Endotoxemia causes central downregulation of sympathetic vasomotor tone in healthy humans

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Sayk F, Vietheer A, Schaaf B, Wellhoener P, Weitz G, Lehnerth H, Dodt C. Endotoxemia causes central downregulation of sympathetic vasomotor tone in healthy humans. Am J Physiol Regul Integr Comp Physiol 295: R891–R898, 2008. First published July 16, 2008; doi:10.1152/ajpregu.90444.2008.—Experimental endotoxemia as a model of the initial septic response affects the autonomic nervous system with profound cardiovascular sequelae. Whether the postsynaptic sympathoneural activity to the muscle vascular bed is altered in the early septic phase remains to be determined. The present study aimed to elucidate the early effects of LPS on muscle sympathetic nerve activity (MSNA) and cardiovascular regulation in healthy humans. Young, healthy volunteers randomly received either an LPS bolus (4 ng/kg body wt, n = 11) or placebo (saline; n = 7). Experimental baroreflex assessment (baseline measurements followed by infusion of vasoactive drugs nitroprusside/phenylephrine) was done prior to and 90 min following LPS or placebo challenge. MSNA, heart rate, blood pressure, and blood levels of catecholamines, TNF-α, and IL-6 were measured sequentially. Endotoxin but not placebo-induced flu-like symptoms and elevated cytokine levels. In contrast to placebo, LPS significantly suppressed MSNA burst frequency 90 min after injection [mean ± SE: 12.1 ± 2.9 vs. 27.5 ± 3.3 burst/min (post-vs. pre-LPS); P < 0.005] but increased heart rate [78.4 ± 3.1 vs. 60.6 ± 2.0 beats/min (post-vs. pre-LPS); P < 0.001]. Baseline blood pressure was not altered, but baroreflex testing demonstrated a blunted MSNA response and uncoupling of heart rate modulation to blood pressure changes in the endotoxin group. We conclude that endotoxin challenge in healthy humans has rapid suppressive effects on postsynaptic sympathetic nerve activity to the muscle vascular bed and alters baroreflex function which may contribute to the untoward cardiovascular effects of sepsis.

baroreceptors; nervous system; sympathetic; MSNA; endotoxin; systemic inflammation

SEPSIS DESCRIBES A COMPLEX clinical syndrome in which the inflammatory immune response to an infectious insult induces dramatic changes to the cardiovascular system, ultimately leading to life-threatening shock with unresponsive hypotension, multiple organ dysfunction, and death. Conceptually, septic shock can be described as a failure of cardiovascular defensive mechanisms to counteract the potentially lethal consequences of the uncontrolled septic immune response (7, 20, 21).

In this respect, the function of the autonomic nervous system during sepsis is of utmost interest. Obviously, both sympathetic as well as parasympathetic branches are affected by the septic response and, interestingly, vice versa, affect immune response during sepsis (2, 8), and this again might be modulated by, e.g., the gram properties of the germ and type of Toll-like receptors involved (6, 30). Previous studies demonstrated that the parasympathetic nervous system is likely to be a key player in septic defensive mechanisms (4, 22); however, many determinants of sympathetic function remain to be elucidated. Under healthy conditions hypotension is immediately detected by baroreceptors that sense the prevailing blood pressure and initiate sympathoexcitation to both the heart and peripheral vessels via central nervous baroreflex centers to restore blood pressure to normal values (14). In animal models and in human sepsis, however, these reflex-responses seem to be impaired (3, 36, 38), which may contribute to the loss of systemic vascular resistance. Proinflammatory cytokines seem to interact with the central autonomic network. TNF-α and IL-6 are highly elevated during sepsis; the experimental injection of TNF-α mimics the clinical picture of septic shock (34).

