Role of prostaglandins in determining the increased cardiac sympathetic nerve activity in ovine sepsis

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Booth LC, Ramchandra R, Calzavacca P, May CN. Role of prostaglandins in determining the increased cardiac sympathetic nerve activity in ovine sepsis. Am J Physiol Regul Integr Comp Physiol 307: R75–R81, 2014. First published April 30, 2014; doi:10.1152/ajpregu.00450.2013.—Effective treatment of sepsis remains a significant challenge in intensive care units. During sepsis, there is widespread activation of the sympathetic nervous system, which is thought to have both beneficial and detrimental effects. The sympathoexcitation is thought to be partly due to the developing hypotension, but may also be a response to the inflammatory mediators released. Thus, we investigated whether intracarotid infusion of prostaglandin E2 (PGE2) induced similar cardiovascular changes to those caused by intravenous infusion of *Escherichia coli* in sheep and whether inhibition of prostaglandin synthesis, with the nonselective cyclooxygenase inhibitor indomethacin, administered at 2 and 8 h after the onset of sepsis, reduced sympathetic nerve activity (SNA), and heart rate (HR). Studies were performed in conscious sheep instrumented to measure mean arterial pressure (MAP), HR, cardiac SNA (CSNA), and renal SNA (RSNA). Intracarotid infusion of PGE2 (50 ng·kg⁻¹·min⁻¹) increased temperature, CSNA, and HR, but not MAP or RSNA. Sepsis, induced by infusion of *E. coli*, increased CSNA, but caused an initial, transient inhibition of RSNA. At 2 h of sepsis, indomethacin (1.25 mg/kg bolus) increased MAP and caused reflex decreases in HR and CSNA. After 8 h of sepsis, indomethacin did not alter MAP, but reduced CSNA and HR, without altering baroreflex control. These findings indicate an important role for prostaglandins in mediating the increase in CSNA and HR during the development of hyperdynamic sepsis, whereas prostaglandins do not have a major role in determining the early changes in RSNA.

Sepsis and septic shock are the chief causes of death in intensive care units with mortality rates of between 30 and 70% when combined with multiorgan failure (2, 20, 21, 28). Although the incidence of sepsis is increasing, our knowledge of the pathology is limited, and current treatments, including volume resuscitation and vasoconstrictors, are only marginally effective. In human septic patients the most common hemodynamic profile is a hyperdynamic circulation, characterized by peripheral vasodilatation and hypotension accompanied by an increased cardiac output (16, 17). These changes are accompanied by activation of the sympathetic nervous system, as demonstrated by increased circulating levels of plasma catecholamines in septic humans (12), increased renal sympathetic nerve activity (RSNA) in endotoxemic rats (22, 30), and increased SNA to the heart and kidneys in sheep with hyperdynamic sepsis (24). It would be expected that an increase in SNA would be beneficial in sepsis, for example, by maintaining arterial pressure; however there is recent evidence that sympatholytic agents have beneficial actions in experimental sepsis in rodents (1, 6, 13, 33). It is, therefore important to identify the mechanisms leading to the organ-selective increase in SNA in sepsis, as this may lead to development of more targeted treatments.

The extent to which sympathetic activation during sepsis results from reduced baroreceptor inhibition due to the hypotension or to actions of inflammatory mediators, such as prostaglandins, is unclear. Both intracarotid and central administration of prostaglandin E2 (PGE2) have been shown to produce similar changes to those seen during sepsis: fever, tachycardia, and an increase in RSNA (3, 4). Furthermore, inhibitors of the cyclooxygenase (COX) pathway, which inhibit prostaglandin production, prevent the tachycardia and the release of catecholamines and stress hormones in response to endotoxin in humans (25), as well as the increase in RSNA in response to LPS in anesthetized rats (30). In addition, the late increase in RSNA following transient, mild exposure to LPS in rabbits was reduced following acetylsalicylate administration (26).

In view of the evidence that PGE2 increases heart rate (HR) and that COX inhibitors prevent endotoxin-induced tachycardia, we investigated whether intracarotid administration of PGE2 increased cardiac sympathetic nerve activity (CSNA) and HR in normal conscious sheep. To determine the role of prostaglandins in driving the increased CSNA in sepsis, we examined the effect of treatment with indomethacin, a nonselective inhibitor of COX 1 and COX2, on the resting levels and baroreflex control of heart rate and CSNA in conscious sheep with early hyperdynamic sepsis.

