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Renal blood flow in experimental septic acute renal failure

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Reduced renal blood flow (RBF) is considered central to the pathogenesis of septic acute renal failure (ARF). However, no controlled experimental studies have continuously assessed RBF during the development of severe septic ARF. We conducted a sequential animal study in seven female Merino sheep. Flow probes were implanted around the pulmonary and left renal arteries. Two weeks later, systemic hemodynamics and RBF were monitored continuously during a 48-h control period and, after a week, during a 48-h period of hyperdynamic sepsis induced by continuous *Escherichia coli* infusion. Infusion of *E. coli* induced hyperdynamic sepsis with significantly increased cardiac output (3.8±0.4 vs 9.8±1.1 l/min; $P<0.05$), decreased mean arterial pressure (89.2±3.2 vs 64.3±5.3 mm Hg; $P<0.05$), and increased total peripheral conductance (42.8±3.5 in controls vs 153.7±24.7 ml/min/mm Hg in septic animals; $P<0.05$). Hyperdynamic sepsis was associated with marked renal vasodilatation (renal conductance: 3.0±0.7 vs 11.4±3.4 ml/min/mm Hg; $P<0.05$) and a marked increase in RBF (262.3±47.7 vs 757.4±250.1 ml/min; $P<0.05$). Serum creatinine increased over 48 h (73±18 vs 305± μmol/l; $P<0.05$) whereas creatinine clearance decreased (95.5±25.9 vs 20.1±19.3 ml/min; $P<0.05$). After 24 h, urine output decreased from 1.4 to 0.3 ml/kg/h ($P<0.05$). Infusion of *E. coli* induced hyperdynamic sepsis and ARF. Septic ARF in this setting was associated with a marked increase in RBF and with renal vasodilatation.

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Acute renal failure affects 5–7% of hospital patients.[1–4] Sepsis and septic shock are important risk factors for ARF and remain the most important trigger for ARF in intensive care units (ICU).[5–9] Further, among septic patients, the incidence of ARF is high[8,10] as is the mortality rate.[2,3,5,6,11]

Our understanding of the pathogenesis of septic ARF is limited. Nonetheless, an increase in renal vascular resistance representing renal vasoconstriction and decreased reduced renal blood flow (RBF) leading to renal ischemia have been repeatedly proposed as central to the pathogenesis of septic ARF.[12–15]

The paradigm that septic ARF is secondary to renal ischemia is derived from animal studies, using a variety of different models and techniques for the induction of sepsis and the measurement of RBF.[16] However, although a majority of such studies reports decreased RBF in sepsis, close to one-third do not[16] and, as shown in a recent systematic review, a high cardiac output (CO) is the most important independent predictor of increased RBF in such models.[16]

In human sepsis, sustained systemic vasodilatation with a high CO is the dominant clinical finding.[17–19] This observation suggests that, for animal studies of septic ARF to be clinically relevant, it is desirable that a hyperdynamic circulation be present[20–22] and sustained for a sufficient period (>24 h). Accordingly, we have developed a reproducible model of sustained, hyperdynamic sepsis. Using this model, we have investigated the changes in renal hemodynamics and function in this setting and now report our findings.

RESULTS

All animals were in a healthy state before commencing the experiments (Table 1). In six of the seven sheep, the *Escherichia coli* infusion was continued for 48 h. One sheep died 12 h after the induction of sepsis. The sheep developed tachypnea, tachycardia, and a temperature of >41°C, and began to use the accessory muscles of respiration. The white blood cells decreased after 48 h of *E. coli* infusion to 1600±800/μl compared with 5400±2900/μl in the control period ($P<0.05$).