Such sepsis-related dysfunction of blood pressure regulation might occur on several levels of the baroreflex arch: 1) reduction in baroreceptor sensitivity, 2) shift of the baroreflex set point to lower blood pressure levels through effects on central nervous baroreflex centers with impaired efferent sympathetic activity, and 3) reduced end-organ responsiveness. Current knowledge about the role of sympathetic branches on circulatory control during sepsis is limited (2, 36, 38), which is partly due to the difficulty to directly examine sympathetic function in septic patients. Many features of early sepsis including circulatory changes have been mimicked and extensively studied in human subjects challenged with a pyrogenic dose of endotoxin (21, 31, 32). Measurements of heart rate and blood pressure, including their variability, demonstrated a marked reduction of both sympathetic and parasympathetic spectral components during endotoxemia (11, 16). This indirect assessment of cardiac sympathovagal balance does not discriminate whether it is the centrally mediated sympathetic outflow or the peripheral neuroeffector transmission that is compromised. Blood catecholamines are elevated during sepsis; however, their levels may not properly reflect vasoconstrictive sympathetic nerve activity to the muscle vascular bed, which is a most important contributor to total peripheral resistance and systemic blood pressure regulation via the arterial baroreflex (9, 17, 18). Microneurographic measurements of muscle sympathetic nerve activity (MSNA), in contrast, have the potential to directly unravel changes in centrally regulated sympathetic outflow to the muscle vascular bed. To explore the sympathetic system in sepsis we used a human endotoxemia model and...
asked the following questions: 1) Does endotoxemia reduce the central vasoconstrictive sympathetic outflow? 2) Does endotoxemia have a blunting effect on the arterial baroreflex?

METHODS

Subjects

Eighteen healthy, male volunteers participated in the study. Participants were normotensive nonsmokers and medication free. A laboratory screening excluded current infectious diseases. Subjects were asked to abstain from alcohol and caffeine for 24 h prior to the experiment. The study followed a single, blinded design and subjects were randomized to either receive endotoxin (n = 11, 28.7 ± 6.6 yr; 79.7 ± 2.9 kg) or isotonic saline (n = 7, 26.3 ± 5.3 yr; 81.2 ± 3.0 kg). The study was approved by the local ethics committee and all participants gave their written informed consent.

Participants were investigated in the neurophysiological laboratory in a comfortable supine position. Continuous ECG-monitoring was digitized online allowing post hoc analysis of heart rate variability (HRV) at selected periods. Blood pressure was measured oscillometrically (Welch Allyn Tyco). An intravenous cannula was inserted into an antecubital vein for repeated blood sampling, infusion of maintenance fluid, and bolus administration of either endotoxin or saline.

Experimental Protocol

The aim of our study was to investigate the influence of systemic endotoxin on vasoconstrictive sympathetic nerve activity and systemic blood pressure regulation via the arterial baroreflex. Therefore, the experimental protocol focused on two recording periods: 1) baroreflex assessment prior to the bolus administration of LPS or saline (preinjection period) and 2) baroreflex reassessment starting ~90 min after injection of either substance (postinjection period) (Fig. 1). Both, the first (i.e., preinjection) and second (i.e., postinjection) recording period consisted of standardized measurements of MSNA, heart rate, HRV, and oscillometric blood pressure during a 15-min resting phase for baseline recordings followed by the administration of vasoactive drugs to challenge baroreflex function as published previously (Fig. 1) (28, 38). In brief, incremental doses of sodium-nitroprusside (0.15 mg·kg⁻¹·h⁻¹ → 0.35 mg·kg⁻¹·h⁻¹ → 0.55 mg·kg⁻¹·h⁻¹) or phenylephrine (0.09 mg·kg⁻¹·h⁻¹ → 0.21 mg·kg⁻¹·h⁻¹ → 0.30 mg·kg⁻¹·h⁻¹) were intravenously infused. Each dose step was maintained for 5 min. The nitroprusside and phenylephrine infusion was separated by a 15-min washout interval.

Microneurographic Recording of MSNA

MSNA was recorded from the peroneal nerve using Tungsten microelectrodes. In brief, the recording electrode was percutaneously inserted into a peroneal muscle nerve fascicle. A reference electrode was positioned subcutaneously at a distance of 2 to 3 cm. Signals were amplified, filtered, and passed through an amplitude discriminator to obtain a mean voltage display of the multiunit nerve activity. Technical details and evidence that the recorded activity is of sympathetic origin has been published previously (12, 35). Analog curves of all parameters (MSNA neurogram, ECG, respiration movements) were digitized online and stored on a computer disk for subsequent computer analysis (PowerLab, ADInstruments, Colorado Springs, CO).