**METHODS**

Experiments were conducted on 12 adult Merino ewes, housed in individual metabolic cages, with free access to food and water. The response to infusion of PGE2 was examined in nine sheep (38±2 kg). At least 24 h later, the effect of indomethacin in sepsis was determined in 10 sheep, seven of which were common to the previous group (39±1 kg). Experiments were conducted once sheep were accustomed to laboratory conditions and human contact. The experimental procedures were approved by the Animal Ethics Committee of the Florey Institute of Neuroscience and Mental Health under guidelines laid down by the National Health and Medical Research Council of Australia.

Surgical procedures. All sheep underwent two surgeries separated by at least 2 wk of recovery. Anesthesia was induced by intravenous thiopental sodium (15 mg/kg) and, following intubation, was maintained with 1.5–2.0% isoflurane in an O₂ and air mixture. In the first surgery, sheep were prepared with carotid arterial loops. In the second operation, infravascular recording electrodes were implanted in the left cardiac and renal sympathetic nerves (24). In all operations, animals were treated with intramuscular antibiotics (900 mg, ilium Propen; procaine penicillin; Troy Laboratories, Smithfield, NSW, Australia). First published April 30, 2014; doi:10.1152/ajpregu.00450.2013.

Address for reprint requests and other correspondence: L. Booth, Florey Institute of Neuroscience and Mental Health, Univ. of Melbourne, Parkville, Victoria 3010, Australia (e-mail: lindsea.booth@florey.edu.au).
Australia) at the start of surgery and then for 2 days postoperatively. 
Postsurgical analgesia was maintained with intramuscular injection of 
flunixin meglumine (1 mg/kg; Troy Laboratories) at the start of 
surgery, then 4 h and 24 h postsurgery.

On the day before implantation of recording electrodes, arterial and 
venous cannulas were inserted into the carotid artery and jugular vein. 
Temperature was measured using a thermocouple (Physitemp Instruments, Clifton, NJ) inserted 20 cm into a jugular venous catheter. 
Experiments were started on conscious sheep 4 days after implantation 
of the electrodes.

**Measurement of SNA.** CSNA and RSNA were recorded differentially 
together with the pair of electrodes with the best signal-to-noise ratio 
(24). The signal was amplified (×100,000) and filtered (bandpass, 
300–1,000 Hz), displayed on an oscilloscope, and passed through an 
audio amplifier and loudspeaker. Sympathetic nerve activity (5,000 
Hz) and arterial blood pressure (100 Hz) were recorded on computer 
using a CED Micro 1401 interface and Spike 2 software (Cambridge 
Electronic Design, Cambridge, UK). Data were analyzed on a beat- 
to-beat basis using custom-written routines in the Spike 2 program. 
Recordings were made for a 15-min resting period, and this level, 
minus background noise, was defined as the 100% baseline level. The 
techniques for spike counting per heartbeat and subtraction of back- 
ground noise were as previously described (32).

**Generation of baroreceptor reflex curves.** Baroreceptor reflex 
curves were constructed from data collected during infusions of 
phenylephrine and sodium nitroprusside, infused in random order 
(32). Briefly, phenylephrine and sodium nitroprusside (67 μg/ml in 
destilled saline) were infused at 30, 60, 120, and 300 ml/min for ~1 min 
at each dose, resulting in a slow, steady change in blood pressure. To 
construct baroreflex curves, SNA burst size, determined as the number 
of discriminated spikes between successive diastolic pressures minus 
baseline, was divided by heart period (32). These data were sorted 
by diastolic blood pressure and averaged in groups of 10. To allow 
data from individual animals to be grouped, spike counts were 
normalized by calculating the percent change in SNA from the mean 
activity recorded during the 15-min resting period, described above. 
Percent SNA was plotted against diastolic pressure and regression 
analysis performed (4-parameter sigmoid relationship; Sigmaplot, 
Systat Software, San Jose, CA). For generation of the HR baroreflex 
curve, data were sorted by systolic blood pressure (32).

**Experimental design.** Studies were performed in a total of nine 
sheep for the PGE2 infusions, seven of which had RSNA and six of 
which had CSNA recordings. Sepsis was performed in 10 sheep, eight 
of which had RSNA and seven of which had CSNA recordings.

