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A burning issue: do sepsis and systemic inflammatory response syndrome (SIRS) directly contribute to cardiac dysfunction?

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1. ABSTRACT

Heart disease is among the leading causes of death in all populations. Cardiac dysfunctions are major complications in patients with advanced viral or bacterial infection, severe trauma and burns accompanied with multiple organ failure – collectively known as systemic inflammatory response syndrome (SIRS). SIRS, which is often subsequent to sepsis, is clinically featured by hypotension, tachypnea, hypo- or hyperthermia, leukocytosis and myocardial dysfunction. The striking association between inflammation and cardiac dysfunction not only prognoses likelihood of survival in patients with SIRS but also prompts the necessity of understanding the pathophysiology of cardiac dysfunction in SIRS, so that effective therapeutic regimen may be identified. Compelling evidence has shown significant and independent link among inflammation, sepsis, insulin resistance and cardiac dysfunction. Several cytokine signaling molecules have been speculated to play important roles in the onset of cardiac dysfunction under SIRS including endothelin-1 and toll-like receptor. Involvement of these pathways in cardiac dysfunction has been convincingly validated with transgenic studies. Nevertheless, the precise mechanism of action underscoring inflammation-induced cardiac contractile dysfunction is far from being clear. Given the substantial impact of inflammation and SIRS on health care, ecosystems and national economy, it is imperative to understand the cellular mechanisms responsible for cardiac contractile dysfunction under inflammation and sepsis so that new and effective therapeutic strategy against such devastating heart problems may be developed.

2. INTRODUCTION

Inflammation takes millions of lives each year. Patients with advanced viral or bacterial infection, severe trauma, burns and cardiopulmonary by-pass surgery experience multiple organ failure and the development of a clinical condition commonly known as systemic inflammatory response syndrome (SIRS). SIRS, which is often subsequent to sepsis, is characterized by hypotension, tachypnea, hypo- or hyperthermia, leukocytosis and depressed myocardial function (1). Cardiovascular morbidity is becoming major health concern globally in patients with inflammatory diseases. Inflammation due to ordinary bacterial infections directly leads to an enhanced propensity of coronary heart disease and is believed to play an even bigger role than cholesterol as a trigger for heart attacks (1-4). The influence of inflammation on biological and socioeconomic systems is substantial, public health care, ecosystems and economy may be affected with the emergence of new inflammatory diseases and the persistence of existing ones. Inflammatory diseases are diverse and complex among hosts, virus/bacteria and external factors, ranging from cellular events to population dynamics. Although new drug discovery has significantly advanced our ability to combat inflammation over the past decades, the current strategies against sepsis and SIRS are nowhere near satisfactoriness. SIRS has a major health impact due to its high prevalence as a result of increased life span and sedentary lifestyle. Inflammation is usually associated with sepsis, insulin resistance and diabetes, all of which may themselves contribute to compromised cardiac contractile function (4-7). It has been demonstrated that cardiac dysfunction complicating sepsis or other causes of

SIRS is usually not accompanied by coronary artery ischemia due to hypotension, myocardial necrosis or interstitial inflammatory infiltration (1). Thus inflammation-induced cardiac dysfunction may belong to a unique entity of heart disease. Although several mechanisms have been postulated for the pathogenesis of inflammation-induced heart dysfunction including accumulation of endotoxin and various cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin (IL-1) and plasminogen activator inhibitor-1 (PAI-1), gene polymorphisms of other cytokines may upregulate the above mentioned cytokines, and the prevalence, morbidity and mortality in patients with sepsis or SIRS (8). Recent evidence suggested that biological markers of inflammation may be used to identify people at high risk of developing coronary heart disease, or an association among infection, inflammatory markers, atherosclerosis and coronary heart disease (9, 10). For example, C-reactive protein (CRP), an acute-phase inflammatory marker, has been used as an indicator for coronary event (9). Elevated levels of CRP are related to insulin resistance, diabetes and metabolic syndrome, suggesting a role for chronic low-grade inflammation and enhanced propensity of heart failure (11). CRP is capable of attenuating the survival, differentiation and function of endothelial progenitor cells through reducing expression of endothelial nitric-oxide synthase (eNOS) (11). To the contrary, rosiglitazone, a peroxisome-proliferator-activator receptor gamma (PPAR gamma) agonist, may inhibit the adverse effects of CRP on endothelial progenitor cells (12), substantiating the role of CRP in proinflammatory and pro-atherosclerotic response. Evidence also implicated a role for the inducible for of NOS (iNOS) in cardiac dysfunction under SIRS. Induction of iNOS by soluble inflammatory mediators, including cytokines, triggers a marked depression in myocyte contractile responsiveness to ß-adrenergic agonists and contribute to cardiac dysfunction complicating SIRS (1). More recently, certain signaling molecules such as endothelin-1 (ET-1), toll-like receptor (TLR) and stress-activated protein kinase (mitogen-activated protein kinase (MAPK)) have all been confirmed to participate in the dampened myocardial contractile function under sepsis, SIRS, heart transplant or cardiopulmonary by-pass surgery (2, 13-15). This review will focus on the mechanisms of action responsible for myocardial contractile dysfunction during sepsis or SIRS and possible way of intervention if applicable against the compromised cardiac function.