Table 1 | Hematological and biochemical variables of six animals during the baseline period and sepsis period

	0 h	12 h	24 h	36 h	48 h
Hb (g/l)					
Baseline	104±9	99±10	103±11	102±7	97±11
Sepsis	103±10	116±18	102±19	98±16	83±12
Hct (%)					
Baseline	35±5	36±3.1	34±3.5	37±2.9	35±4.7
Sepsis	34±1.9	39±5.7	34±2.4	33±3.8	29±2.7
Leukocytes (10^9/l)					
Baseline	5.5±1.8	6.9±1.6	5.6±2.0	6.3±1.5	5.4±2.9
Sepsis	4.2±2.3	2.4±2.2	2.3±1.3	2.3±1.3	1.6±0.8
Sodium (mmol/l)					
Baseline	145±1	144±2	144±1	147±1	145±2
Sepsis	146±2	145±3	145±3	144±5	146±5
Potassium (mmol/l)					
Baseline	4.2±0.4	4.3±0.4	4.2±0.2	4.5±0.2	4.3±0.2
Sepsis	4.4±0.4	4.3±0.4	4.4±0.3	4.7±0.3	4.8±1.4
Chloride (mmol/l)					
Baseline	108±1	110±2	110±2	110±2	108±2
Sepsis	110±3	111±2	111±3	110±4	112±6
Creatinine (μmol/l)					
Baseline	74±17	74±17	69±16	80±23	73±18
Sepsis	81±15	106±21	133±22	157±32	325±153
Urea nitrogen (mmol/l)					
Baseline	2.7±0.5	3.0±0.5	2.8±0.8	3.5±1.1	2.5±0.5
Sepsis	3.4±0.9	3.3±0.5	4.4±0.7	6.7±1.2	16.7±3.6

Abbreviations: Hb, hemoglobin; Hct, hematocrit.

Systemic hemodynamic pattern

Administration of *E. coli* induced hyperdynamic sepsis with a delayed onset. After 10 h of *E. coli* infusion, CO had increased significantly and continued to increase throughout the infusion to a maximum of 9.8±1.1 l/min compared with 3.8±0.4 l/min in the control period ($P<0.05$). Significant hypotension occurred at the same time and blood pressure continued to decrease during the infusion of *E. coli* (89.2±3.2 vs 64.3±5.3 mm Hg; $P<0.05$). Heart rate increased rapidly in response to administration of *E. coli* reaching a plateau at 9 h that was maintained during the 48-h infusion (65.0±7.3 vs 161.1±18.3 beats/min; $P<0.05$). There was marked peripheral vasodilatation as shown by the increase in total peripheral conductance, which reached significance 10 h after *E. coli* injection and reached a maximum of 153.7±24.7 ml/min/mm Hg compared to 42.8±3.5 ml/min/mm Hg during the control period ($P<0.05$). The central venous pressure (CVP) tended to increase in both periods without reaching a significant difference between them (Figure 1).

Renal hemodynamic and functional parameters

At 3 h after the injection of *E. coli*, RBF increased transiently and continued to increase over the following 6 h, returning to baseline by 12 h. Then, RBF began to increase again reaching a maximum of 757.4±250.1 ml/min after 45 h compared to a control value of 262.3±47.7 ml/min ($P<0.05$). This change was dependent on increased renal vascular conductance (3.0±0.7 ml/min/mm Hg vs 11.4; $P<0.05$) (Figure 2).

After 24 h, the serum creatinine significantly increased in the sepsis period, reaching a value of 325±153 μmol/l at 48 h compared to 73±18 μmol/l in the control period. The creatinine clearance (CC) decreased after *E. coli* infusion (20.1±19.3 ml/min) compared to the control period (95.5±25.9 ml/min) ($P<0.05$). The filtration fraction decreased in parallel from 23±8% at baseline to 3±3% in the sepsis period (Figure 2). Urinary output increased briefly after the induction of sepsis and then decreased to below 0.5 ml/kg/h (Figure 2). During the 24–48 h period, hourly urinary output was 1.4 ml/kg/h in controls compared to 0.3 ml/kg/h in septic animals. The fractional excretion of sodium (FeNa) initially increased and then significantly decreased over time in the sepsis period compared to baseline. The fractional excretion of urea nitrogen immediately decreased after injection of the *E. coli* in the sepsis period and remained decreased compared to the control period (Figure 2).