Endotoxin Administration

Purified LPS prepared from Escherichia coli O:113 (U.S. Standard Reference Endotoxin, Lot G-1; Food and Drug Administration, Bethesda, MD) was injected intravenously as a bolus (4 ng/kg body wt) (32) and flushed by normal saline to ensure complete delivery. Control subjects received a bolus of isotonic saline.

Biochemistry

For assays of TNF-α, IL-6 venous blood was obtained before, as well as 90 and 180 min after, the administration of endotoxin or saline. Blood sampling for catecholamines was performed at 30-min intervals starting from the beginning of the preinjection period until 180 min postinjection. Blood samples were centrifuged immediately, and the plasma was stored at −80°C until further analysis.

Plasma TNF-α and IL-6 levels were measured using the human TNF-α UltraSensitive ELISA Kit and the human IL-6 UltraSensitive Kit (both from BioSource, Camarillo, CA). The sensitivity of the kits was <0.09 pg/ml for TNF-α and <0.1 pg/ml for IL-6, respectively. Plasma norepinephrine and epinephrine levels were determined by high-performance liquid chromatography and subsequent electrochemical detection.

Data Analysis

Cardiovascular parameters and MSNA were analyzed during both the preinjection period, i.e., before LPS- or saline-administration, and the subsequent postinjection period starting 90 min after injection. Previous studies have shown that hemodynamic changes (including loss of systemic vascular resistance) are most distinct after this time period (11, 21, 31). MSNA, heart rate, HRV, and oscillometric blood pressure were determined according to the methods described for baroreflex characterization previously (28, 33). All recordings were analyzed by the same observer, who was unaware of the substance (saline or LPS) administered to the subject.

Sympathetic bursts were visually identified by inspecting the mean voltage neurogram, and MSNA was quantified with the aid of analytical software that also analyzed heart rate from the ECG (Chart 5.02, ADInstruments) (12). Artifacts were distinguished from real bursts by the following characteristics: 1) sharp sudden upstroke, 2) short duration and high amplitude (“needle-shaped”), and 3) shift of the isoelectric baseline due to movement. A recording was considered suitable for analysis when the signal-to-noise ratio was >3. Nerve activity was expressed as burst rate (number of bursts/min). A difficulty in intraneural recordings of MSNA is the fact that the results are critically affected by the position of the electrode in relation to the sympathetic fascicle. To document constant recording quality, microelectrodes remained in an intraneural position during the entire experiment. Whereas sudden alterations in electrode position are easy to detect, it may be difficult to recognize minor successive changes. Subtle changes will usually affect the mean voltage amplitude or surface area of the burst rather than their mere detection. Therefore, burst rate is a robust measure of activity. Additionally, the quality of
the recording signal was scrutinized by comparison of the burst characteristics (morphology, amplitude) during sympathoexcitatory apnea and nitroprusside infusion at both recording periods, maneuvers that regularly stimulate MSNA even in sympathosuppressive conditions. Following these strict criteria, we were able to include seven complete recordings of each condition into the final analysis. Clinical and biochemical data, in contrast, were analyzed from all subjects of both the endotoxin (n = 11) and placebo group (n = 7).

Statistics. Data are expressed as means ± SE. Statistical analysis based on analysis of variance with the repeated-measures factor time (preinjection vs. postinjection) and the group factor treatment (placebo vs. LPS). When the overall analysis indicated significance, post hoc testing was performed and a Greenhouse-Geisser corrected \( P < 0.05 \) was considered significant. Correlations were calculated using the two-tailed Pearson test (SPSS for Windows, Chicago, IL).

