Abnormalities of Vascular Reactivity in the Sepsis Syndrome*

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Multiple organ failure (MOF) denotes a clinical syndrome that is characterized by a process of dysfunction and ultimately failure of vital organs. Commonly found in association with infection in critically ill patients, it has supplanted refractory hypoxemia as the major cause of late mortality in patients with the adult respiratory distress syndrome (ARDS). Although ARDS is often an initial manifestation of MOF, dysfunction of the circulatory, hepatic, renal, and other organ systems may follow if the underlying processes responsible for this syndrome of progressive organ dysfunction are not identified and adequately managed.

Many lines of evidence point to the likelihood of significant disturbances in the regulation of tissue oxygen delivery (QO2) in the sepsis syndrome. Paradoxically, such alterations in tissue QO2 during sepsis complicate a process that is typically characterized by increased tissue needs for O2. For example, Bihari et al. proposed that a "covert" O2 debt characterized some critically ill patients. Rashkin et al. correlated death with the presence of a low systemic QO2 and elevated arterial lactate concentrations in patients with sepsis. Shoemaker et al. demonstrated that maintaining a "supranormal" systemic QO2 differentiated the survivors of a critical illness from the nonsurvivors. On the basis of these, as well as other data, some investigators have proposed that in sepsis, dysregulation of the circulatory processes governing tissue O2 availability leads to diffuse organ dysfunction due to ischemia. When the functional reserve of specific organs is exceeded by this process of diffuse ischemic injury, biochemical and then clinical MOD ensues.

In the sepsis syndrome, abnormalities that could significantly destabilize the appropriate matching of tissue QO2 to tissue O2 needs have been demonstrated within the 3 levels of the circulation. For example, at the central level, an inability to maximally augment systemic QO2 will complicate a reduction in arterial O2 saturation secondary to a sepsis-induced pulmonary microcirculatory lesion, (eg, ARDS or depression in myocardial performance). The latter may arise for a number of reasons in the sepsis syndrome, including the effects of a circulating myocardial depressant factor, ventricular interference consequent on pulmonary hypertension, and myocardial edema. At the regional levels of the circulation, the distribution of flow (Q) between organs is significantly altered during sepsis. Within the microcirculations, pathologic supply dependence of systemic O2 consumption (VO2), together with a depression in the ability of extrapulmonary tissues to maximally extract O2 (O2E), has been demonstrated at the whole-body level, as well as within some individual organs. Among other possible causes, Nelson and colleagues hypothesized that sepsis-induced changes in vascular reactivity could be an important cause of the altered distribution of Q both between and within individual organs in the sepsis syndrome.

In this review, we will discuss the evidence for depression in vascular responsiveness in the sepsis syndrome. We will also examine the functional consequence of such a circulatory lesion at the level of the control of issue QO2.

Vascular Reactivity in Health

Organ O2 needs normally dictate the level of organ Q. This coupling of metabolic need to the circulatory control of tissue QO2 (ie, the metabolic regulation of tissue O2 flux) is mediated by local changes in vascular resistance. The metabolic control system for O2 may be confused with the term "autoregulation," which more correctly describes processes whereby organ Q is maintained at constant levels despite wide variations in perfusion pressure.

When O2 need exceeds available supply, cellular O2 availability is augmented through acute circulatory adjustments that occur at both the microregional and regional levels of the circulation. Initially, metabolic by-products of ischemia augment capillary surface area through actions on precapillary sphincters, and local O2E increases. Subsequently, this metabolic feedback process further augments QO2 at the microcirculatory level by mediating vasodilation of flow-controlling sites at the level of resistance arterioles. This circulatory response to local metabolic need may be opposed in some organs when neurohumoral mechanisms override local metabolic signals and effectively shunt Q from "nonvital" organs to maintain Q to the "vital" organs, as they do in hemorrhagic hypotension. Thus, alterations in organ Q are primarily determined by changes in the caliber of small arteries and arterioles, a process requiring smooth-muscle contraction. This resistance may be regulated locally or through a generalized systemic response that includes neurohumoral mechanisms.

Organs differ in their ability to regulate O2 availability through variations in O2 extraction at the microregional level. Vital organs such as the heart and brain are distinguished by a limited O2E reserve and, therefore, by the need to meet increases in O2 need through parallel increases in organ Q. On the other hand, nonvital organs (eg, the splanchic circulation) demonstrate a local O2E reserve that is sufficient to compensate for a redistribution in Q to the vital organs.

In summary, the metabolic regulation of tissue O2 availa-
bility involves an integrated response at all of the central, regional, and microregional levels of the circulation. Normal vascular reactivity is important to the proper functioning of this process, with shifting balances between vasconstriction and vasodilation of resistance arterioles to different organs responsible for maintaining tissue $O_2$ availability at levels such that significant ischemia does not normally occur.