DISCUSSION

We conducted a controlled experimental study to continuously measure RBF, renal vascular conductance, and renal

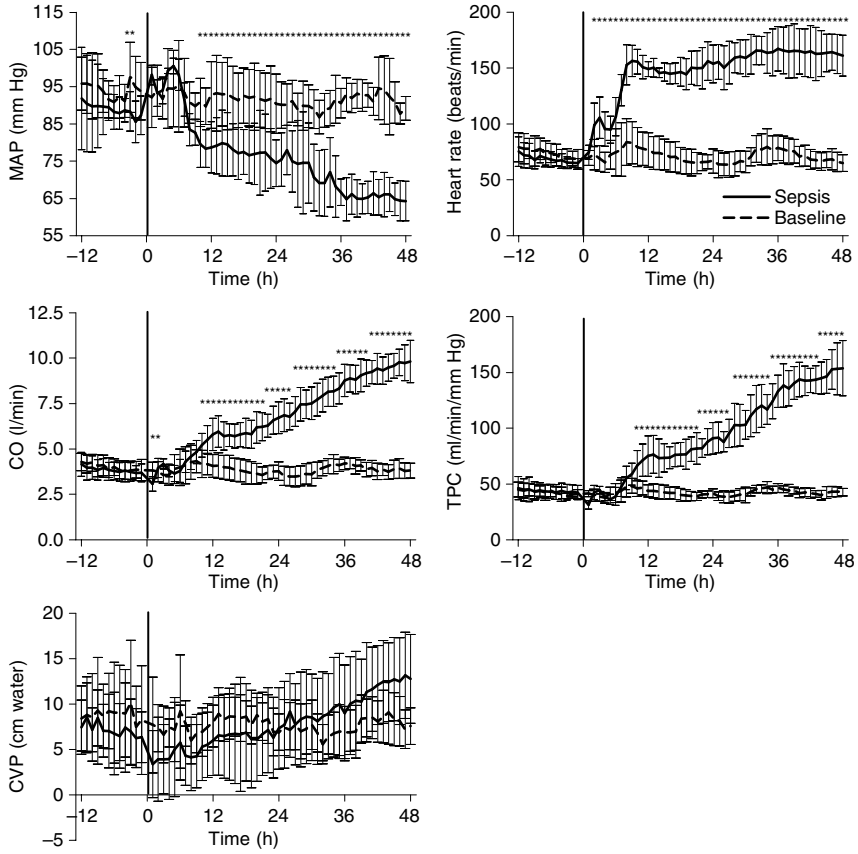

Figure 1 | Hemodynamic variables in the baseline and septic period in six conscious sheep. The line at time 0 indicates the beginning of the *E. coli* infusion. *$P<0.05$. MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; TPC, total peripheral conductance; CVP, central venous pressure.

function in a model of ARF induced by sustained Gram-negative hyperdynamic sepsis in conscious sheep.

We found that the animals developed ARF with oliguria, a fourfold increase in serum creatinine and an 80% decrease in CC. According to the recently proposed Risk of renal dysfunction; Injury to the kidney; Failure of kidney function; Loss of kidney function; Endstage renal disease classification of acute renal dysfunction, our animals developed acute renal failure,[23] the highest of the three level of severity (risk, injury, and failure) in this classification. Contrary to explanations proposed in the literature, we found that such ARF occurred in association with a striking increase in both renal vascular conductance (vasodilatation) and RBF (hyperemia). These findings provide *proof of concept* that vasoconstriction and/or decreased RBF are not necessary for ARF to occur during sustained sepsis. As these findings challenge widely held paradigms, they require detailed discussion.

First, in our model, infusion of *E. coli* induced a sustained hyperdynamic septic state with peripheral vasodilation. Total peripheral conductance progressively increased more than three times (systemic vasodilatation) after 48 h of *E. coli* infusion, mean arterial pressure (MAP) progressively decreased and there was a marked increase in CO. These systemic changes are important because they mimic those typically seen in critically ill septic patients in whom ARF develops.[17–19] In addition, a report about a patient who self-administered *Salmonella* endotoxin found hyperdynamic sepsis with an elevated CO and low systematic vascular resistance in combination with an increase in serum creatinine (1.6 mg/dl).[24]

In contrast, many previous animal models of sepsis induced a hypodynamic circulation, which, in critically ill septic patients, is uncommon.[17] In the majority of such reports, sepsis was induced by lipopolysaccharide injection, which resulted in a decrease in CO.[25–34] The different hemodynamic profile with lipopolysaccharide may be due to a cytokine release pattern different to that seen in septic man.[35] In such hypodynamic models, it is not possible to determine whether renal dysfunction results from the reduced CO or the effects of sepsis on the kidney *per se*.