3. MYOCARDIAL DYSFUNCTION IN SEPSIS – CYTOKINES AND ENDOTHELIN-1 (ET-1)

Sepsis is a severe infection of the body and bloodstream which leads to shock, a reaction caused by reduced blood flow to the peripheral of the body. It is associated with an explosive inflammatory reaction and multiple organ failure. Sepsis is secondary to bacterial, fungal or viral infection and triggers acute circulatory failure (septic shock). Septic shock is believed to be responsible for nearly 200,000 deaths each year in the United States (16). Both clinical and experimental evidence has suggested that sepsis leads to depressed myocardial function (17-19). Bacterial factors, along with host inflammatory mediators, initiate a spectrum of cardiac dysfunction characterized by decreased ventricular ejection fraction, ventricular dilatation and increased cardiac output (20). Global ischemia is often not considered to be a major factor for cardiac dysfunction during sepsis (20). In fact, septic hearts are more susceptible to myocardial injury induced by calcium paradox. It has been demonstrated that inflammatory mediators may trigger myocardial dysfunction by interrupting coronary microcirculation and producing myocardial edema. Surprisingly, anti-inflammatory agents failed to successfully improve survival rate of septic shock (20). At the multi- or single cellular levels, sepsis-induced myocardial dysfunction is characterized by decreased rates of ventricular relaxation and contraction in isolated heart preparations (21) or depressed cardiomyocyte contraction associated with prolonged relaxation duration in isolated ventricular myocytes (22). An altered myofilament function assessed by minimal and maximal ATPase activities and myofilament calcium-sensitivity is believed to contribute to the ventricular dysfunction under sepsis (23). Presence of certain components of membrane of pathogenic agents in systemic circulation leads to release of various mediators in cascade, notably cytokines and TLR, which are believed to contribute to cardiac dysfunction under sepsis. Release of these pro-inflammatory mediators is often considered a hallmark during the initial phase of sepsis and may provoke acquired immunodepression. In sepsis, certain cytokines are predominantly pro-inflammatory (TNF-alpha, IL-beta) whereas others, produced simultaneously, are anti-inflammatory in nature (e.g., IL-10). Many of these cytokines have multiple intrinsic effects including immune defense and intervening coagulation or complement systems. Since endothelium plays a key role in vascular function, sepsis-induced abnormalities in endothelial injury, thrombomodulation, and perturbed anticoagulation (including reduced pro-fibrinolytic protein C and antithrombin) may deteriorate the already compromised ventricular systolic function and worsen prognosis (20, 24).

Several mechanisms have been postulated for the impaired myocardial function during sepsis including accumulation of reactive oxygen/nitrogen species especially peroxynitrite, generated from a fast reaction of NO and superoxide anion (20, 25). Excessive endogenous NO production and altered NO signaling pathway within cardiac myocytes and other cellular constituents of cardiac muscle are believed to participate in the pathogenesis of heart failure originated from sepsis or SIRS. Induction of iNOS by soluble inflammatory mediators, including cytokines, causes marked depressed myocyte contractile responsiveness to ß-adrenergic agonists (1, 26). The link between NO and myocardial depression in sepsis and SIRS will be discussed in more detail in later section. Currently, clinical therapy against sepsis-induced myocardial dysfunction and heart failure remains essentially limited to minimizing infection with antibiotics and supportive care such as fluid resuscitation, use of inotropes and vasopressors (20). Recent investigations indicated that new anti-inflammatory strategies (e.g. tyrosine kinase inhibitors) may offer better efficacy over those that target at a single mediator (20). Although the involvement of