**PGE2 infusion.** Mean arterial pressure (MAP), CSNA, RSNA, 
temperature, and HR (calculated from systolic peaks) were recorded 
for 30 min before and during a 30-min bilateral intracarotid infusion 
of PGE2 (50 ng·kg⁻¹·min⁻¹; Sigma-Aldrich, Castle Hill, NSW, 
Australia), dissolved in ethanol (stock solution of 1 mg/ml) and 
diluted in 60 ml of saline. Arterial baroreflex curves were generated 
during the control period and 10 min after the start of the PGE2 infusion.

**Indomethacin treatment during sepsis.** During the experiment, 
15-min measurements of MAP, CSNA, and RSNA were made at 
hourly intervals. During the first hour of the control period, baroreflex 
curves were generated. At the end of the control period, sepsis was 
induced by intravenous infusion of live *E. coli* [3 × 10⁹ colony- 
forming units (cfu) in 15 ml of saline over 15 min] and then 
maintained with a continuous infusion of 1.5 × 10⁹ cfu/h for 8 h. 
After 2 and 8 h of *E. coli* infusion, arterial baroreflex curves were 
generated before and after intravenous infusions of indomethacin 
(1.25 mg/kg; Sigma-Aldrich) dissolved in 2 ml Na₂CO₃ and 13 ml 
sterile saline, infused through a Millipore filter over 15 min. Data 
from the 15 min prior to indomethacin infusion were used as the 
preindomethacin control, which was compared with data from a 
15-min period during indomethacin when cardiovascular changes had 
stabilized, before the postindomethacin baroreflex curves were 
generated.

At the end of the protocol, sheep were killed with an intravenous 
overdose of pentobarbital sodium (100 mg/kg). To establish that the 
2-h dose of indomethacin did not influence the later responses, in a 
pilot study in two sheep, we established that the development of sepsis 
from 3 to 8 h and the response to indomethacin at 8 h did not appear 
to be altered by previous treatment with indomethacin. The finding 
that temperature increased back to preindomethacin levels within 45
min of the end of infusion of indomethacin is further evidence that in sepsis, the ability of indomethacin to inhibit the synthesis of endogenous prostaglandins was of short duration. In initial studies, a third dose of indomethacin was administered after 24 h of sepsis, but this led to severe renal and cardiovascular failure; therefore, subsequent experiments were ended after the 8-h indomethacin treatment.

Statistics. Statistical analysis was performed in R and Rcmdr (11, 23). Data sets were assessed for normality and log-transformed or square root-transformed as appropriate. For negative data, differences from baseline were also considered. Changes in cardiovascular variables and baroreflex data in response to PGE2 were analyzed using repeated-measures ANOVA with Greenhouse-Geisser correction, and post hoc analysis was performed using paired sample t-tests with Bonferroni correction for multiple comparisons. *P < 0.05 was considered statistically significant. Normally distributed data are presented as means ± SE, and log and square root-transformed data are presented as geometric mean (95% CI).

RESULTS

Response of normal sheep to bilateral intracarotid infusions of PGE2. Intracarotid infusion of PGE2 did not change MAP [92 (84.99) vs. 92 (85.98) mmHg], but significantly increased HR [78 (69.99) to 117 (93.146) bpm; P < 0.005; Fig. 1]. There was an increase in CSNA [102 (100.105) to 179 (152.209) % baseline; P < 0.005], whereas RSNA was unchanged [100 (97.104) to 97 (86.108) % baseline]. PGE2 infusion significantly increased temperature (39.2 ± 0.2 to 39.8 ± 0.2°C; P < 0.005).

With PGE2 infusion, there was a significant increase in the lower plateau of the HR baroreflex curve (P < 0.01 compared with baseline; Table 1, Fig. 2). There were no significant differences in any parameter of the CSNA or RSNA baroreflex curves.