RESULTS

Clinical, Cytokine and Catecholamine Response

Administration of endotoxin induced the expected flu-like symptoms in all subjects having received LPS. Symptoms started after a clinically silent interval of 45 to 60 min with a brief episode of shaking chills, and subjects were covered with blankets to achieve more comfortable conditions. Constitutional symptoms culminated at about 1.5 to 3 h after endotoxin injection with varying degrees of headache, nausea, general malaise, myalgia, and arthralgia and had completely disappeared after 5 h. Orally measured temperature showed mildly febrile values at the end of the experiment in contrast to placebo.

Endotoxin but not saline produced the expected systemic inflammatory cytokine response. The increase of TNF-\( \alpha \) level was about 100-fold at 90 min and 50-fold at 180 min after LPS-injection (6.3 ± 3.7 vs. 611.6 ± 113.6 and 292.6 ± 66.5 pg/ml). IL-6 levels increased about 50-fold at both 90 and 180 min after injection (2.1 ± 1.2 vs. 96.0 ± 2.0 and 101.9 ± 2.4 pg/ml). Preinjection plasma catecholamine levels did not differ between both groups. However, in response to endotoxin but not placebo both norepinephrine and epinephrine levels were significantly increased (Fig. 2).

Cardiovascular Parameters and Baroreflex

Volunteer drop out. Cardiovascular parameters of both groups with respect to baseline and baroreflex testing of the pre- and postinjection period are reported in table 1. Microneurographic recordings of three volunteers had to be excluded form further analysis of the baseline period, and, additionally, one volunteer with regard to baroreflex testing due to movement artefacts with electrode dislocation during intermittent chills according to the strict criteria described (i.e., sudden persistent baseline shift, reduced burst amplitude during defined sympathoexcitatory maneuvers). Analysis of MSNA and other cardiovascular parameters were, therefore, based on complete recordings from seven subjects of the placebo group and seven out of eleven subjects of the endotoxin group.

Blood pressure. At baseline, within-group or intergroup comparison showed no significant differences of oscillometric systolic, diastolic, and mean arterial pressure for both the pre- and postinjection period. As displayed in Fig. 3, administration of three incremental doses of nitroprusside caused a progressive decrease, and infusion of phenylephrine resulted in a progressive elevation of blood pressure, respectively, without any significant differences regarding absolute or net values at the preinjection periods of both groups and the pre- and postinjection period of the placebo group. Following endotoxin, in contrast, the net blood pressure decrease in response to nitroprusside was more pronounced, leading to significantly lower mean blood pressure values.

MSNA. At the preinjection periods, baseline MSNA did not differ significantly between both groups. At the postinjection
period, baseline MSNA of the placebo group was significantly increased compared with the preinjection data. After endotoxin administration, in contrast, baseline MSNA was strongly reduced compared with the preinjection period or compared with the corresponding postinjection data of the placebo condition (Table 1).

During nitroprusside infusion, MSNA increased in response to the decrease in blood pressure. The increase of MSNA per millimeters of mercury of blood pressure reduction was comparable at the preinjection periods of both groups as well as the pre- and postinjection period of the placebo condition. Following endotoxin, however, the relative increase of MSNA was significantly smaller compared with the preinjection period, or to the corresponding placebo postinjection data, respectively (Fig. 4).

Heart rate and HRV. Heart rate did not show any differences between both groups at baseline and during baroreflex modulation of the preinjection period. Additionally, no differences were found when pre- and postinjection data of the placebo condition were compared. Following endotoxin, however, baseline heart rate was significantly increased compared with the preinjection period or to the corresponding placebo postinjection data. Moreover, heart rate did not adapt to baroreflex stimulation or deactivation, but remained fixed on an elevated level regardless of the prevailing blood pressure (Table 1).

In conformity with previous studies (2, 11, 16), all frequency domain measures of HRV were significantly reduced following LPS-injection, not only at baseline but also during baroreflex stimulation or deactivation compared with the preinjection period or the corresponding placebo condition (data not shown).