**Vascular Responsiveness in Sepsis**

It is generally held that vascular responsiveness is depressed in the sepsis syndrome. However, a review of the available literature permits neither a precise description nor an all-inclusive understanding of the changes in vascular responsiveness that accompany the sepsis syndrome. The fact that published data demonstrate a broad range of alterations in vascular responsiveness complicating sepsis highlights the lack of consensus on this important issue and is likely explained by one or more of the following arguments:

1. Animal models of sepsis, from which the vast majority of data describing vascular responsiveness have originated, are not generally comparable in the stage of clinical sepsis they purport to represent. The host response to a focus of infection (i.e., the "sepsis syndrome") describes a spectrum of pathophysiologic abnormalities that are not precisely reproduced by any of the different animal models of sepsis currently available. Like Wicherman et al., we prefer to distinguish between models representing the early and late stages of sepsis in the context of describing sepsis-induced changes in vascular resistance, since it is easily envisaged that changes demonstrated in key indicators of this disease process according to the stage of the disease might also be evident when examining vascular responsiveness.

2. Many studies of the influence of sepsis on vascular reactivity have simultaneously employed anesthetics. By virtue of their independent action on vascular reactivity, these agents confuse any description of the effects of sepsis on the regulation of vascular tone.

3. Experiments may also differ when a hypotensive response complicates the septic insult. Thus, the possibility of an independent influence of coexistent shock on vascular reactivity may further confuse a description of the effects of sepsis alone.

**Depression of Vascular Responsiveness in Clinical Sepsis?**

Despite these methodologic reservations, a large body of evidence supports the notion that depressed vascular responsiveness complicates the clinical sepsis syndrome. Thus, clinical studies have repeatedly demonstrated a profound arterial vasodilation in the later stages of sepsis, such that a depression in vascular tone has been demonstrated to precede death even when systemic $Q_o$ begins to fall. This situation, whereby death in septic shock is accompanied by absence of appropriate vasoconstriction, has been referred to as "vascular paralysis." Furthermore, scattered clinical reports demonstrate that potent sympathomimetic agents with vasoconstricting properties can be administered to patients with sepsis without the same increase in arterial perfusing pressures and vascular resistance typically noted when administered to patients without sepsis. Finally, Hartl et al. reported 2 patterns of reactive hyperemia in sepsis. In early sepsis, the normal vasodilatory response to an ischemic stimulus in the limb was maintained. However, in the later stages of sepsis, circulatory failure progressing to death was accompanied by a loss of the previously demonstrated reactive hyperemia in response to an ischemic insult. While this study did not allow a determination of whether a loss in vascular reactivity directly contributed to circulatory failure and death or whether it was simply part of a systemic process, it did demonstrate that sepsis is associated with a loss of normal metabolic vasoreactivity, albeit perhaps late in the clinical process.

**Depression of Vascular Responsiveness in Animal Models of Sepsis**

As has been shown in some clinical studies, a depression in normal vascular responsiveness to the application of exogenous catecholamines has been demonstrated in various animal models of sepsis. Pomerantz et al. reported that the normal increase in arterial pressure to norepinephrine was depressed following an infusion of endotoxin. In a study of the effects of exogenous sympathomimetics on the distribution of systemic $Q_o$, in sheep, we found that the onset of sepsis necessitated an increase in the doses of adrenergic agonists required to sustain an increase in $Q_o$. Fink et al. and Burnier et al. also reported a diminished pressor response to the infusion of sympathomimetic agents in animals in a septic state and further demonstrated that pretreatment with cyclo-oxygenase inhibitors ameliorated this potentially negative interaction of sepsis on the response of arterial perfusing pressures to the administration of a sympathomimetic.

Another approach has been the examination of vascular responsiveness under various conditions in vitrō. Using aortic vascular rings, Wakabayashi et al. reported that the in vitrō contractility in response to a phenylephrine stimulus was transient when sepsis was reproduced in rats by the injection of endotoxin. In a model that may represent early sepsis more closely than an endotoxin infusion does, McKenna et al. reported that aortic ring contraction in response to norepinephrine was depressed in rats in which sepsis was induced by cecal ligation and perforation. The contractile response in this latter study was partially restored by denuding the aortic ring of endothelium, which suggested that an excessive production of endothelium-derived relaxing factor might contribute to arterial vasodilation when observed in sepsis. Cytokines are likely important mediators in sepsis. Beasley et al. demonstrated that aortic rings exposed to interleukin-1 in vitrō have submaximal phenylephrine responses; this latter effect was not dependent on endothelium.

