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Sepsis-induced cardiomyopathy: A Review of pathophysiologic mechanisms

Myocardial depression is a major contributor to mortality and morbidity in septic patients. Contractile dysfunction in the septic heart is manifest as biventricular dilatation, reversible decrease in ejection fraction, diminished blood pressure response to IV fluids, and blunted ability to augment cardiac output despite increased levels of circulating catecholamines [1]. Traditionally the physiologic disturbances have classically been described in a biphasic spectrum: early hyperdynamic shock characterized by increased cardiac output, decreased systemic vascular resistance (SVR) and warm, perfused skin, followed by cold hypodynamic shock, during which SVR increases to compensate for worsened cardiac output, resulting in tissue hypoperfusion, cool skin and eventual organ failure [1]. However, recent research suggests that hypodynamic shock is a mere manifestation of inadequate volume resuscitation, and may be prevented by appropriate volume loading [2].

Experimental evidence indicates that even patients with so-called "hyperdynamic" shock exhibit myocardial dysfunction relative to non-septic controls [3]. These patients have lower stroke work indices (stroke volume x mean arterial blood pressure, standardized for body surface area) as a function of end-diastolic volume, marking a downward and rightward shift of the Frank-Starling mechanism [4]. In fact, dilatation of the left ventricle in this setting is seen as an adaptive response that preserves cardiac output via the Starling mechanism, and it has been associated with lower mortality and improved prognosis in septic patients [5]. Earlier studies [6] note survivors of septic cardiomyopathy have significantly more dilated left ventricles (LV) and decreased ejection fractions (EF) relative to non-survivors [6]. However, newer literature has shown that lower ejection fractions translate into poorer prognoses [2].

In recent years, investigators have focused their attention on cytokines as the possible mediators of the myocardial depression of sepsis. Several types of nucleated cells produce and locally release these proteins in response to surgical, traumatic, ischemic or septic insults [7]. Studies performed on rodent models of sepsis show significant decreases in measures of contractility in cardiomyocytes exposed in vitro to TNF-α, IL-1β [8], and IL-6 [9]. Accordingly, patients with sepsis demonstrate higher levels of interleukins and complement components in their bloodstream [2].

The cellular mechanisms underlying cytokine-mediated cardiomyopathy are not entirely clear. Inducible nitric oxide (NO) production, intracellular calcium currents, oxidation-reduction imbalance, and disrupted respiratory chain activities have all been invoked in explanation. The remainder of this review will focus on the physiology of septic cardiomyopathy. We will review normal excitation-contraction (E-C) coupling in the cardiomyocyte in order to

illustrate possible mechanisms of disturbance. Special attention will be directed towards the interplay between endothelial NO expression and sarcoplasmic calcium currents, as well as the roles of cytokines.

Normal E-C coupling

Myocardial contraction and relaxation is regulated by the interplay amongst contractile proteins (thin actin and thick myosin filaments), regulatory proteins (troponin and tropomyosin) and calcium ions. In the resting state, tropomyosin blocks the site of actin-myosin interaction, while the troponin-I subunit inhibits the actin-myosin ATPase [10]. Extracellular calcium (Ca) enters the myocyte through sarcolemmal L-type Ca channels (LTCC) during phase 2 of the cardiac action potential. This, in turn, triggers stored intracellular Ca release from the sarcoplasmic reticulum (SR) into the cytoplasm via ryanodine receptors (RyR). As the intracellular Ca concentration increases, the ion binds the c-subunit of troponin, leading to conformational changes that relieve troponin and tropomyosin inhibition. Actin and myosin are then free to crosslink and contraction proceeds with ATP hydrolysis [10].

Ca channel closure at the end of phase 2 prevents extracellular influx, while cytoplasmic Ca is pumped back into the SR by the SR Ca ATPase (SERCA). This drop in intracellular Ca concentration allows troponin and tropomyosin to reassume their inhibitory configurations, and myocardial relaxation ensues. SERCA activity is regulated principally by phospholamban, an SR membrane protein that, in its dephosphorylated state, inhibits Ca uptake by SERCA [10].