Responses to intravenous infusion of E. coli. Sepsis was induced by intravenous infusion of live E. coli. Temperature was elevated at 2 and 8 h of sepsis (baseline: 38.8 ± 0.2°C; 2 h: 40.2 ± 0.1°C; 8 h: 40.7 ± 0.4°C; P < 0.05). Infusion of E. coli caused an initial increase in MAP in 2 h [from 86 (82.90) to 99 (95.104) mmHg; P < 0.05] followed by a decrease to control levels by 8 h [87 (83.91) mmHg; Fig. 3]. There was no significant increase in HR at 2 h of sepsis [77 (70.85) vs. 79 (69.90) bpm; not significant (NS)]; but, by 8 h of sepsis, HR was significantly elevated above control values [127 (120.135) bpm; P < 0.05]. Similarly, after 2 h of sepsis, CSNA was not significantly increased [101 (99.103) vs. 102 (64.148) % baseline; NS]; however, by 8 h, CSNA had more than doubled [232 (175.297) % baseline P < 0.05; Fig. 3]. In contrast, RSNA was significantly lower after 2 h of sepsis [100 (99.102) to 23 (9.44) % baseline; P < 0.05] and then increased back to baseline values by 8 h of sepsis [129 (101.159) % baseline; Fig. 3].

Effect of treatment of septic sheep with indomethacin. The effectiveness of the dose of indomethacin used was demonstrated by the finding that it significantly reduced temperature at both 2 and 8 h of sepsis (to 38.4 ± 0.3°C and 39.2 ± 0.3°C, respectively; P < 0.05 vs. preindomethacin). Treatment with indomethacin at 2 h of sepsis significantly increased MAP [to 112 (104.120) mmHg; P < 0.05], decreased HR [to 54 (50.59) bpm; P < 0.05] and reduced CSNA [to 20 (8.37) % baseline; P < 0.05; Fig. 3].

At 8 h of sepsis, indomethacin had no effect on MAP [87 (83.91) vs. 91 (84.98) mmHg; NS], but reduced HR from 127 (120.135) to 103 (94.113) bpm (P < 0.05). CSNA decreased from 232 (175.297) to 114 (55.193) % baseline (P < 0.05). After 8 h of sepsis, RSNA was similar to control levels, and the level was not significantly altered by indomethacin.

Effect of indomethacin on the baroreflex control of HR, CSNA, and RSNA in sepsis. The baroreflex control of HR, CSNA, and RSNA in sepsis was tested using repeated-measures ANOVA with Greenhouse-Geisser correction, and post hoc analysis was performed using paired sample t-tests with Bonferroni correction for multiple comparisons. *P < 0.05 was considered statistically significant. Normally distributed data are presented as means ± SE, and log and square root-transformed data are presented as geometric mean (95% CI).

DISCUSSION

This study investigated the role of prostaglandins in mediating the cardiovascular changes in early hyperdynamic sepsis in conscious sheep. In the first study, in normal sheep, bilateral intracarotid infusion of PGE2 increased CSNA, HR, and temperature, with no changes in MAP or RSNA, or in the baroreflex control of sympathetic nerve activity. These responses are similar to changes seen in septic sheep (24), suggesting they may be mediated by PGE2. To examine the role of prostaglandins in sepsis, we studied the effect of the nonselective COX inhibitor, indomethacin, at 2 and 8 h following the start of E. coli infusion. The findings indicate that prostaglandins, possibly together with downstream inflammatory mediators, contribute to the increased CSNA and HR in sepsis.
In normal sheep, bilateral intracarotid infusions of PGE2 increased temperature and heart rate, in agreement with previous studies (4, 5). In addition, we showed that PGE2 caused a rightward shift in the HR baroreflex curve and increased the lower plateau of the curve, changes that partly accounted for the increase in HR. Furthermore, we showed that PGE2 increased resting CSNA, but there were no significant changes in baroreflex control of CSNA. The increase in the bottom plateau of the HR baroreflex curve, with no similar change in the CSNA baroreflex curve, is, thus, most likely due to a reduction in vagal tone. This is supported by previous findings that propranolol alone did not prevent PGE2-induced tachycardia (4). In contrast, we found that PGE2 did not alter the resting level or baroreflex control of RSNA. Overall the responses to PGE2 were similar to changes following administration of live E. coli in conscious sheep (24), suggesting that PGE2 may be an important pathophysiological mediator of the response to hyperdynamic sepsis.