In contrast to these latter results, recent work from our laboratory has demonstrated that the depression in vascular responsiveness reported in aortic rings by McKenna et al. may not be shared by all vascular beds in this syndrome (unpublished data). Scheidkrantz and Carlson studied pulmonary artery pressure responses in a whole-lung preparation 4 h after cecal ligation and perforation. A decreased response to prostaglandin $F_2$ was not seen if the animals had been pretreated with ibuprofen, while angiotensin-II responses were normal throughout. These observations serve to illustrate the likelihood that there is a dissociation of the effects of sepsis on vascular responsiveness both
within different organs and with different agonists. Therefore, sepsis may preferentially modify organ QO2 during the early stages of the septic syndrome that the ocular ligation and perforation model represents.

Some studies have examined sepsis-induced changes in vascular reactivity with in vivo studies using intravital microscopy. Cryer's group demonstrated intense vasoconstriction in the circulation of the gut when sepsis was induced by an infusion of Escherichia coli organisms. In contrast, a vasodilatory response was noted in the hepatic circulation during an infusion of endotoxin. The latter data were used to argue for a microcirculatory cause of the ischemic injury that has been reported to complicate sepsis in various animal models. Subsequently, Cryer et al. also reported differential arteriolar vasoreactivity in skeletal muscle in a septic model, as small arteriolar dilatation and large arteriolar construction were demonstrated by means of intravital microscopy. Because of the greater contribution of small arteriolar dilation to the calculated systemic resistance, this group also proposed that the differential arteriolar response was sufficient to explain the depressed systemic vascular resistance in sepsis.

In summary, variable depression in vascular responsiveness has been demonstrated in septic animal models, with apparently differing degrees of illness severity. The majority of studies point to depressed vasconstrictor responses, although in vivo studies suggest that these abnormalities may not necessarily be shared by all vascular beds at the level of the resistance arterioles. Chernow and Roth have summarized current opinion regarding the specific site in the conductance and resistance arteries from which a depression in vascular responsiveness may arise in the sepsis syndrome (Table 1).

### Table 1 — Some Proposed Causes of Depression of Vascular Responsiveness in Sepsis

<table>
<thead>
<tr>
<th>Cause</th>
<th>Response</th>
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<tr>
<td>Down-regulation of α1-adrenergic receptors</td>
<td>May require sympathomimetics to maintain adequate pressures</td>
</tr>
<tr>
<td>Endotoxin-mediated depression in vascular adrenergic action</td>
<td>May require sympathomimetics to support hypodynamic circulation</td>
</tr>
<tr>
<td>Impaired endogenous norepinephrine release due to action of an</td>
<td>May be profoundly depressed</td>
</tr>
<tr>
<td>endogenously released opioid peptide</td>
<td></td>
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<tr>
<td>Impairment of adrenergic function by endogenous prostanoids</td>
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<tr>
<td>Impaired vascular smooth muscle function in response to vasoconstrictors</td>
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<tr>
<td>Dysfunction of the endothelium</td>
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#### Functional Significance of Altered Vascular Responsiveness in Sepsis

As previously discussed, the appropriate regulation of the QO2 of an organ requires a finely integrated process that links vascular resistance to Q in the feeding arterioles of the organ. The control of organ Q is therefore complex and involves several mechanisms, including metabolic breakdown products, humoral/hormonal factors, autonomic control, and endothelium-dependent vasoemotion.

Conceptually, a depression in vascular responsiveness complicating the sepsis syndrome could describe a spectrum ranging from an incomplete to a complete lesion (Fig 1). A complete lesion may be best exemplified by some of the data that originated from endotoxemic models of sepsis. In some of the endotoxemic models, particularly those in which mean arterial perfusing pressures were concurrently depressed, organ Q was demonstrated to be primarily regulated by changes in arterial perfusing pressures. In another model of endotoxemic sepsis, Nelson et al. demonstrated depression in the vasodilatory response of the gut circulation to an ischemic insult (ie, depressed metabolic hyperemia).

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**Figure 1.** Sepsis syndrome can be seen as a spectrum of severity ranging from sepsis without shock to sepsis with shock. Simultaneously, abnormalities in vascular reactivity are likely to be more manifest in sepsis with shock than in sepsis without shock.
Although mean arterial perfusing pressures were not depressed, this study suggested that endotoxemic sepsis disrupted the vascular feedback loop, which normally responds to ischemia with vasodilation to increase local Q. Therefore, we conclude that both the metabolic regulation of tissue O₂ and pressure autoregulation are lost in such models, which likely represent the later phases of the sepsis syndrome.¹³