Figure 1. ROLE OF CALCIUM IN NORMAL CARDIOMYOCYTE CONTRACTION

Figure 1. Extracellular Calcium (Ca^{2+}) enters through the sarcolemmal L type calcium channels (LTCC) which in turn triggers Ca^{2+} release from the Sarcoplasmic Reticulum (SR) through the Ryanodine receptors (RyR) known as Calcium Induced Calcium Release (CICR). The increase in calcium concentration within the cardiomyocyte induces conformational changes in the actin myosin filaments resulting in contraction. Once contraction is over, the Ca^{2+} is pumped back into the SR by the SR Ca ATPase (SERCA) whose activity is regulated by phospholamban. Calcium is also returned extracellularly via the sodium-calcium exchanger.

Figure 2. ACTIN – MYOSIN INTERACTION AT REST AND DURING CONTRACTION

Sarcoplasmic Ca concentration determines the force of myocardial contraction. Higher intracellular levels lead to greater relief of troponin inhibition, rendering more actin-myosin complexes active. β-adrenergic stimulation augments cardiac contractility by increasing intracellular Ca influx via a G-protein (G_S) /cAMP-mediated mechanism. The end-result is downstream protein kinase activation and phosphorylation of the LTCC, promoting Ca influx. β-agonism also promotes myocyte relaxation via phosphorylation of phospholamban, enhancing SERCA activity and preserving diastolic function [10]. Cholinergic stimulation, in turn, decreases contractility by downregulating intracellular Ca influx. An inhibitory G protein (G_I) responding to acetylcholine transmission both inhibits adenylyl cyclase (decreasing cAMP levels) and opens myocyte potassium channels, hyperpolarizing the cell [10].

Nitric Oxide

The effects of nitric oxide (NO) produced by nitric oxide synthase (NOS) have garnered heavy interest over the last 15 years as potential mediators of septic cardiomyopathy. NOS exist in three forms: NOS 1 and NOS 3 which are constitutive forms and as NOS 2 which is an inducible form [11]. Experiments in cultured cardiomyocytes of murine models show reduced β-adrenergic-induced inotropy upon exposure to activated immune cells [12]. Cytokine products of the activated cells include the enzyme NOS. Furthermore, NOS inhibitors such as N^G-monomethyl-L-arginine (L-NMMA) block the negative inotropic effects of cytokines [13]. However One illustrative experiment by Balligand et al [14] showed the interplay of bacterial endotoxin, macrophage stimulation, NOS induction, cGMP production and reduced contractility. Here, rat macrophages were stimulated by exposure to lipopolysaccharide (LPS, a component of bacterial endotoxin) and then incubated with rat cardiomyocytes for 24 hours. Amplitude of shortening of myocytes stimulated by β-agonists was significantly reduced by LPS exposure relative to controls, and this reduction was abolished by addition of the NOS inhibitor L-NMMA. Additionally, LPS exposure increased both nitrite production in myocytes and cGMP formation in reporter fibroblasts, suggesting a possible cGMP-mediated mechanism for NO-induced negative inotropy. Another experiment by Chung et al implicated inhibition of the adenylyl cyclase/cAMP second messenger system as the explanation for reduced contractility in the presence of NO [15]. Peroxynitrite, a product of interaction between NO and the superoxide anion, has also been proposed as a possible cardiodepressant [2, 16].

Returning to our model of E-C coupling, G_S stimulation by β-agonists ultimately leads to increased cAMP and phosphorylation of the LTCC, increasing Ca influx into myocytes. Cholinergic stimulation, alternatively, decreases cAMP levels while promoting cGMP-mediated myocardial relaxation. Though endothelial cells, myocytes, vascular smooth muscle cells, neurons and inflammatory cells all demonstrate NOS activity, it is not yet clear precisely how NO affects the cholinergic/adrenergic modulation of contractility.