peroxynitrite in sepsis-induced myocardial dysfunction, the peroxynitrite neutralizers such as mercaptoethylguanidine sodium succinate and 5,10,15,20-tetrakis(4-sulfonatophenyl)-porphyrinato iron (III) (FeTPPS) showed some promises against endotoxin-induced myocardial contractile dysfunction, their clinical value in sepsis or SIRS remains to be thoroughly examined (25). One of the mechanisms involved in myocardial depression during sepsis is mediated through endotoxin lipopolysaccharide-induced cardiomyocyte TNF-alpha production. (27). In a recent study, Feng and colleagues reported that the gp91phox-containing NADH oxidase is a pivotal player in LPS-induced TNF-alpha expression and cardiac depression. These investigators revealed that LPS-mediated activation of NADH oxidase is mediated by ERK1/2 and p38 MAPK pathway, suggesting a potential therapeutic target for the gp91phox-containing NADH oxidase in sepsis-associated myocardial dysfunction (28). Another scenario regarding cardiac dysfunction under sepsis postulated by A. Sharma and colleagues indicated that the endothelin converting enzyme (ECE-1) may play a crucial role in cardiomyocyte dysfunction through increased caspase-3 activity and p38-MAPK phosphorylation (29). These authors further suggested that metalloendopeptidases-dependent endothelin-1 (ET-1) and NO mechanisms may be involved in endotoxemia-induced altered p38-MAPK phosphorylation (30). Enhanced expression of ET-1 along with another vasoactive peptide adrenomedullin has been demonstrated in multiple organs including hearts within 6 hrs of LPS-induced septic shock. The LPS-induced upregulation of ET-1 suggest that up-regulation of ET-1 may serve as a major pathway en route to dysregulation of systemic and regional vascular tone as well as heart dysfunction (31). ET-1, especially cardiac myocyte-derived ET-1, has been shown to contribute to the pathogenesis of Chagasic cardiomyopathy (a non-viral infectious myocardial disease) (32) and compromised heart contractile function (33). In fact, cardiac overexpression of ET-1 itself is sufficient to trigger increased inflammatory cytokines (nuclear factor-kappaB translocation, TNF-alpha, interferon (IFN)-gamma, IL-1 and IL-6), interstitial inflammatory infiltration and an inflammatory cardiomyopathy leading to heart failure and death (33, 34). The involvement of ET-1 in sepsis-related heart dysfunction was substantiated with the observation that tezosentan, a dual endothelin-A and -B receptor antagonist, reconciles endotoxemic shock.-induced cardiac dysfunction (35). Tezosentan administration improves cardiac index, stroke volume index, left ventricular stroke work index and left ventricular end-diastolic area index, which were compromised in endotoxemic shock. Tezosentan-elicited improvement of cardiac function was accompanied with reduced systemic and pulmonary vascular resistance. However, it is worthy mentioning that higher dose of tezosentan exhibits toxic effect manifested as deterioration of cardiac performance and increased mortality rate (35). Although ET-1 has emerged as an important regulator in the pathophysiology of a wide variety of cardiac diseases where it acts in an endocrine, paracrine or autocrine fashion, its biosynthesis, receptor-mediated signaling and functional consequences in sepsis and inflammation-associated cardiac dysfunction warrant further intensive study to reveal the therapeutic value of ET-1 receptor antagonists.