Cardiac and vascular baroreflex set point and sensitivity. To further characterize the cardiac and vascular baroreflex set point and sensitivity, blood pressure at baseline and during pharmacologic baroreflex modulation was correlated to the corresponding heart rate and MSNA, respectively (Fig. 5). This simplified model yields a stimulus response curve that defines the vascular or cardiac baroreflex set point as the threshold of

### Table 1. Cardiovascular parameters of the LPS and placebo group with respect to the pre- and postinjection periods, within-group comparison of both periods, and comparison of corresponding periods between both the endotoxin and placebo condition

<table>
<thead>
<tr>
<th>Recording Period</th>
<th>Endotoxin</th>
<th>Placebo</th>
<th>P</th>
<th>Endotoxin</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preinjection</td>
<td>Postinjection</td>
<td></td>
<td>Preinjection</td>
<td>Postinjection</td>
<td></td>
</tr>
<tr>
<td>Mean BP, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL</td>
<td>91.3±2.5</td>
<td>90.4±2.7</td>
<td></td>
<td>89.5±2.4</td>
<td>90.8±2.5</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>80.3±2.3</td>
<td>71.4±3.4</td>
<td>a</td>
<td>79.1±2.8</td>
<td>80.2±3.7</td>
<td></td>
</tr>
<tr>
<td>P3</td>
<td>102.1±3.2</td>
<td>97.7±2.7</td>
<td>a</td>
<td>99.1±4.4</td>
<td>98.7±4.3</td>
<td>d</td>
</tr>
<tr>
<td>MSNA, burst/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL</td>
<td>25.4±3.2</td>
<td>11.2±3.1</td>
<td>c</td>
<td>20.0±3.4</td>
<td>27.3±4.5</td>
<td>b,d</td>
</tr>
<tr>
<td>N3</td>
<td>49.6±5.4</td>
<td>25.0±5.4</td>
<td>b</td>
<td>43.4±3.4</td>
<td>50.4±4.1</td>
<td>c</td>
</tr>
<tr>
<td>P3</td>
<td>5.1±2.6</td>
<td>1.8±0.9</td>
<td></td>
<td>10.3±3.4</td>
<td>10.8±3.0</td>
<td>d</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>60.6±2.0</td>
<td>78.4±3.1</td>
<td>c</td>
<td>63.0±3.3</td>
<td>63.3±2.9</td>
<td>e</td>
</tr>
<tr>
<td>N3</td>
<td>71.8±4.1</td>
<td>86.7±4.1</td>
<td>b</td>
<td>76.1±3.4</td>
<td>77.4±4.7</td>
<td>e</td>
</tr>
<tr>
<td>P3</td>
<td>51.5±2.4</td>
<td>84.2±2.7</td>
<td>c</td>
<td>54.1±4.3</td>
<td>52.5±3.0</td>
<td>f</td>
</tr>
</tbody>
</table>

Values are means ± SE n = 7 for both groups. BP, blood pressure; MSNA, muscle sympathetic nerve activity; BL, baseline recording; N3 and P3, final dose step of nitroprusside and phenylephrine, respectively. *P < 0.05, **P < 0.01, ***P < 0.001 for within-group comparison; †P < 0.05, ‡P < 0.01, §P < 0.001 for comparison between groups.
reflex activation of MSNA or heart rate at unaffected rest (baseline). Baroreflex sensitivity is determined by the net changes in MSNA or heart rate in relation to blood pressure changes during baroreflex testing.

During endotoxemia, set point and stimulus-response curve of the vascular baroreflex evidently were displaced to decreased muscle sympathetic activity levels, and the efferent baroreflex response to blood pressure changes was attenuated, indicating that vascular baroreflex sensitivity was significantly reduced (Fig. 5A). As depicted in Fig. 5B, baroreflex-mediated adaptation of heart rate to blood pressure changes was abolished following endotoxin application, and heart rate seemed to be uncoupled from autonomic baroreflex control during endotoxemia.

**Correlation of proinflammatory cytokines with changes of sympathetic activity.** Plasma levels of TNF-α measured 90 min after LPS-injection were positively correlated with the percentage decrease of MSNA (postinjection baseline; n = 8) from the preinjection period (P = 0.033; Pearson −0.747) (Fig. 6). The corresponding plasma levels of IL-6, however, were negatively correlated (P = 0.036; Pearson +0.739). Relative changes of heart rate did not correlate with plasma cytokine levels.