Complicating the issue is the observation that cyokines exert cardioinhibitory effects in vitro over different time frames and both with and without NOS induction. Prolonged (>18 hour) exposure to LPS, TNF-α, or IL-1β decreased contractility of guinea pig cardiomyocytes, while increasing cGMP content and NOS 2 levels [8]. All of these effects were abolished when the steroid dexamethasone was added to culture. Dexamethasone has been shown to inhibit induction of NOS 2 but not the activity of constitutively-expressed NOS (NOS 1 or NOS 3). This seems to suggest that NO-mediated cardiodepression is dependent on the transcription and translation of an inducible protein. Yet we know from other cytokine studies that early myocyte depression and reduced intracellular Ca occur within minutes of exposure to IL-6 [17], and that TNF-α can block β-adrenergic effects on contractility without increasing mRNA for iNOS [18]. This implicates constitutive NOS 1 and 3 activation as the culprit in early septic myocardial depression, whereas inducible NOS 2 may mediate contractile depression that occurs in late sepsis [16].

The concept of NOS localization to subcellular domains helps clarify the complicated interplay between NO and the cardiovascular system. This paradigm proposes that: 1) NOS exists as various isoforms in each of the subcellular components in which it acts; and 2) NO acts as a second messenger within these compartments via post-translational covalent nitrosylation of cysteine thiol groups [19]. By this theory, the NOS 3 isoform found in the sarcolemmal membrane produces NO that modifies the LTCC so as to inhibit Ca entry, promoting myocardial relaxation. Concomitantly, NO derived from NOS 1 in the SR nitrosylates RyR channel proteins in a manner that promotes Ca efflux from the SR, causing contraction [19]. NO signaling by nitrosylation is fast, reversible, and affected by the overall nitroso-redox balance of the system [20].

Figure 3. LOCALIZATION OF VARIOUS ISOFORMS OF NITRIC OXIDE SYNTHASE
Figure 3. Nitric oxide (NO) produced by NOS 1 located in the Sarcoplasmic Reticulum (SR) acts on the Ryanodine Receptor (RyR) promotes Calcium efflux (Ca2+) thereby promoting contraction. NO produced by NOS 3 in the Sarcolemmal membrane acts on the L type Calcium Channels (LTCC) to inhibit calcium entry thereby promoting myocardial relaxation.

The oxidase enzymes NADPH oxidase and xanthine oxidase, as well as mitochondrial oxidative phosphorylation, generate the biologically relevant reactive oxygen species superoxide, hydrogen peroxide and the hydroxyl radical [21]. Reactive oxygen species (ROS) can be cytotoxic at high levels through a number of mechanisms. Aside from causing direct damage to DNA strands, proteins and lipids, ROS compete with NO for thiol substrates. Progressive oxidation of these substrates is irreversible, rendering them incapable of interacting with NO, thereby disrupting physiologic NO signaling [21]. Furthermore, NOS isoforms may directly interact with ROS-generating enzymes in a regulatory manner, such that NOS deficiency results in uncontrolled ROS production [19, 21]. Several animal models of heart failure have investigated the contributions of oxidative imbalance. Notably, Bendall et al [22] showed mice deficient in a catalytic subunit of NADPH oxidase had less ventricular hypertrophy and interstitial fibrosis after exposure to angiotensin II relative to wild-type mice. Two other studies illustrated how inhibition of xanthine oxidase (XO) with allopurinol improves parameters of endothelial function in smokers and diabetics, two populations prone to atherosclerosis and resultant endothelial dysfunction [23, 24]. However, no trials in humans with CHF to date have shown that XO inhibition leads to significant improvements in symptoms, functional performance, or clinical outcomes [21].