In sepsis, there are large increases in the levels of proinflammatory cytokines, but these molecules do not have direct effects on the brain because they do not cross the blood-brain barrier (BBB). There is, however, evidence that cytokines, including TNFα and IL-1β, act on perivascular cells to induce COX-2 activity, leading to production of PGE2 that crosses the BBB and activates E-prostanoid receptors on central neurons to modulate cardiovascular control and sympathetic nerve activity (15, 34). Indeed, intracarotid infusions of PGE2 have been shown to increase arterial pressure and heart rate (4), and intracerebroventricular PGE2 increased MAP, HR, and RSNA (35). The bilateral intracarotid infusion of PGE2 in the current study was designed to primarily target the central nervous system, but the lack of an increase in MAP may reflect some spillover of PGE2 into the periphery where it has vasodilatory effects (8, 9), which may have counteracted a central sympathetically mediated action to increase arterial pressure.

Although it is well established that inhibition of prostaglandin synthesis in sepsis reduces fever (10), only a few studies have investigated the effects of COX inhibitors on sympathetic activity in sepsis. In anesthetized rats with LPS-induced endotoxemia, indomethacin did not change the fall in MAP, but it prevented the increase in RSNA (30) and, in human volunteers administered E. coli endotoxin, treatment with ibuprofen attenuated the increases in heart rate and plasma catecholamines (25). The effects of COX inhibitors on the resting levels or baroreflex control of CSNA have not, however, been investigated. Therefore, the present study investigated the effects on CSNA of inhibiting prostaglandin synthesis early in sepsis (2 h) and in the tachycardic prehypotensive stage of hyperdynamic sepsis (8 h). Two hours after the start of E. coli infusion, intravenous indomethacin increased MAP, similar to the transient increase in MAP seen with indomethacin in normal sheep (18) and reduced HR and CSNA. The decrease in these variables is most likely a reflex response to the indomethacin-induced increase in MAP. In support of this notion, indomethacin did not affect the baroreflex control of HR, CSNA, or RSNA after 2 h of sepsis. At both 2 and 8 h of sepsis, intravenous indomethacin reduced the elevated body temperature to normal, indicating the effectiveness of the dose administered.

After 8 h of sepsis, sheep were tachycardic, CSNA was elevated to ~200% of baseline levels, and RSNA had returned to control levels. Interestingly, in contrast to what was seen after 2 h of sepsis, indomethacin did not increase MAP, suggesting a shift from prostaglandin-dependent vasodilatation to other vasodilator mechanisms, possibly nitric oxide. Supporting this, rats administered endotoxin did not show widespread increases in nitric oxide until 3 h postendotoxin (31), and we have found that after 24 h of nonhypotensive, hyperdynamic sepsis in sheep, intrarenal infusion of L-NAME increased MAP and total peripheral resistance (14).

Despite not increasing blood pressure, indomethacin at 8 h of sepsis decreased CSNA and HR toward normal levels but...
had no effect on RSNA. These effects of indomethacin suggest that prostaglandins, possibly PGE2 or downstream inflammatory mediators, have direct central actions that increase CSNA and HR at this stage of sepsis. Although CSNA was close to normal values after indomethacin at 8 h, HR had not completely returned to control levels. This is not surprising as additional mechanisms, such as reduced baroreflex inhibition with developing hypotension and reduced vagal tone, are likely to contribute to the increased HR. Indeed, a reduction in vagal tone in sepsis has been shown using spectral analysis of HR in anesthetized endotoxic rabbits (29). In addition, vagal impairment would account for the increase in the bottom plateau of the HR baroreflex curve in sepsis, since this part of the CSNA baroreflex was unchanged at 2 and 8 h of sepsis. A similar blunting of the decrease in HR with increased pressure has been reported in healthy human volunteers after LPS infusion (27).

This study has a number of strengths and limitations. Importantly, studies were conducted in conscious animals avoiding the confounding effects of anesthesia. As with all experimental animal models of disease, the relevance of the findings to the clinical situation is unclear, but as most human sepsis is hyperdynamic in nature, it is likely that this model with a...
Table 2. Baroreflex parameter variables at baseline, eight hours after the start of sepsis and following indomethacin

