Heat Shock Protein Expression During Cardiac Surgery

Ahmad Z. Chaudhry · Michael D. Diodato ·
Malek G. Massad

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There has been a great deal of interest in a group of cellular proteins collectively called heat shock proteins (HSPs) to identify their role in the inflammatory and cell-mediated responses that occur during heart surgery [1]. Although most patients do fine after cardiopulmonary bypass (CPB), some develop an inflammatory response clinically resembling a sepsis-like state. At the cellular level, several stress-related proteins, clustered as HSPs, participate in the inflammatory cascade mostly by acting as chaperons. Their basic role is to maintain the structural integrity of proteins under stress states by keeping them in their folded state, but their overexpression can lead to an inflammatory response.

The *ex vivo* environment created during CPB exposes blood to nonendothelial circuitry, thereby triggering responses in the complement, coagulation, and humoral cascades. Chaperone HSPs play a significant role in inciting and modulating these triggers and responses. HSP-60, for example, is mostly intracellular; but in stress states it is overexpressed on endothelial cells. This protein is taken up by macrophages, which in turn cause it to trigger the immune system by signaling T and B lymphocytes. An HSP-60 lipopolysaccharide (LPS) complex then activates dendritic cells, causing release of interferon- γ (INF γ) and interleukin-12 (IL-12). This complex depends on toll-like receptors (TLRs) to gain entry into the cell via CD14 receptors. TLR 2, along with HSP-60, causes a T-cell response that down-regulates the secretion of tumor necrosis factor- α (TNF α) and INF γ and up-regulates the secretion of transforming growth factor- β (TGF β) and

IL-10. Intracellularly, the HSP60–LPS complex assembles nuclear factor κ B (NF- κ B) components, which in turn lead to initiation of cytokines, chemokines, and growth factor synthesis. This cascade leads to the hyperdynamic sepsis-like syndrome sometimes seen following CPB.

The HSP-70s are yet another complex set of proteins that include HSP-73, HSP-72, HSP-70 (which is stress inducible), and HSP70L1. This HSP family, however, is protective in nature. In stress states, HSP-70 enters the nucleus and activates poly (ADP-ribose) polymerase enzyme, involved in DNA repair. Overexpression of the latter enzyme can cause cellular energy depletion by overconsumption of ATP and NAD⁺ often seen after rapid reperfusion. The deleterious effects of poly (ADP-ribose) polymerase can be neutralized by HSP-70 synthesized by inducing heat shock. This family of proteins also stabilizes the membranes of lysosomes, thereby preventing autolysis and apoptosis. HSP-70 is released into the extracellular compartment and also uses the CD-14 receptor along with TLR-2 and TLR-4 to stimulate nucleic synthesis of NK- κ B, ultimately leading to monocyte stimulation. HSP-70 is detected after cardiac surgery and more so during myocardial damage wherein high expression correlates with high creatine kinase, myocardial bound (CK-MB) and troponin-T levels. Its expression peaks 2 h after surgery and is fourfold lower during off-pump heart surgery compared to on-pump heart surgery. This is unlike HSP-60 levels, which seem to be unaffected regardless of whether CPB is used [2].

Other proteins that are increased during CPB include HSP-27, which prevents apoptosis by halting activation of caspase through sequestering cytochrome c and procaspase 3 and by stabilizing the cytoskeleton. Its levels rise with stress and decline when stress is attenuated; and it is increased twofold with use of CPB. HSP-90 α is another

A. Z. Chaudhry · M. D. Diodato · M. G. Massad (✉)
Division of Cardiothoracic Surgery, University of Illinois at
Chicago, 840 S. Wood Street, CSB Suite 417(MC 958), Chicago,
IL 60612, USA
e-mail: mmassad@uic.edu

protein that maintains the architecture of the cytosol and serves to present tumor antigens to T cells. Proteasome 20S is a novel protein that promotes apoptosis, antigen presentation, nuclear receptor binding, and intracellular transport. It is also seen in twice the levels after CPB when compared to off-pump surgery. Whereas the levels of all the previously mentioned proteins (i.e., HSP-27, HSP-70, HSP-90 α) rise 60 min after surgery, proteasome 20S is released 24 h later [3].

Cytoprotective proteins such as HSP-72 can be used for ischemic preconditioning as they have been shown to reduce infarct size and delay ischemic injury [4]. HSP-72 can be induced under stress using iatrogenic triggers such as heat, hypoxia, ethanol, amino acids, and metabolic inhibitors [5]. Glutamine has been shown to induce HSP-70, leading to increased nitric oxide (NO) production in an attempt to reduce the inflammatory response [6].