Intracellular Energetics

Cardiac dysfunction in sepsis has been linked to impaired intracellular calcium homeostasis and disrupted high-energy phosphate production. In the cecal ligation and puncture (CLP) model of sepsis in the cat heart, cardiac sarcoplasmic reticulum shows a 46% reduction in the rate of ATP-dependent Ca uptake during hypodynamic sepsis [25]. The SR Ca-ATPase (SERCA) and its main regulatory protein, phospholamban (PL), control reuptake of Ca into the SR. cAMP-dependent protein kinases normally phosphorylate PL and activate SERCA. This implicates defective phosphorylation of SR proteins in the myocardial dysfunction of late sepsis [25].

Cytopathic hypoxia refers to the phenomenon of impaired mitochondrial oxygen consumption by septic muscle despite adequate oxygen supply, which leads to uncoupled oxidative phosphorylation and diminished ATP production [26]. Chen et al studied this phenomenon in late (>18 hour) CLP-induced sepsis in rats and its susceptibility to “heat shock” pre-treatment [26]. They found decreased enzymatic activity of electron transport chain cytochrome c reductases, decreased expression of mitochondrial respiratory chain enzymes, and ultrastructural deformity in the mitochondria in the hearts of late sepsis rats. This translated to diminished ATP content in cardiomyocytes. Interestingly, all of the above septic-induced changes could be attenuated or reversed by whole-body heating rats to 41-42° C for 15 minutes prior to CLP. The group proposed heat-induced expression of “heat shock proteins” (Hsp) as the protective mechanism, and demonstrated how the expression of 2 such proteins (Hsp 72 and Grp 75) was preserved in heat shock relative to control. Functionally, Hsp 72 helps transfer newly-synthesized cytoplasmic proteins into mitochondria, while Grp 75 assists in mitochondrial protein folding and protein complex assembly [27, 28]. The group concluded

that mitochondrial respiratory chain protein dysfunction correlates with clinical deterioration in sepsis, and may be alleviated by the heat shock response.

Cellular Adhesion Molecules

Elaboration of TNF-α and IL-1 in LPS models of sepsis leads to neutrophil recruitment and inflammatory damage to both liver and lung tissue [29,30]. Intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) mediate neutrophil infiltration [31]. Raeburn et al demonstrated a 40% decrease in left ventricular developed pressure of isolated mice hearts 6 hours after LPS injection, associated with temporal increases in expression of ICAM-1, VCAM-1 and myocardial neutrophils [31]. Antibody blockade of either ICAM or VCAM abrogated contractile dysfunction, but neutrophil depletion by either antibody blockade or vinblastine pre-treatment did not. The authors suggested alteration in intracellular Ca fluxes and generation of oxygen free radicals by antibody crosslinking of adhesion molecules as possible explanations that warrant further investigation.

Complement

The humoral immune response becomes activated in sepsis, triggering a cascade of complement proteins. Eventual cleavage of C5 generates C5a, a potent anaphylatoxin, and C5b, a component of the terminal membrane attack complex, which lyses bacterial membranes [1]. C5a is a powerful pro-inflammatory agent known to increase neutrophil chemotaxis, granular enzyme release, reactive oxygen species production, and synthesis of cardiodepressant cytokines [1]. Overproduction of C5a and its receptor (C5aR), which is expressed on cells in the heart, lungs, liver and kidneys, could contribute to the dysregulated immune response characteristic of sepsis and multi-organ dysfunction. Niederbichler et al examined the effects of C5a in CLP-induced sepsis on rat hearts in vivo and isolated cardiomyocytes in vitro [32]. CLP resulted in significantly decreased left ventricular pressure in whole hearts, an effect reversed by administration of anti-C5a antibody (Ab) immediately after CLP. In isolated cardiomyocytes, exposure to recombinant C5a reduced contractility (measured as peak sarcomere shortening) in both CLP and sham-operated rats, but to a greater degree in CLP rats. There was a corresponding time-dependent increase in C5aR mRNA and protein extracted from CLP cardiomyocytes relative to sham cells. The authors proposed that constitutive expression of C5aR on cardiomyocytes mediates early C5a-induced cardiodepression, but sepsis enhances in vivo C5a production and C5aR expression on cardiomyocytes, resulting in delayed cardiomyopathy.