4. MYOCARDIAL DYSFUNCTION IN INFLAMMATION-RELATED INSULIN RESISTANCE OR DIABETES

Obesity, insulin resistance, hyperinsulinemia, hyperlipidemia, hypertension, type 2 diabetes, atherosclerosis and coronary heart disease are the main members of metabolic syndrome X (36, 37). One thing in common for all these diseases is that they are associated with elevated plasma inflammatory markers CRP, IL-6 and TNF-alpha, suggesting that metabolic syndrome X is likely a low-grade, systemic, inflammatory condition (38, 39). Not surprisingly, clinical anti-inflammatory interventions are beneficial in halting progression of metabolic syndrome X especially diabetes and insulin resistance. The close association between inflammation and metabolic syndrome X may provide an “insulin resistance”-originated explanation of inflammation – probably a chronic one. Both insulin resistance and diabetes themselves may directly contribute to cardiac dysfunction manifested as impaired systolic, but mainly diastolic function (40). In experimental diabetes, myocardial mechanical properties are significantly altered at whole heart, multi- and single cellular levels, characterized by prolonged contraction and relaxation and a marked reduction of relaxation velocity (40-42). Impaired systolic and diastolic ventricular contractile functions are both characteristic of diabetes or insulin resistance-related heart dysfunction (40-42). Myocardium and ventricular myocytes from diabetic rodent hearts exhibit reduced contractility, prolonged duration and slowed rate of contraction and relaxation (40-47), which are correlated with prolonged action potential duration (45, 48), depressed calcium reuptake by sarcoplasmic reticulum (SR) (49), isozyme switch from alpha- to beta-myosin heavy chain (MHC) (50), alteration in cardiac troponin T expression and troponin I phosphorylation (51, 52). One of the most crucial electrophysiological alterations in diabetes or insulin resistance-related cardiomyopathy is the prolonged action potential duration in ventricular myocytes (45), consistent with prolonged relaxation duration during sepsis (22). It has been demonstrated that reduction in reploarizing outward K^+ currents is responsible for the prolonged reploariztion phase (phase III) of cardiac action potential (53). For detailed description and discussion of cellular and molecular mechamisms underscoring cardiac dysfuction in diabetes and insulin resistance, refer to our recent articles for details (42, 54, 55).

Chronic low-grade systemic inflammation is commonly seen in patients with diabetes, obesity and insulin resistance (56, 57). This is essentially due to the fact that diabetes, obesity and insulin resistance are linked to infiltration and proinflammatory activity of macrophages in adipose tissue, which may interfere with insulin signaling, mitochondrial function, lipid storage and beta cell function. Alleles of genes encoding immune/inflammatory mediators may be associated with diabetes, insulin resistance and obesity. In addition, environmental factors such as diet and exercise, which directly contribute to the risk of diabetes, insulin resistance and obesity, possess a direct effect on systemic immune or inflammatory mediators (56, 57). It has been shown that selective manuever of immune or

inflammory genes leads to enhanced or suppressed the ptogression of diabetes and obesity (56, 57). Although the mechanism behind inflammation-induced diabetes, insulin resistance and obesity has not been fully elucidated, activation of IkappaB kinase (IKKss) and Jun NH_2-terminal kinase (JNK) leading to increased serine phosphorylation of IRS-1 has been speculated to play an important role. The mouse Pelle-like kinase (mPLK, homolog of human IL-1-receptor-associated kinase (IRAK)) seems to play a key role in inflammation-interrupted insulin signaling (58). Wild-type mPLK is capable of phosphorylating full-length IRS-1 *in vitro*. This phosphorylatory response may be enhaced when mPLK is immunoprecipitated with TNF-alpha. This may lead to over-activation of endogenous mPLK/IRAK in response to TNF-alpha or IL-1, the essential inflammatory cytokines. In addition, it was found that IL-1 or TNF-alpha treatment of FAO cells stimulated increased phosphorylation of endogenous IRS-1 (considered substarte of mPLK) at Ser24. It is therefore concluded that the inflammatory cytokine TNF-alpha-stimulated phosphorylation of IRS-1 by way of mPLK/IRAK may sereve as a crucial "cross-talking" pathway between inflammatory signaling and insulin signaling, which may contribute to insulin resistance (58). Last but not the least, cardiac dysfunction in inflammation-related diabetes, insulin resistance and obesity may also be attributed to presence of certain hemostatic factors. It was shown that patients with type 2 diabetes were much more likely to have higher levels of hemostatic and inflammatory markers such as tissue plasminogen activator antigen, blood viscosity and coagulation factors VII, VIII and IX than non-diabetic patients (4). Diabetes and insulin resistance are believed to be accompanied with increased levels of hemostatic markers, indicating that diabetes and insulin resistance are associated with increased prevalence of coronary heart disease and of activated hemostasis. Good management of diabetets and insulin resistance should reduce the overall risk of developing thrombosis and coronary heart diseases (4).

