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Sepsis-induced myocardial dysfunction and myocardial protection from ischemia/reperfusion injury

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1. ABSTRACT

Sepsis, bacteremia and inflammation cause myocardial depression. The mechanism of the dysfunction is not clearly established partly because dysfunction can be elicited by many different mechanisms which can all manifest in disruption of myocardial mechanical function. In addition the models of sepsis and bacteremia and inflammation may vary drastically in the sequence of the coordinated immune response to the inflammatory or septic stimulus. Patterns of cytokine expression can vary as can other responses of the immune system. Patterns of neurohumoral activation in response to the stress of sepsis or bacteremia or inflammation can also vary in both magnitude of response and temporal sequence of response. Stress induced activation of the sympathetic nervous system and humoral responses to stress have a wide range of intensity that can be elicited. The fairly uniform response of the myocardium indicating cardiac dysfunction is surprisingly constant. Systolic performance, as measured by stroke volume or cardiac output and pressure work as estimated by ventricular pressure, are impaired when myocardial contraction is compromised. At times, diastolic function, assessed by ventricular relaxation and filling, is impaired. In addition to the dysfunction that occurs, there is a longer term response of the myocardium to sepsis, and this response is similar to that which is elicited in the heart by multiple brief ischemia/reperfusion episodes and by numerous pharmacological agents as well as heat stress and modified forms of lipopolysaccharide. The myocardium develops protection after an initial stress such that during a second stress, the myocardium does not exhibit as much damage as does a non-protected heart. Many agents can induce this protection which has been termed preconditioning. Both early preconditioning (protection that is measurable min to hours after the initial stimulus) and late preconditioning (protection that is measurable hours to days after the initial trigger or stimulus) are effective in protecting the heart from prolonged ischemia and reperfusion injury. Understanding the mechanisms of sepsis/bacteremia induced dysfunction and protection and if the dysfunction and protection are the products of the same intracellular pathways is important in protecting the heart from failing to perform adequately during severe sepsis and/or septic shock and for understanding the multitude of mechanism by which the myocardium maintains reserve capacity.

2. INTRODUCTION

The effects of gram negative sepsis or bacteremia on the myocardium have been observed in patient studies (1-4) and in animal studies using various models of infection, bacteremia or inflammation (5-9). Most studies demonstrate alterations in ventricular function during infection but the method of inducing sepsis or infection may vary and the mechanism of the ventricular dysfunction may vary. Sepsis induced effects on the myocardium have been investigated using the intact organism, isolated organs and isolated cells. Each of these methodologies has advantages and disadvantages for assessing ventricular contractile function and each has been useful in determining that sepsis does indeed cause changes in intrinsic contractile function, i.e. function independent of extrinsic influences on contraction such as those mediated by the autonomic nervous system, hormones and paracrine or autocrine influences. In addition to the detrimental effects of sepsis on cardiac function, sepsis has also been shown to stimulate the myocardium to initiate protein synthesis and develop protection of the heart from a second injury (10). This type of protection seems to be particularly effective in protecting the heart from ischemia reperfusion injury as the secondary insult. Protection of the heart from ischemia/ reperfusion injury is termed preconditioning and is a very widely investigated phenomenon. The term preconditioning was first used to describe the protection initiated by several short repetitions of ischemia and reperfusion (11), which resulted in protection of the heart from a longer ischemia/reperfusion episode. Endotoxin (11-14), nontoxic derivatives of endotoxin (15-16) and cytokines (17-18), heat shock (19-21), and administration of a number of pharmacological agents such as adenosine (22-24), norepinephrine (25), acetycholine (26), nitric oxide (nitroglycerin) (27-28), opioids (29), volatile anesthetics (30), and gram negative bacteremia (31-32) have also been shown to protect the heart from prolonged ischemia and reperfusion. Although preconditioning can be demonstrated within minutes of the preconditioning stimulus (33), there is also a late phase of preconditioning which requires several hours to develop and lasts for several days (33-36). This late preconditioning or second window of protection is the protection of the heart that seems to correlate chronologically with the protection elicited by sepsis/bacteremia, endotoxin or cytokines. This review will briefly discuss sepsis induced myocardial dysfunction and potential mechanisms for sepsis induced myocardial protection.