Other cytokine effects

Cytokines are peptides sporadically produced by nucleated cells in response to some stress or challenge [7]. Surgical insults, trauma, ischemia or sepsis can all induce the local release of these proteins from both somatic cells (endothelial, epithelial, fibroblasts) and immune cells (neutrophils, lymphocytes, macrophages). The cytokine signal serves as a language between the challenged cells [7]. This language is not determined by one or two peptides in isolation, but rather by the confluent effects of circulating binding proteins, levels of cytokine receptor expression and the overall cytokine milieu.

As such, we have been largely unsuccessful in translating knowledge about cytokine behavior in vitro to efficacious therapeutic manipulations in vivo. For example, TNF-α and IL-1β are 2 potent proinflammatory cytokines released by macrophages in sepsis that have each demonstrated in vitro depression of cardiac contractility [33, 34]. A trial conducted in the early 1990s on 10 patients with refractory septic shock using a monoclonal TNF-α antibody (Ab) revealed a transient but statistically significant decrease in heart rate and increase in left ventricular stroke-work index [35]. Nevertheless, no large scale clinical trials have shown a mortality benefit with TNF-α Ab in septic shock [4]. Similarly, a large phase III placebo-controlled trial of nearly 700 septic patients treated with IL-1 receptor antagonist failed to show any difference in 28-day mortality [36].

TNF-α may also trigger cardiac apoptosis in the LPS model of sepsis. Carlson et al examined TNF-α-dependent apoptotic pathways in isolated mouse cardiomyocytes that worked via activation of specific proteases termed capsases [37]. They found LPS injection increased capsase-3 activity in cardiomyocytes, in association with pro-apoptotic patterns of gene expression and depressed left ventricular developed pressure in ex vivo hearts. TNF-α receptor knockout mice challenged with LPS exhibited markedly decreased capsase activity despite elevated TNF-α concentrations. Administration of the capsase-3 inhibitor zVAD in wild-type mice attenuated LPS-induced cardiodepression. However, LPS was still able to trigger some degree of decreased contractility in knockout mice, indicating the presence of TNF-α-independent mechanisms of contractile disturbance. It has been suggested that caspase-3 activation may be associated with decreased sensitivity of the myofilaments to calcium, or even structural breakdown of the sarcomere itself. Given the relative reversibility of septic cardiomyopathy, further studies are necessary to delineate the exact role of caspases and apoptosis.

Summary

Experimental models of sepsis show clear evidence of myocardial contractile disturbance both in vivo and in vitro. This disturbance is present even in early "hyperdynamic" shock, when aggressive volume replacement and adaptive left ventricular dilatation can combine to preserve cardiac output [38]. What exactly triggers septic cardiomyopathy is still unknown. As normal cardiac contractility depends on intracellular Ca fluxes and ATP-consuming reactions, we have proposed mechanisms based on impaired cellular Ca homeostasis and uncoupled oxidative phosphorylation. We have examined the interplay between cellular products upregulated in sepsis, such as cytokines and nitric oxide, and the adrenergic/cholinergic/G protein-mediated regulation of contractility. Several investigators have successfully manipulated components of the regulatory pathway to reverse septic cardiodepression on a cellular level in vitro, yet the results of large clinical trials targeting these components in humans with septic cardiomyopathy are disappointing. Initial studies with NOS inhibitors such as NMMA in patients with septic shock are conflicting. Even though peripheral circulatory failure is reversed by increasing vascular tone and thereby reducing the requirement for pressors [40], use of NOS inhibitors have been associated with increased mortality [41].Perhaps our models of sepsis fail to accurately portray the complex biological processes occurring in the live human [39]. Alternatively, we may not fully grasp the protective effects of the systemic inflammatory response we are attempting to modify [38]. Future advances in the management of septic shock will likely depend on our ability to reconcile adaptive physiologic responses with pathologic dysregulation of the immune response.

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