Moderate hyperthermia used during CPB induces HSP-72 as a means to attenuating the inflammatory response. HSP-72 up-regulation has been detected in endothelial cells, macrophages, and myocytes. Both HSP-72 levels and messenger RNA encoding have been demonstrated in assays using moderate hypothermia [7]. HSP-70, HSP-27, and HSP-90 α are seen at higher levels with CPB.

Atrial fibrillation (AF), a common complication following cardiac surgery, has been studied with reference to how the cytoprotective effects of HSPs play a role in its onset and perhaps prevention. HSP-70, for example, restricts apoptosis of cells following exposure to oxidative stress. At higher levels, the protective effects of HSP-70 are manifested via its ability to reduce production of the potent inflammatory mediator TNF α . HSPs have been shown to prevent the adverse atrial remodeling leading to AF and also to halt its progression from paroxysmal to persistent AF. There is structural and functional degradation of atrial myocytes whereby cells remain viable but are functionally impaired, causing contractile dysfunction leading to AF. HSP-B1 is a protein found to be inversely related to the duration of AF and extent of myolysis [8]. It is also found to have higher levels in patients with paroxysmal AF than in those with persistent AF [9], suggesting a role for HSP-B1 in preventing the transition from paroxysmal to persistent AF. It has also been shown that with higher levels of atrial HSP-A1A there is a lower incidence of postoperative AF in patients in sinus rhythm undergoing cardiac surgery [10].

Given that some HSPs are at high levels in patients with no or only paroxysmal AF, can their modulation be a means to prevent or treat postoperative AF? Prevention of adverse atrial remodeling that leads to AF has been attempted using agents such as Ca²⁺ channel blockers, Na⁺/H⁺ exchange inhibitors, and angiotensin-converting enzyme inhibitors. Amiodarone, mibefradil, statins, and

glucocorticoids have also been shown to prevent atrial remodeling in AF. The last two categories of drugs induce HSP-B1 expression. Hence, agents that cause induction of these HSPs may prevent the atrial remodeling that leads to AF, thereby affording a new possible therapeutic modality in managing this common complication.

Better understanding of HSPs is needed if their augmentation is to be utilized in the clinical setting to prevent cellular destabilization and degradation leading to complications such as AF, systemic inflammatory response syndrome (SIRS), and multiorgan system failure. Time has arrived for studies focusing on randomizing subjects based on preexisting factors or risks of complications such as atrial fibrillation or SIRS and evaluating agents that induce protective HSP. This will ascertain whether they truly play a role in predicting, and possibly preventing, adverse outcomes after cardiac surgery.

References

1. Lin CY, Yang TL, Hong GJ, et al (2010) Enhanced intracellular heat shock protein 70 expression of leukocytes and serum interleukins release: comparison of on-pump and off-pump coronary artery surgery. *World J Surg*. doi:10.1007/s00268-010-0419-2
2. Schäfler AE, Kirmanoglou K, Balbach J et al (2002) Heat shock protein 60 expression in patients undergoing cardiac operations. *Basic Res Cardiol* 97:258–261
3. Szerafin T, Hoetzenecker K, Hacker S et al (2008) Heat shock proteins 27, 60, 70, 90, and 20s proteasome in on-pump versus off-pump coronary artery bypass graft patients. *Ann Thorac Surg* 85:80–87
4. Yellon DM, Latchman DS, Marber MS (1993) Stress proteins: an endogenous route to myocardial protection—fact or fiction? *Cardiovasc Res* 27:158–161
5. Morimoto R, Tissieres A, Georgopoulos C (eds) (1990) Stress proteins in biology and medicine. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY
6. Hayashi Y, Sawa Y, Fukuyama N et al (2002) Preoperative glutamine administration induces heat-shock protein 70 expression and attenuates cardiopulmonary bypass-induced inflammatory response by regulating nitric oxide synthase activity. *Circulation* 106:2601
7. Qing M, Vazquez-Jimenez F, Schumacher K et al (2002) Moderate hypothermia during cardiopulmonary bypass increases intramyocardial synthesis of heat shock protein 72. *J Thorac Cardiovasc Surg* 124:724–731
8. Brundel BJ, Robert H, Ke L et al (2006) Heat shock protein upregulation protects against pacing-induced myolysis in HL-1 atrial myocytes and in human atrial fibrillation. *J Mol Cell Cardiol* 41:555–562
9. Yang M, Tan H, Cheng L et al (2007) Expression of heat shock proteins in myocardium of patients with atrial fibrillation. *Cell Stress Chaperones* 12:142–150
10. Rammos K, Koullias GJ, Hassan MO et al (2002) Low preoperative HSP70 atrial myocardial levels correlate significantly with high incidence of postoperative atrial fibrillation after cardiac surgery. *Cardiovasc Surg* 10:228–232