**DISCUSSION**

An acute bacterial infection is a stressful and potentially life-threatening insult with profound alterations in the function of the immune, endocrine, and autonomic nervous systems. Any dysfunction of either of these integrating systems could contribute to the untoward health effects of sepsis. Experimental endotoxemia represents a defined model for a short-term, sepsis-like response with well-known hemodynamic sequelae (21, 31, 32). The present study focused on changes of the sympathetically mediated cardiovascular regulation in healthy young males during endotoxin challenge. As previously described, low-dose LPS provoked a clear systemic inflammatory response of the innate immune system with profound increases in TNF-α and IL-6, serologically, as well as flu-like symptoms clinically.

In the present study, we demonstrated that MSNA was severely reduced 90 min after endotoxin administration. Mea-

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**Fig. 4.** MSNA at rest baseline (BL) and during baroreflex testing with 3 increasing doses of nitroprusside (N1–3) and phenylephrine (P1–3) during the pre- (A) and postinjection period (B). ● LPS; ○, saline. (⁎ P < 0.05; ⁎⁎ P < 0.01; ⁎⁎⁎ P < 0.001).

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**Fig. 5.** Correlation between mean arterial blood pressure and MSNA (A) or heart rate (B) of the endotoxin (●, preinjection; ■, postinjection) and placebo group (△, preinjection; ▽, postinjection); (⁎⁎⁎ P < 0.01). Please note that physiologically the stimulus-response curve of the baroreflex is rather sigmoid, not linear. However, linear regression helps to visualize the apparent differences of vascular baroreflex-sensitivity (MSNA) and uncoupling of heart rate. The slope, y-intercept and regression coefficient (R²) of the linear best-fit lines are: A: ●: y = −2.0173 x + 208.54; R² = 0.9932; ■: y = −0.7895 x + 80.573; R² = 0.8427; △: y = −1.8098 x + 184.73; R² = 0.9478; ▽: y = −2.1008 x + 218.47; R² = 0.9928. B: ●: y = −0.9325 x + 144.71; R² = 0.9756; ■: y = −0.0817 x + 91.208; R² = 0.0654; △: y = −1.1491 x + 166.6; R² = 0.9629; ▽: y = −1.4322 x + 193.89; R² = 0.9628.
measurements of MSNA directly unravel central sympathetic outflow to the muscle vascular bed, which is a key factor in baroreflexive blood pressure regulation being, in turn, affected by the prevailing blood pressure. Thus, under physiological conditions, a reduction in MSNA would most likely result from an increase in blood pressure. In the present study, however, MSNA was reduced during the endotoxemic recording period without concomitant blood pressure elevation. Additionally, MSNA was not appropriately increased, and blood pressure more profoundly decreased during nitric oxide-induced vasodilation (nitroprusside). In fact, baroreflex function itself has been altered during endotoxemia, and this has obvious effects on autonomic defense mechanisms against blood pressure decreases. This points to the possibility that the septic immune response directly suppresses sympathetic outflow to the muscle vascular bed via central nervous mechanisms leading to a blunted baroreflex sensitivity. Such disturbances of the counterregulating increase of MSNA in response to blood pressure decreases could have particular clinical relevance in concert with local vasodilatory mechanisms known to evolve in septic patients (1, 23, 37). In contrast, the net blood pressure increase in response to infusion of the α1-agonist phenylephrine was not altered, indicating that the (peripheral) vascular responsiveness to α-adrenergic stimulation was well preserved. This is in accordance with previous observations in rodents (27).