5. ROLE OF TOLL-LIKE RECEPTOR (TLR) IN INFLAMMATION-INDUCED CARDIAC DYSFUNCTION

Although the immune, nervous, endocrine systems and heart may play important role in depressed cardiac contractility under inflammation, the emergence of a new concept of TLR has definitely changed our classical dogma of cytokine involvement. Using a TLR4-deficient mouse model, investigators found that endotoxin-induced contractile dysfunction measured by Langendorff apparatus (shown as reduction in maximal ventricular pressure, +dP/dtmax, and –dP/dtmax) were absent in the TLR4-deficient mice, indicating a permissive role of TLR4 for endotoxin-induced contractile depression (59). What's more convincing regarding the role of TLR4 was the fact that bone marrow-derived TLR4 may restore the endotoxin-induced myocardial dysfunction. The Toll/IL-1 pathway was first described in Drosophila melanogaster embryogenesis and was later implicated in anti-fungal immunity in this organism (60). Eleven TLRs have been identified in mammals (61), sharing a similar cytoplasmic domain and using leucine-rich repeats for their extracellular components (62-64). Receptor activation turns on the signaling cascade by binding of MyD88 to the receptor complex, which interacts with inactive IRAK-1 (65-67). With phosphorylation of IRAK, it uncouples from the receptor and begins to interact with TRAF6, leading to propagation of cell signal to multiple downstream targets such as NFkappaB, JNK and apoptotic cascade (68).

Receptors which activates the above mentioned cellular pathways, including IL-1R1, TLR2, and TLR4, have been found in various organs including hearts (69, 70). Among these receptors, TLR4 is responsible for activation of the immune response in endotoxin-mediated sepsis (71) and left ventricular dysfunction upon LPS exposure (72). The molecular mechanisms responsible for LPS-induced injury in sepsis or SIRS are complex involving cytokine induction, necrosis and apoptosis. C3H/HeJ mice, which are resistant to LPS-induced apoptosis, carries a mutated TLR4 gene (71). Although studies with TLR4-deficient mice suggest that TLR4 function is rather important in endotoxin-mediated contractile depression, it is still not known which tissue compartments TLR4 signaling is required to function (73, 74). Previous work indicated that the adoptive transfer of wild-type macrophages is sufficient to restore the lethal effects of LPS in endotoxin-insensitive mice (75).

Elevated levels of TLR4 are seen in patients with enteroviral-associated dilated cardiomyopathy or noninfectious heart failure (76), suggesting that myocardial TLR4 is pertinent to cardiac contractile dysfunction. It is highly possible that contractile dysfunction may represent a cumulative effect of TLR4 function in multiple tissues. Nonimmune tissues may serve as relay stations for myocardial depression through TLR4 signaling. Toll/IL-1 signaling may thus have a role in non-immune physiology such as cardiac contractile function. The complex interplay between cardiac contractile and signaling proteins remains the focus of future research. In addition to inflammation and endotoxin, Toll/IL-1 pathway can also be activated by endogenous signals such as heat shock proteins and degradation products of hyaluronan (77, 78). It is quite likely that Toll/IL-1 pathway may ultimately develop into therapeutic target for a number of cardiac diseases especially those involve inflammation.

6. ROLE OF NO AND TETRAHYDROBIOPTERIN (BH_4) IN INFLAMMATION-INDUCED HEART DYSFUNCTION

Recently, attention has been drawn towards the role of NO and its reactive compounds in the development of inflammation-induced cardiac complications. NO, a highly reactive gas with chemical properties of free radicals, is synthesized by a variety of cell types including cardiomyocytes (79). NO participates in a cascade of pathophysiological processes when formed in excess or in the presence of other pro-oxidants (80, 81). Enhanced endogenous production of NO or addition of NO donors have been documented to result in compromised cardiac function and enhanced apoptosis (80), illustrating the