A depression in vascular responsiveness complicating sepsis could also represent an incomplete lesion. In this scenario, changes in vascular responsiveness at the level of resistance arterioles might result in disruption of the normal ability to distribute systemic Q according to the O₂ needs of individual organs, thus forcing some tissues into O₂ supply limitation. This type of lesion seems most evident in animal models in which sepsis has followed creation of an inflammatory focus, such as by cecal ligation and perforation. In this type of model, we and others have demonstrated significant alterations in the normal distribution of organ Q. However, these data have inconsistencies when one attempts to generalize to sepsis-induced alterations in vascular responsiveness in all organ systems. For example, we found that an increase in Q heart in septic sheep parallelled an increase in heart work similar to data reported by Dhainaut et al in a clinical study of septic shock patients. This suggested appropriate vascular responsiveness within the coronary circulation in hyperdynamic sepsis, since vasodilation supported an increased local QO₂ when O₂ needs of the heart were increased. In contrast, Lang et al reported that an increased heart Q in a rat model of intraperitoneal sepsis was dissociated from changes in heart work, suggesting that changes in coronary vascular responsiveness were independent of changes in the O₂ needs of the heart in sepsis.

While changes in vascular responsiveness have seemed appropriate in some vascular beds, in some septic models further examination has demonstrated a reduction in the vasodilatory reserve necessary to deal with added increases in tissue O₂ needs. For example, we found that animals in which sepsis was induced by cecal ligation and perforation did not manifest the normal redistribution in Q from the splanchnic organs to the myocardium when positive-end expiratory pressure depressed systemic Q. This finding was similar to the effect of a burn injury to interfere with a normal redistribution in Q to the myocardium during hemorrhagic shock. Furthermore, we found that the administration of exogenous sympathomimetic agents to septic animals was also accompanied by a failure to maximally redistribute Q from the splanchnic circulations to the myocardium, primarily to subserve the increased O₂ needs of the myocardium imposed by the augmented heart work accompanying the sympathomimetic infusion. Why vascular resistance fails to support the anticipated redistribution in Q from the gut to vital organs such as the heart in sepsis remains speculative. This may be another example of the spectrum of failure of vascular responsiveness in sepsis, such that inappropriate vasodilation of the splanchnic circulation prevented a redistribution in Q. On the other hand, failure to redistribute Q from the gut to the heart may reflect appropriate changes in splanchnic vascular resistance. Nelson et al speculated that the gut loses its O₂E reserve during sepsis and thereby becomes more flow-dependent to maintain QO₂. This suggests that failure to redistribute gut flow during a depression in systemic Q in burns and sepsis is due to local metabolic signals antagonizing systemic responses that would otherwise have directed Q away from the gut. If this is indeed the case, altered vascular reactivity in sepsis may represent an appropriate shift in the balance of the usual regulatory mechanisms. More important, however, data from the cecal ligation and perforation models of sepsis indicate that altered vascular reactivity in models that represent an earlier phase of sepsis than that reproduced by endotoxin infusion demonstrate variable depression vascular responsiveness, which may vary between organs and indeed within individual organs.

Conclusions

A discussion of changes in vascular responsiveness during sepsis is rendered difficult by virtue of the many different animals models that have been used to mimic sepsis and the fact that this disease represents a spectrum of injury to the host. Thus, differences in vascular reactivity during sepsis are likely different in the early and late stages of this host response to a focus of infection.

In early sepsis, vasodilation within the coronary and splanchnic circulations likely subserves an increase in the respective organ Q, thereby supporting increased O₂ needs within these organs. In this circumstance, these vascular responses would be considered appropriate.

However, early sepsis also initiates a process that depresses the ability of the gut to utilize its QO₂E reserve to support increased O₂ needs. Therefore, this organ does not easily give up its Q to support increases in O₂ needs within other organs imposed during sepsis. Again, vascular responsiveness at the local level in the gut would be considered appropriate in this regard, given that local metabolic needs establish priority in the governance of Q over the effect of sympathetic activity, which would otherwise distribute Q to other organs.

In contrast to the apparent appropriateness of vascular responsiveness in the early phases of sepsis, the later stages of this syndrome seem accompanied by a well-characterized depression in vascular responsiveness. Both in vivo and in vitro studies have demonstrated a depression in vascular responsiveness at most levels of the arterial circulation in animal models that mimic the later stages of sepsis. The precise cause of this abnormality remains undefined, although altered adrenoreceptor or smooth muscle function, the influence of vasoconstrictor prostanooids, and the presence of other circulating mediators may be involved. The clinical correlate of this failure of normal vascular responsiveness seems to be the inability to demonstrate increased systemic resistance in nonsurvivors of septic shock when systemic Q has fallen. At the organ level, failure of normal vascular responsiveness to metabolic and neurohumeral signals likely establishes conditions in which QO₂ to some organs is depressed below need, so that organ ischemic injury results, a process that would accentuate or indeed cause MOF.

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