3. SEPSIS INDUCED MYOCARDIAL DYSFUNCTION

Gram negative bacteremia and sepsis cause myocardial depression (1-9). This dysfunction has been noted in septic patients (1-4) and animals (5-9) and has been thought to contribute, along with altered vascular tone (37-38), to death. Early therapy to prevent cardiovascular collapse has been shown to be beneficial in the treatment of patients in the transition from systemic inflammatory response syndrome to severe sepsis to septic shock (38). This early therapy entails manipulation of myocardial preload, afterload and contractility to normalize arterial lactate concentration, pH and base deficit and mixed venous oxygen saturation. Normalization of these parameters suggests better matching of oxygen delivery to oxygen demand (38). Although both vascular and cardiac function are necessary for matching of oxygen delivery to oxygen demand, support of myocardial performance can be provided by increasing contractility and/or increasing preload or ventricular filling and the heart from septic patients at least partly seems to rely on dilation and increased preload to support generation of a “normal” cardiac output (2).

Early studies using injection of endotoxin, a component of the cell wall of gram negative bacteria, into animals (8, 9, 12-14) showed that myocardial depression occurs after endotoxin administration. Recent studies have indicated that cytokines may be involved in endotoxin induced dysfunction (39), that calcium homeostasis is altered (40-44) and that many intracellular signaling pathways are activated resulting in nuclear factor kappa B (NFkB) entry into the nucleus and alterations in gene transcription and protein synthesis (45-46). Animal studies of heart function in sepsis have sometimes not demonstrated dysfunction especially if in vivo function is assessed (47-48). However, measurement of in vivo function does not dissociate intrinsic contractile dysfunction from support of function by neurohumoral mechanisms. Sympathetic nervous system induced increases in contractility may mask contractile dysfunction. Indeed, we have shown in an isolvolumic heart preparation that hearts from septic rats have depressed function but can respond to isoproterenol administration to achieve the same index of contractility, the left ventricular developed pressure, achieved by hearts from sham treated control animals (49-50). Thus neurohumoral support of myocardial function in vivo can mask contractile dysfunction and make it seem that cardiac function in normal. A weakened heart actually seems to be performing normally because of neurohumoral support and reliance on the Frank Starling mechanism to maintain apparently normal performance. However, the heart may subsequently fail to adequately perfuse the peripheral organs when intrinsic dysfunction becomes more severe and/or the myocardium can no longer respond to neurohumoral stimuli (51) and increased preload to maintain contractile performance.

In order to study the myocardial response to inflammation and infection, we have been studying the effects of sepsis/bacteremia on the myocardium using various rodent models including two peritonitis models, one of which consists of injection of an aliquot of fecal inoculum into the abdomen (52-53) and the other of which involves the isolation, ligation, and puncture of

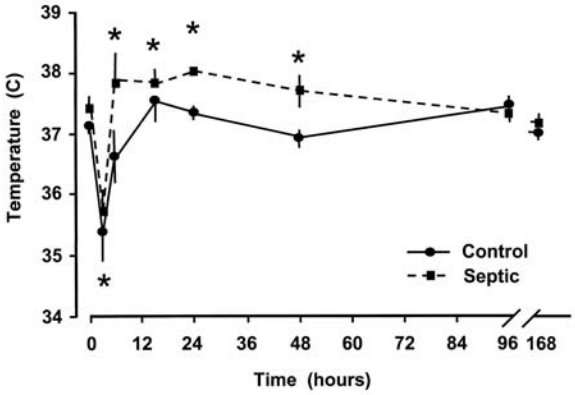

Figure 1. Temperature response after the administration of *Escherichia coli*. The colonic temperature in rats receiving either saline (control) or *E. coli* (septic) in the dorsal subcutaneous space at different time points after induction of sepsis. * = $p < 0.05$ different from before sepsis surgery. The decrease in temperature at 3 hr after surgery is due to anesthesia.