While MSNA was depressed, catecholamine levels were elevated. However, in contrast to healthy conditions, previous studies have shown that plasma levels of catecholamines during sepsis do not properly reflect sympathetic activity, and loss of vascular resistance during sepsis occurs despite the elevation of circulating catecholamines (13, 17). Several mechanisms including inappropriate inactivation of catecholamines have been discussed (1, 18, 37). Our study adds the finding that, obviously, the increase in plasma catecholamines is not induced by an increase in vasoconstrictive MSNA and, thus, rather originates from other sources like the adrenals, the pulmonary, and/or the splanchnic vascular bed (9). Previous studies in rodents demonstrated that during systemic inflammation, sympathetic nerve activity to the spleen and adrenals is increased, whereas activity of other sympathetic branches is decreased (19, 26). These alterations seem to occur independently from the vascular and cardiac baroreflex (36), which might contribute to the discrepancy of circulating catecholamines and blood pressure control during endotoxemia. Consistently, the arterial baroreflex was found to be not essential in mediating sympathoadrenal activation during endotoxemia in conscious sinoaortic-denervated rats (40).

Microneurographic protocols of long duration always carry the risk of electrode dislocation during the course of the experiment, especially in the presence of chills. In the present study, special emphasis was put on recording quality throughout the experiment, and analysis of microneurographic data was restricted to unequivocally comparable recordings. These strict criteria excluded the possibility that the results were artificially induced by electrode dislocation. In contrast to the endotoxin group, MSNA of the placebo condition significantly increased during the postinjection resting period compared with the initial baseline, whereas blood pressure and heart rate showed no significant changes. Such increases of sympathetic nerve activity are a well-known phenomenon during recording protocols of long duration (15) and are explained as reaction to urinary bladder filling and discomfort due to the restricted body position (10).

LPS challenge not only affected the vascular but also the cardiac baroreflex function. Heart rate was accelerated at rest and did not react to any blood pressure modulation, indicating that heart rate was uncoupled from baroreflex regulation. Furthermore, both sympathetic and parasympathetic spectral components of HRV were considerably reduced, which is in accordance with previous reports (2, 11, 16). Decreased physiologic variability, culminating in complete disintegration of homeostatic oscillators seems to represent a generalized response during the early septic response (24, 25) and to result from disruption of interorgan communication. Thus, while the vascular baroreflex response was considerably blunted and did not react appropriately against nitric oxide-induced (nitroprusside) blood pressure decreases, the cardiac baroreflex showed complete uncoupling from the prevailing blood pressure. The combination of these LPS effects could have deleterious consequences especially in those subjects with restricted autonomic defense mechanisms for example due to a preexisting reduction in cardiac reserve.

The mechanisms leading to central suppression of vasoconstrictive sympathetic drive and disintegration of cardiac baroreflex function are unknown. Recently, bidirectional interactions of sepsis-related cytokines with the cholinergic branches of the autonomous nervous system have gained new attention leading to the concept of a cholinergic anti-inflammatory pathway (4, 22). Vagal efferent activity was found to be impaired through
inflammatory cytokine interactions during experimental sepsis, and electrical or pharmacologic vagal stimulation prevented cytokine production and reversed clinical disease including septic shock (4). In the present study, we found new evidence that not only the parasympathetic, but also the sympathetic system, including baroreceptor reflex-mediated circulatory control is severely compromised. Elevated plasma levels of proinflammatory TNF-α during endotoxemia were positively correlated to the relative reduction in MSNA, whereas IL-6 levels were negatively correlated. This observation warrants further exploration; however, it supports the hypothesis that the systemic inflammatory response critically affects the central autonomous network. Cytokine interactions seem to be involved in the central downregulation of sympathetic vasoconstrictor activity. However, the precise pathways of interaction with central blood pressure control via the baroreflex need further clarification (5, 29, 39).

In conclusion, the present findings clearly indicate that sympathetic control of blood pressure via vascular and cardiac baroreflex mechanisms is severely compromised during experimental endotoxemia. This dysfunction is characterized by a severe reduction of sympathetic outflow to the muscle vascular bed at unaffected rest and the inability to adequately increase vasoconstrictive sympathetic activity to counteract nitric oxide-induced hypotension. Moreover, heart rate is uncoupled from baroreflex control. Our results suggest that baroreflex dysfunction is induced and modulated by the systemic cytokine response.

Perspective and Significance