potential toxic properties of NO. NO and superoxide anion react rapidly (second-order rate constant = 6.7×10^9 M/s) to generate peroxynitrite ($ONOO^-$), which rapidly decomposes to highly oxidant species such as nitronium ion (NO^{2+}) (82-84). Overproduction of the free radical NO with subsequent development of local oxidative stress has been proposed to be one of the significant pathophysiological mechanisms for sepsis and SIRS-induced cardiac dysfunctions (85, 86), consistent witrh the finding that LPS directly stimulate the gp91phox containing NADPH oxidase (28). As indicated earlier, the $ONOO^-$ neutralizers such as mercaptoethylguanidine sodium succinate and 5,10,15,20-tetrakis(4-sulfonatophenyl)-porphyrinato iron (III) (FeTPPS) may effectively alleviate endotoxin-induced myocardial contractile dysfunction (25), similar to their beneficial effect in diabetes or hyperglycemia-induced cardiomyocyte contractile dysfunction (81). The involvement of NO in sepsis, SIRS or endotoxin-induced cardiac dysfunction received support from the finding that NOS inhibitors prevent cardiac dysfunction under these conditions (26). Perfusion of septic hearts *in vitro* with the iNOS inhibitor S-methylisothiourea did not reverse sepsis-induced contractile dysfunction. However, treatment of septic animals with S-methylisothiourea or dexamethasone, a glucocorticoid that prevents the synthesis of the iNOS, at the time of induction of sepsis resulted in partial reversal of myocardial dysfunction elicited by sepsis (26). It may be concluded that myocardial dysfunction in *E. coli* sepsis was not solely due to NO produced by iNOS. This was supported by other investigators who failed to block ventricular dysfunction with nonselective NOS inhibitor (20). Recently, it was indicated that the interaction between cytokines and NOS co-factor tetrahydrobiopterin (BH_4) may play a significant role in the NO theory of sepsis or SIRS-induced cardiovascular dysfunction (87). BH_4 is an essential cofactor required for the production of NO by each of the NOS isoforms. Synthesis of BH_4 involves several steps which converts guanosine-5'-triphosphate (GTP) into BH_4 using the enzyme GTP cyclohydrolase I (GTPCH I) (88). Defective BH_4 metabolism appears to be a major mechanism in pathogenesis of vascular endothelial dysfunction and uncoupled NOS activity (87, 89). This notion received support from BH_4 supplementation study when endothelial dysfunction induced by hypercholesterolemia, diabetes, hypertension and smoking is protected (87, 89). Transcriptional regulation of GTPCH I is essential to BH_4 synthesis and metabolism. Paralellel induction of GTPCH I and iNOS gene expression was reported by inflammatory cytokines such as TNF-alpha, IFN-gamma or IL-1beta, suggesting that basal levels of BH_4 is insufficient for optimal iNOS function (87, 90). It is thus possible that the enhanced production of BH_4 in the presence of cytokines is designed to provide “extra fuel” for iNOS enzymatic activity. A recent study revealed that GTPCH I induction requires the activation of both NFkappaB and signal transducer and activator of transcription-1 (STAT1), cytosolic transcription factors that mediate gene transcription (91). With comparison of the individual signaling pathways of TNF-alpha and IFN-gamma, it was concluded that TNF-alpha alone was responsible for the degradation of IkappaB and the nuclear translocation of NFkappaB, which turns on GTPCH1 (91). Although NO, iNOS and GTPCH1 may participate in cardiovascular abnormalities especially myocardial dysfunction under sepsis and SIRS, whether the upregulated NOS function is directly resulted from accumulation of cytokine has not been clarified. It was indicated recently that the increased substrate availability for ET-1 at the time of sepsis-induction may be responsible for iNOS induction, activation of stress signaling such as p38-MAP kinase and cardiac diastolic dysfunction (92). Further study is mandated to elucidate the interaction between the ET-1 and NO signaling in association with cardiac contractile dysfunction under inflammation.

7. CONCLUSION

The scenario behind sepsis and SIRS-induced myocardial dysfunction and increased propensity of heart failure may be attributed by multiple factors including cytokines and signaling molecules such as TLR, NO and ET-1. The presentation, investigation and treatment of inflammation-induced heart disease and management and assessment of overall cardiac health in patients with inflammatory diseases deserve intensive further investigation.

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