the cecum (CLP) (49, 54). In these models, blood pressure is maintained; and heart rate is increased. Cardiac output is either elevated (52, 53) or normal (54) and mortality is low. In a third model of bacteremia, Escherichia coli are injected into the dorsal subcutaneous space and animals become bacteremic within a few hours (55). After an initial drop in body temperature because of anesthesia, there is an increase in colonic temperature up through 48 hr compared to the pre-sepsis temperature (Figure 1). Very few animals die by 24 hr with an approximate 20-25% mortality over the next few days. The mortality however can be increased by introduction of more bacteria such that 100% of the animals die within one day. This ability to modulate the severity and lethality of sepsis/bacteremia gives the investigator the ability to study factors that potentiate sepsis induced myocardial depression such as chronic alcoholism (56) and severe diabetes (57) or attenuate dysfunction such as treatment of animals with antagonists to the inducible nitric oxide synthase (iNOS) (58). Myocardial dysfunction occurs 1 day after the induction of sepsis/bacteremia by injection of a fecal inoculum into the peritoneal cavity (6), cecal ligation and puncture (54) and injection of Escherichia coli into the dorsal subcutaneous space after clearing the sub-dermal space on the entire dorsal surface of the animal (31,32). We have studied hearts as either working hearts, i.e. as hearts that pump buffer against an outflow resistance, or as isovolumically beating hearts, i.e. hearts in which a compliant balloon has been placed into the left ventricle and the volume of fluid in the balloon remains constant during a cardiac cycle. The working heart model is very sensitive to changes in cardiac reserve, especially in the ability of the left ventricle to pump volume. The isovolumic preparation is an excellent preparation for studying left ventricular diastolic function and for assessing the responsiveness of the heart to inotropic agents. Studies with the isovolumic preparation have shown that despite a decrease in ventricular reserve, i.e. depression of the ventricular function curve, hearts from septic rats can increase contractility in response to beta adrenergic stimulation (49, 50). Interestingly, hearts from septic rats can also increase chronotropy in response to beta adrenergic agonist but there is a shift of the dose response curve to the left indicating an increased sensitivity of the nodal tissue for beta agonist induced increases in heart rate (59). In all preparations used to study heart function, myocardial contractile function is compromised by sepsis/bacteremia. Myocardial reserve is decreased because intrinsic contractility is depressed. Myocardial function decreases progressively but dysfunction is statistically demonstrated at 24 hours and is reversed by day 7 in both the fecal inoculum model (6) and in the E. coli model (Table 1). Impaired myocardial blood flow does not seem to be the cause of the dysfunction since flow is not generally significantly decreased in the hearts from septic/bacteremic rats.

Although cytokines such as tumor necrosis-factor alpha (TNF) have been implicated in endotoxin induced myocardial dysfunction (46), in this model of sepsis/bacteremia induced myocardial depression, TNF levels are low. Plasma TNF levels are detectable at 3 hr and 15 hr but not at other time points measured after the induction of sepsis (Table 2). Myocardial levels of TNF, although tending to be greater in the septic animals than in the controls, were not significantly elevated. In addition, administration of an anti TNF-alpha immunoglobulin (IgG) prior to the induction of sepsis/bacteremia, did not prevent myocardial dysfunction (Table 3). In these studies using the isolated working heart preparation, myocardial work, measured as cardiac output x aortic peak systolic pressure, was significantly decreased in the septic groups compared to the control group whether they were pretreated with nonimmune IgG or anti-TNF-alpha IgG. Coronary flow in the two septic groups was similar at all preloads to the coronary flow of the control group and therefore hypoperfusion of the heart was not responsible for depression of cardiac performance. The plasma TNF-alpha levels averaged 17 ± 6 pg/ml in the nonimmune IgG treated septic group and were undetectable in rats in the anti-TNF-alpha IgG group.

4. MYOCARDIAL PRECONDITIONING

4.1. Myocardial protection

Stress causes many tissues to initiate mechanisms to protect the tissue from a second insult or injury. The myocardium has been shown to develop protection (preconditioning) in response to a multitude of stimuli. The most commonly studied form of preconditioning is ischemic preconditioning. Short (4-6 min) periods of ischemia and reperfusion are repeated several times resulting in protection of the myocardium from prolonged ischemia and/or reperfusion induced injury (11). Protection is manifested by improved contractile performance, less tissue infarct and less tendency for arrhythmias following prolonged ischemia and reperfusion.

