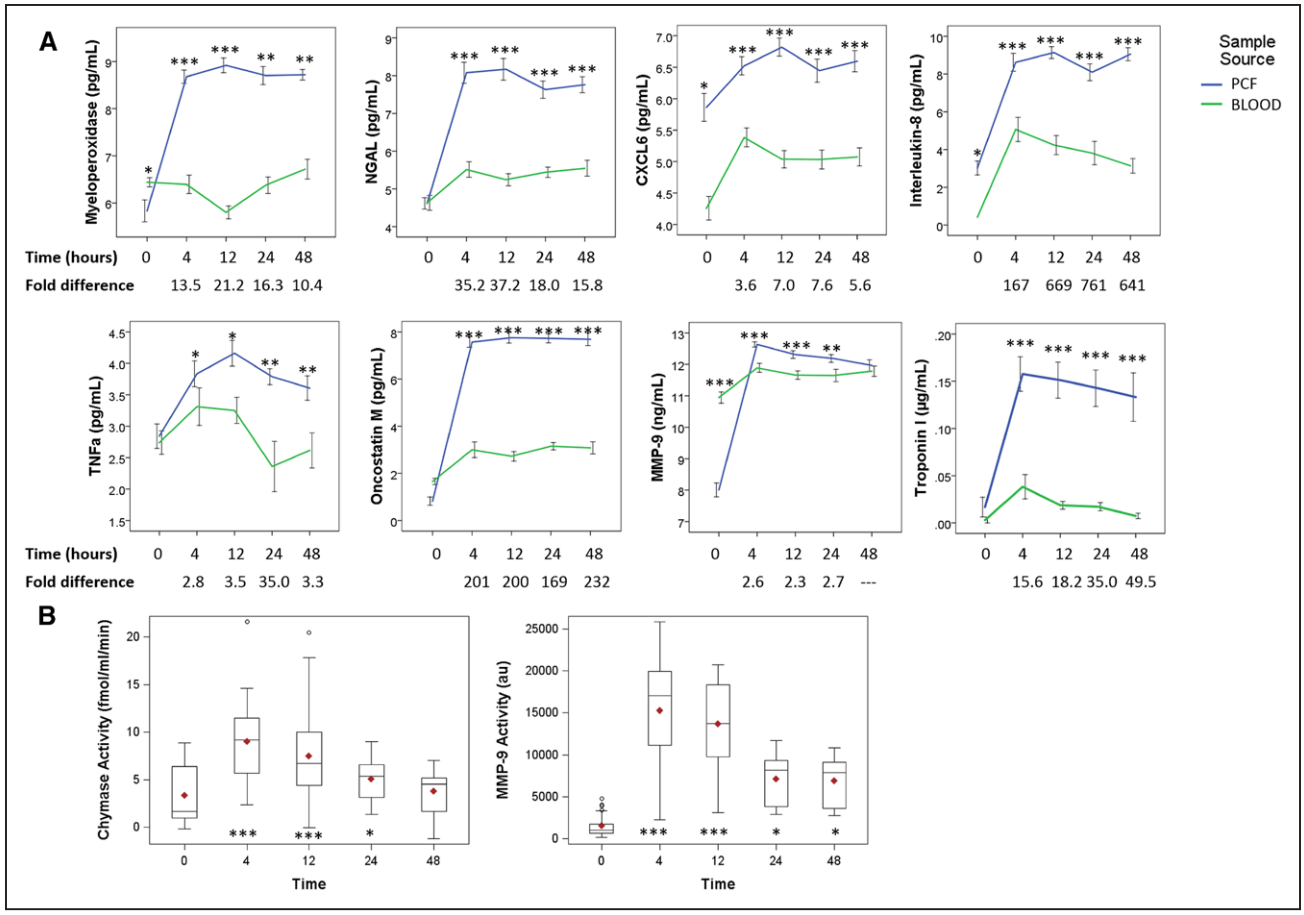

Figure. Proinflammatory proteins and troponin in PCF versus blood and enzymatic activity in PCF over time. **A,** Neutrophil (top row), cytokine (second row, left graphs), MMP-9, and troponin (second row, right graph) were higher in PCF than in blood after cardiac surgery. Multilevel modeling and Bonferroni adjusted least-squares means analyses were used to determine differences in measures between PCF and blood values at each time point (n=8 at time 0; n=19 at 4, 12, and 24 hours). Lines represent mean±standard error (**P*≤0.05, ***P*≤0.01, ****P*≤0.001 PCF vs. blood.) **B,** Enzymatic activity in PCF. Chymase and MMP-9 in PCF over time. (**P*<0.05, ***P*<0.01, ****P*<0.001 compared with time 0.) au indicates arbitrary units; CXCL6, C-X-C motif chemokine ligand 6; MMP-9, matrix metallopeptidase-9; NGAL, neutrophil-gelatinase associated lipocalin; PCF, pericardial fluid; and TNFa, tumor necrosis factor-α.

blood levels returned to normal suggests a defective PCF clearance mechanism but cannot rule out ongoing myocardial injury.

In a previous study, Kramer et al[2] demonstrated increased neutrophil infiltration in PCF at 4 to 48 hours postcardiac surgery over PCF levels at time 0. Lipid peroxidation products of arachidonic acid–derived isoprostane 8-iso-prostaglandin $F_{2\alpha}$ and its stereoisomer 8-iso-15-prostaglandin $F_{2\alpha}$ (F2 isoprostanes) were elevated in PCF at 4 and 12 hours following surgery and returned to PCF levels at time 0 by 24 to 48 hours.[2] Here we demonstrate sustained inflammation up to 48 hours postsurgery mediated by inflammatory cell products that include neutrophil myeloperoxidase and neutrophil-gelatinase–associated lipocalin, mast cell chymase, and inflammatory cytokines such as tumor necrosis factor-α and oncostatin M. Such high concentrations of these pathological stimulants coupled with underlying atrial myocardial pathology can amplify the direct myocardial insult of a cardiac operation and may potentially contribute to the risk for postoperative AF.[3]

The rapid rise in the neutrophil chemotactic attractants C-X-C motif chemokine ligand 6 and interleukin-8 in PCF after cardiac surgery likely leads to increased neutrophil recruitment into the PCF, reflecting the sustained increase of the PCF neutrophil products myeloperoxidase, neutrophil-gelatinase–associated lipocalin, and MMP-9, in addition to increased tumor necrosis factor-α and oncostatin M mast cell chymase and MMP-9 activities.

Multiple circulating inflammatory factors, including tumor necrosis factor-α, neutrophil-gelatinase–associated lipocalin, myeloperoxidase, oncostatin M, and MMP-9, have been linked to postoperative AF in multiple studies.[3,4] Here we demonstrate a local 4- to 700-fold increase of these inflammatory factors for a 48-hour period in PCF in comparison with blood and PCF values at time 0. A recent study demonstrated a higher incidence of complications

with early drain removal within 24 hours.[5] The highly inflammatory postoperative PCF that can only be cleared by suction leads us to speculate that early drain removal may potentiate postoperative cardiac complications, in particular, postoperative AF.

As opposed to systemic pharmacological approaches to neutralize the highly inflammatory PCF, direct introduction of anti-inflammatory medications into or washing of the pericardial space for the first 48 hours could potentially be beneficial. Other solutions might include therapies such as a slow-release mesh/medication delivery system with antioxidants or anti-inflammatory medications. Although the findings of this study raise interesting questions, a larger cohort is required to assess associations of clinical outcomes and temporal patterns of PCF inflammation.

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DISCLOSURES

None.

AFFILIATIONS

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FOOTNOTES

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