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>8-h Sepsis</th>
<th>8-h Sepsis + Indomethacin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baroreflex control of HR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, bpm</td>
<td>122 ± 8</td>
<td>92 ± 8</td>
<td>86 ± 11</td>
</tr>
<tr>
<td>Max gain</td>
<td>-7.7 ± 0.9</td>
<td>-6.0 ± 0.5</td>
<td>-6.6 ± 1.0</td>
</tr>
<tr>
<td>BP50, mmHg</td>
<td>94 ± 4</td>
<td>101 ± 2</td>
<td>100 ± 3</td>
</tr>
<tr>
<td>Lower plateau, bpm</td>
<td>55 ± 3</td>
<td>85 ± 6*</td>
<td>78 ± 4*</td>
</tr>
<tr>
<td><strong>Baroreflex control of CSNA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, %baseline</td>
<td>360 (287,451)</td>
<td>427 (317,573)</td>
<td>540 (358,814)</td>
</tr>
<tr>
<td>Max gain</td>
<td>-12.8 ± 1.8</td>
<td>-16.7 ± 3.9</td>
<td>-16.6 ± 3.4</td>
</tr>
<tr>
<td>BP50, mmHg</td>
<td>64 ± 2</td>
<td>75 ± 3</td>
<td>74 ± 8</td>
</tr>
<tr>
<td>Lower plateau, %baseline</td>
<td>-2 ± 6</td>
<td>-2 ± 4</td>
<td>-5 ± 3</td>
</tr>
<tr>
<td><strong>Baroreflex control of RSNA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, %baseline</td>
<td>261 (216,311)</td>
<td>240 (197,286)</td>
<td>246 (194,304)</td>
</tr>
<tr>
<td>Max gain</td>
<td>-7.3 ± 0.8</td>
<td>-10.6 ± 1.5</td>
<td>-8.8 ± 0.7</td>
</tr>
<tr>
<td>BP50, mmHg</td>
<td>79 ± 3</td>
<td>77 ± 2</td>
<td>76 ± 3</td>
</tr>
<tr>
<td>Lower plateau, %baseline</td>
<td>-7 ± 1</td>
<td>-11 ± 2</td>
<td>-3 ± 4</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE or geometric mean (95% CI). BP50, pressure at midpoint of heart rate/SNA range. Changes were tested using repeated-measures ANOVAs followed by post hoc t-tests with Bonferroni correction for multiple comparisons. *P < 0.05 vs. baseline.

similar hemodynamic profile has clinical relevance. Cardiac output was not measured in the present study, but in a study using a similar protocol for induction of sepsis, we showed that cardiac output increased slowly over 6 h (7), paralleling the increase in CSNA, and highlighting the importance of the increase in CSNA during this stage of sepsis.

**Perspectives and Significance**

These studies demonstrate the differential control of sympathetic outflow to the heart and kidneys by prostaglandins, firstly by the ability of PGE2 to increase cardiac, but not renal SNA, and secondly by the ability of indomethacin to reduce CSNA, but not RSNA, in sepsis. The similar patterns of response to PGE2 and sepsis suggest that prostaglandins or their downstream inflammatory mediators may mediate the increases in CSNA and HR in mild hyperdynamic sepsis, and this was confirmed by the responses to indomethacin. In contrast, the responses of RSNA to indomethacin were mainly reflex-mediated in response to the changes in MAP. Although this study investigated the differential effects of indomethacin on renal and cardiac SNA in sepsis, the effects on other sympathetic nerves, such as those innervating muscle, gut, and spleen, remain to be determined. It also remains to be determined whether selectively reducing the increase in CSNA early in sepsis is associated with improved outcome in hyperdynamic sepsis; however, this is supported by the finding that central sympatholytics and β-blockers have beneficial effects in human and experimental sepsis (1, 6, 13, 19, 33).

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

Author contributions: L.C.B., R.R., and P.C. performed experiments; L.C.B. analyzed data; L.C.B., R.R., and C.N.M. interpreted results of experiments; L.C.B. prepared figures; L.C.B. drafted manuscript; L.C.B., P.C., and C.N.M. edited and revised manuscript; L.C.B., R.R., P.C., and C.N.M. ap-

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**Fig. 4.** Baroreflex curves for heart rate (HR; bpm) against systolic blood pressure (sBP; mmHg) and cardiac sympathetic nerve activity (CSNA; %baseline) and renal SNA (RSNA; %baseline) against diastolic BP (DBP; mmHg) during the control period (solid lines), 8 h after the start of sepsis (dashed lines) and following indomethacin infusion (dotted lines). Symbols represent mean resting points ± SE.
REFERENCES