Table 1. Left ventricular developed pressure (LVDP) and coronary flow (CF) in hearts from control rats and septic rats at various time points after the induction of sepsis

	PRE-ISCHEMIA	
GROUP	LVDP (mmHg)	CF (ml/min)
Control (n=15)	127 ± 7	13.1 ± 0.5
3 hr (n=7)	101 ± 7	13 ± 0.8
6 hr (n=10)	97 ± 11	10 ± 0.7
15 hr (n=11)	91 ± 9	11.2 ± 0.7
24 hr (n=10)	61± 7*	10.8 ± 0.8
48 hr (n=7)	59 ± 9*	11.4 ± 1.5
96 hr (n=5)	102 ± 11	13.4 ± 1.3
7 day (n=5)	114 ± 5	15.2 ± 2

Values are mean +/- SEM, * p< 0.05 vs. control

Table 2. The time course of changes in plasma and myocardial TNF-alpha levels in control and septic rat hearts

GROUP	**Plasma TNF-alpha (pg/ml)**	**Myocardial TNF-alpha (pg/mg)**
Control (n = 4,7)	ND	695 ± 88
3hr (n = 6,6)	33.3 ± 7.6	1005 ± 82
6hr (n = 4,6)	ND	925 ± 61
15hr (n = 3,5)	27.6 ± 6.6	977 ± 95
24hr (n = 4,4)	ND	723 ± 122
48hr (n = 3,6)	ND	901 ± 95
96hr (n = 3,4)	ND	764 ± 37
7 day (n = 3,6)	ND	1351 ± 200

ND = not detectable (detectable limit < 4 pg/ml)

Table 3. Myocardial work, cardiac output x aortic peak systolic pressure, as a function of preload, left atrial filling pressure (LAFP)

LAFP, cm H2O	**Control - Sham**	**Septic plus anti- TNF IgG**	**Septic plus nonimmne IgG**
15	6863 *± 197	4299± 429	3813± 610
10	4869 *± 437	3138± 457	3057± 382
12.5	5901 *± 132	5050± 582	4025± 600
15	6741 *± 406	4418± 539	4548± 723
17.5	7688 *± 406	4624± 542	4295± 776
20	8084 *± 355	4461± 527	4491± 785
22.5	7601 *± 329	4485± 582	4412± 705
15	6743 *± 153	3632± 388	3954± 536
15 X	7173 *± 856	3461± 604	4503± 969

Cardiac output x aortic peak systolic pressure = CO x PSP, ml/min x mmHg; left atrial filling pressure = LAFP. * p< 0.05, control different from anti-TNF-alpha IgG and nonimmune IgG. 15 x refers to a filling pressure of 15cm H2O with the aortic outflow tract occluded in order to achieve the maximum afterload stress.

4.2. Early preconditioning

Ischemic preconditioning, recently reviewed by Yellon and Downey (33) and Tsai and coworkers (36), was initially shown to induce protection of the heart from prolonged ischemia within minutes of the stimulus. Protection lasts for one to two hours and is not dependent upon protein synthesis. Improved collateral blood flow to the ischemic region during the prolonged ischemia does not appear to be the mechanism of protection. Besides repetitions of short ischemia reperfusion episodes, adenosine, which may be produced during the preconditioning ischemic challenge, can induce preconditioning when given exogenously by activating A1/A3 receptors on the cardiac cell surface (22-24). Norepinephrine can precondition through myocardial alpha adrenergic receptors (25). Bradykinin (26) and opioids (29) can also induce early preconditioning. It is thought that these four molecules are released during the brief preconditioning stimulation and therefore when given exogenously can also precondition the heart. Other molecules that are not necessarily produced during the brief ischemic periods can also precondition. For example, acetylcholine can precondition through a muscarinic receptor and agonists that activate Gi-coupled receptors can elicit transient protection (33). The signaling pathways are diverse and probably redundant including multiple kinases – protein kinase C, tyrosine kinases, MAP kinases and PI-3 kinase. Reactive oxygen species, possibly produced in mitochondria subsequent to K ATP channels opening, may be upstream to the PKC and tyrosine kinase activation. The reactive oxygen species are produced during the brief reperfusion periods and are required for triggering protection. The activated kinases and the mitochondrial K ATP channels may be important in

