EDITORIAL: ENDOTHELIAL AND MYOCARDIAL STUNNING

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Until recently, myocyte stunning from inadequate cardiac protection has been the main focus of interest and is most relevant in damaged hearts (ie, hypertrophy, unstable angina, and reduced ejection fraction) in which vulnerability is accentuated. This injury is transient, since stunning recovers after brief inotropic or mechanical support. This editorial focuses on an expanding recognition that *both* the myocyte and the endothelium can be injured or stunned, as the two limbs are interrelated.

Damaged hearts exhibit loss of endothelium-dependent factors and reduced nitric oxide formation. The result is perioperative vasospasm, adherence of platelets, and leukocyte attachment that also causes capillary obstruction with inhomogeneous flow. The essential theme is that the endothelium is injured, because neutrophils do not attach, then roll, and finally have parenchymal influence for oxygen radical injury without such damage. This clinical report is the application of an experimentally proven method to reduce the consequences of endothelial damage.

The transient nature of stunning is clear. Brief leukocyte depletion (ie, > 95% white blood cell reduction in this study) is quickly reversed by blood with a normal white cell count. However, the persistence of functional benefits indicates that residual protection is retained, including experimental markers of reduced endothelial adherence of white cells.

The expertise of Dr Roth's surgical team[1] is apparent, with no intra-aortic balloon counterpulsations or deaths in high-risk patients. Their carefully defined data characterize the advantages of white blood cell reduction in patients with ejection fractions of about 20%, through reduced needs for dopamine, absent enoxamine for hemodynamic support, raised ejection fraction, diminished troponin release (a myocardial marker of cellular injury), less ventricular fibrillation after aortic unclamping (presumably from improved excitation/contraction coupling), and, finally, shorter intensive care unit stay (48 vs 60 hours), even though the last variant is not *significant* due to increased vulnerability. These aforementioned "soft or surrogate" end points conform precisely to their referenced reports of benefits of leukocyte depletion in damaged hearts. Conversely, no benefit of leukocyte depletion has been established in patients with an ejection fraction of more than 40%.

The merits of cardiac versus systemic leukocyte depletion are clear, since systemic doses allowed only 38% reduction at the time of aortic unclamping. The white cell filter becomes less functional after more than 1000 mL blood delivery, so that selection of one versus two white blood filters becomes dependent on defining the role of leukocyte depletion throughout all periods of cold blood cardioplegia during aortic clamping, and/or *only* in the warm 500- to 700-mL reperfusate.

Surgical reperfusion strategies become confusing to our basic science and cardiology colleagues, who address single events after short ischemic intervals, whereas we confront prolonged ischemia for surgical repair. Unidimensional focus on one element will not be successful because ischemia unmasks many changes. Our study, quoted in the reference list,[2] showed that white blood cell depletion alone reduced reperfusion injury but failed to restore contractility unless leukocyte depletion supplemented a more complex cardioplegic approach. The composite approach is clear from this study, since their blood cardioplegic solutions contain potassium, glucose, citrate, and a buffer with good clinical results, even without white blood cell depletion.[1]

We must establish cardiac surgical recognition of global endothelial stunning and develop efforts to reduce this injury during myocardial protection. In damaged hearts, conventional cardioplegic solutions can completely prevent myocyte injury, yet allow endothelial damage with resultant white blood cell adherence.[3] A principal underlying mechanism is endothelial loss of nitric oxide production, subsequently allowing the neutrophil and platelet adherence

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and changing vasoactivity to impair subsequent vasodilatation. White blood cell adhesion is *only one step* in this injury.

Our principal surgical dilemma relates both to *dealing* with global stunning and *understanding* why this occurs. The neutrophil filter addresses the lesions after they are present, with acceptance that brief reperfusion interventions can reduce endothelial injury. Studies that focus on maintaining the intrinsic endothelium-dependent protective component, nitric oxide generation, may be useful. Hiramatsu,[4] Mizuno,[3] Kronon,[5] and their colleagues, discovered that delivery of the natural nitric oxide precursor, L-arginine, limits endothelial and myocyte damage, even without white blood cell depletion. Consequently, leukocyte depletion adds to the expanding catalog of strategies for surgical correction, but efforts at preventing endothelial stunning, rather than treating the injury, must be considered in the future.

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