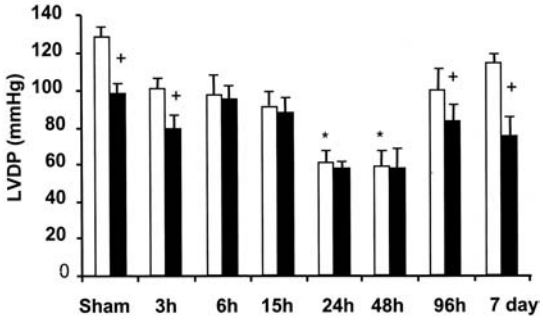

Figure 2. Left ventricular function, before and after ischemia, in sham and septic rat hearts. Left ventricular developed pressure (LVDP) in control or sham surgery rat hearts and hearts from rats at various time points after receiving E. coli in the dorsal subcutaneous space. The white bar represents LVDP prior to induction of ischemia and reperfusion in each group and the black bar represents the LVDP after 35 min ischemia and 30 min reperfusion. * = $p < 0.05$ vs. Sham and + = $p < 0.05$ post ischemic different from pre-ischemic LVDP.

stabilizing the mitochondria and prevent opening of the mitochondrial transition pore. Opening of this pore results in disruption of mitochondrial function and potentially destruction of the mitochondrial and the cell. The exact mechanism of protection is not clear but as suggested by the multiple stimuli, signaling pathways and mitochondrial roles, preconditioning is a powerful, redundant mechanism that improves that likelihood of cell survival during oxygen lack.

4.3. Late preconditioning

Preconditioning with multiple replications of short ischemia/reperfusion episodes results not only in short term protection but also protection at 24 hr. This has been termed the "second window of protection" or late preconditioning and has been reviewed recently (33-36). This form of protection may involve some of the same mechanisms as those induced by endotoxin, monophosphoryl lipid A (MLA), cytokines, and sepsis to induce protective mechanisms. This second window of protection (SWOP) lasts up to 3 days but is lost by 4 days, a similar time frame to the protection we have found with sepsis/bacteremia. Many of the agents that induce early preconditioning can also elicit late preconditioning although the mechanisms of protection may vary (34). Inhibition of PKC and tyrosine kinases before the preconditioning stimulus prevents protection. Translocation of PKC epsilon seems to be important for late ischemic preconditioning (61). It also appears that the late preconditioning involves oxygen free radical; the myocardial protection induced by sepsis, endotoxin and cytokines may also be elicited by oxygen free radicals (12).

Late preconditioning to stunning also involves nitric oxide both as a trigger for the induction of late preconditioning and a mediator. If the constitutive nitric oxide synthase is inhibited before the first preconditioning episode, late preconditioning does not occur. If the inducible nitric oxide synthase is blocked prior to the late preconditioning testing, protection from stunning is not seen (33, 35). Most recent studies indicate that Src Protein kinases play a role in late preconditioning to stunning but not the same role in protection to infarct leading to the concept that there is a divergence in mechanisms not only between early preconditioning and late preconditioning but also between protection as measured in stunning, infarction and arrhythmia models of ischemia/reperfusion injury. Studies of the intracellular signaling pathways have led to the hypothesis that signaling modules may be involved in the pathways leading to protection (62). Protein kinase C epsilon can be immunoprecipitated with molecules in the mitogen activated protein kinase (MAPK) family and some of these complexes are associated with mitochondrial proteins. Preconditioning may inactivate the mitochondrial permeability transition pore thereby preventing disruption of mitochondrial function during ischemia and reperfusion (63).

Recent studies have indicated that both TNF and interleukin-6 (IL-6) are necessary for ischemic preconditioning against infarction. Mice deficient in TNF or IL-6 cannot be preconditioned by multiple ischemia/reperfusion episodes (63, 64). In the wild type mice, ischemic preconditioning is linked with activation of several transcription factors such as NFkB and upregulation of iNOS. NFkB seems to be an essential link in ischemic preconditioning and is one of the transcription factors that is known to be activated in sepsis/bacteremia as part of the inflammatory response. Calcium activated K channels (65) and phosphorylation of serine in troponin I by PKC (66) have also been implicated in late preconditioning.

4.4. Sepsis/bacteremia and inflammation induced protection

The form of the prior stress that induces late protection by sepsis/bacteremia and inflammation can be quite variable - 24 hr pretreatment with a nonlethal dose of endotoxin (12-14) or the nontoxic derivative of LPS, MLA (15-16), TNF (18) or IL-1 (17), 24 hr pre-exposure to a hyperthermic environment or heat shock (19-21) and 24 hr exposure to gram negative bacteria (10, 31, 32) have all been shown to protect the heart from ischemia reperfusion injury. This protection occurs by approximately 24 hr although protection can be seen as early as 6 hr after the initial injury (12) but cannot be demonstrated as early as 1 hr after endotoxin administration. With gram negative sepsis, protection is apparent at 6 hr after the induction of sepsis (Figure 2). The potential mediators of this protection may be increases in antioxidant levels such as catalase; induction of heat shock proteins, which may stabilize enzymes/proteins and may be involved in attenuating stress induced activation of NFkB; increased production of cGMP which may result in phosphorylation of contractile proteins; activation of K_{ATP} channels which may help maintain mitochondrial integrity and mechanism to attenuate calcium overload. Complex signaling pathways are involved including protein kinase c, tyrosine kinase, MAPKs, phosphatidylinositol 3-OH kinase (PI-3 kinase), mitochondrial K ATP channels and reactive oxygen species (33).

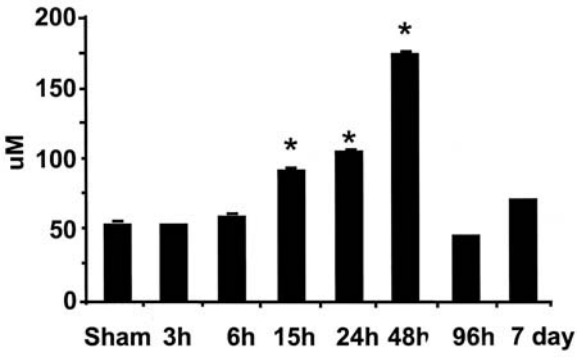

Figure 3. Nitrite/nitrate in plasma of sham and septic rats. * = $p < 0.05$ different from sham.

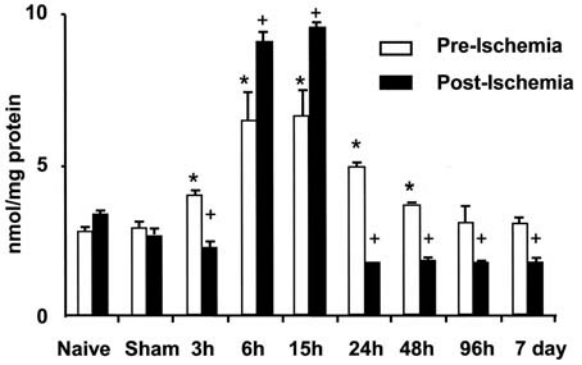

Figure 4. Catalase activity in hearts from naïve rats (no prior surgery or anesthesia), and sham surgery rats and from septic rat hearts at various times after the induction of sepsis. The white bars represent catalase activity in hearts that did not undergo ischemia whereas the black bars represents catalase activity in hearts that were perfused as isolated isovolumically beating hearts that were made ischemic for 35 min and reperfused for 30 min. * = $p < 0.05$ different from naïve and sham; + = $p < 0.05$ post-ischemic different from pre-ischemic value.

The time course of protection in sepsis/bacteremia induced protection is very similar to the time course of late ischemic preconditioning. As shown in (figure 1), septic animals have an increase in colonic temperature early after recovery from anesthesia during which sepsis in induced by administration of *E. coli* into the dorsal subcutaneous space. As shown in (Figure 2) left ventricular developed pressure (LVDP) is significantly decreased in control hearts after reperfusion (black bars) compared to the pre-ischemic LVDP (white bars) as studied in isolated isovolumic beating hearts. This impairment of LVDP after ischemia and reperfusion is obvious in septic rat heart 3 hr after induction of sepsis but by 6 hr there is no decrement in function after ischemia and reperfusion; this sepsis mediated protection, i.e. prevention of a loss in LVDP due to ischemia and reperfusion, is maintained at 15 hr, 24 hr 48 hr even though pre-ischemic LVDP is significantly decreased from control at 24 and 48 hr of sepsis/bacteremia. The 6 hr and 15 hr results suggest that sepsis induced protection precedes sepsis induced dysfunction and the two may not be directly linked through similar intracellular mechanisms. Interestingly however, sepsis induced protection can still be manifested when sepsis induced depression is noted – i.e. at 24 and 48 hr.

The protection induced by *E. coli* sepsis/bacteremia in this model is not due to preservation of high energy phosphates since ATP and CP levels are similarly decreased in ischemic septic and control groups. Although coronary flow at 5 min reperfusion is greater than prior to ischemia in septic rat hearts in contrast to a severely decreased coronary flow in control hearts, when the coronary flow in not allowed to increase under experimental conditions in which coronary flow is held constant, septic rat hearts still have no decrement in LVDP after ischemia and reperfusion whereas control hearts do show a significant decrease in LVDP after reperfusion (32). Sepsis induced protection is not blocked by inhibition of K ATP channels (with an antagonist that blocks both sarcolemmal and mitochondrial K ATP channels) (31). Sepsis induced protection is however, blocked by dexamethasone, which inhibits synthesis of inducible enzymes by sepsis/bacteremia (67). We have also shown that sepsis induced protection can be blocked by adenosine receptor antagonism with 8-phenyltheophylline (32).

The responses to sepsis/bacteremia that seem to correlate with and possibly mediate protection included increased catalase activity, induction of heat shock proteins, cyclooxygenase-2 (COX-2), heme oxygenase-1 and iNOS. All of these have been implicated in late preconditioning. Carbon monoxide can induce late preconditioning (68); COX-2 production of prostacyclin appears to medicate opioid induced late preconditioning (69) and iNOS is one of the mediators of ischemic late preconditioning (34, 35). The increased iNOS expression in septic rat hearts is evident by Western blot and there are increases in nitrite/nitrate in the plasma by 15 hr. Levels continue to increase up through 48 hr of sepsis (figure 3). We have hypothesized that iNOS may be a source of NO in septic rat hearts that allows for the increased recovery of coronary flow early during reperfusion thus potentially washing out ischemic waste products at increased rates. However, as mentioned previously, the increased recovery of coronary flow does not seem to be essential for sepsis induced protection. The role of iNOS in myocardial dysfunction and protection is currently under investigation.

The increased catalase activity present in hearts from septic animals (figure 4) is present to some extent by 3 hr of sepsis prior to ischemia (white bars) and is progressively increased at 6 and 15 hr. Catalase activity is still increased, although not at such a high level of activity, at 24 and 48 hr. Thus the increase in catalase activity precedes and accompanies sepsis induced protection. Interestingly, catalase activity is altered in the isolated hearts by ischemia and reperfusion in the hearts of the septic animals. At 6 and 15 hr activity actually increases after ischemia and reperfusion whereas at 24, 48, 96 and 7 days, catalase decreases after ischemia and reperfusion. These data suggest that during early sepsis/bacteremia, gene

expression may be upregulated for catalase and this upregulation continues even in the isolated heart. Increased catalase activity may mediate more rapid clearance of reactive oxygen species during reperfusion and may play a role in sepsis induced protection.

5. SUMMARY AND PERSPECTIVE

In summary, sepsis/bacteremia induces myocardial dysfunction but also stimulates the heart to develop protection from a second injury such as ischemia reperfusion injury. The protection developed by sepsis/bacteremia is very strong in that recovery of left ventricular developed pressure is complete after 30 – 40 min of global ischemia in the isolated heart. Future studies will be required to demonstrate if the sepsis induced protection is able to protect the heart under *in vivo* conditions in which the effects of ischemia and reperfusion are even more complicated than under the fairly well controlled conditions in which the isolated heart can be studied. In addition, identification of the specific proteins that may be induced by sepsis/bacteremia and the role of these proteins in either myocardial dysfunction and/or myocardial protection will clarify if sepsis/bacteremia dysfunction is a unique type of preconditioning stimulus for the heart or if it parallels the preconditioning pathways activated in response to classical preconditioning with multiple short ischemia reperfusion episodes. Other interesting possibilities for future study include the hypothesis that myocardial dysfunction resulting from sepsis/bacteremia may be a mechanism by which the heart downregulates its function to help protect the heart from overstimulation by immune and neurohumoral modulators and to ensure the matching of myocardial oxygen delivery to myocardial oxygen demand.

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