Furthermore, in contrast to our investigation, in previous experimental studies, sepsis was often induced immediately after surgery or in anesthetized animals.[16] These interventions, even in the absence of sepsis, can reduce CO and blood pressure, thus adding important confounders to data analysis and interpretation.[16] To avoid such confounders, we conducted our study in conscious, unsedated animals, at least 2 weeks following surgery. In addition, we used live *E. coli* instead of lipopolysaccharide and, in order to avoid

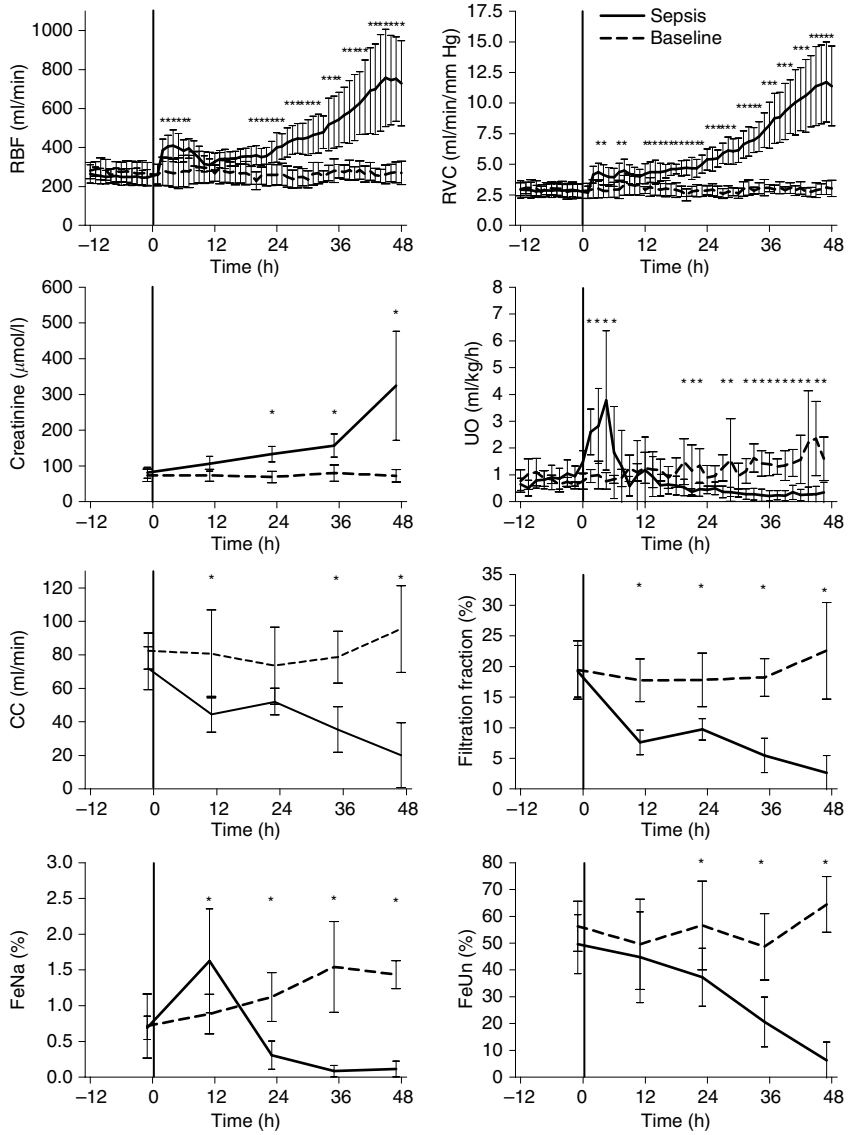

Figure 2 | Renal hemodynamic and functional variables in the baseline and septic period in six conscious sheep. The line at time 0 indicates the beginning of the *E. coli* infusion. *$P<0.05$. RBF, renal blood flow; RVC, renal vascular conductance; UO, urinary output; CC, creatinine clearance; FF, filtration faction; FeNa, fractional excretion of sodium; FeUn, fractional excretion of urea nitrogen.

hypovolemia as a confounding variable, we administered fluids and maintained an elevated central CVP.

Many previous studies of sepsis focusing on renal function have been short-term in nature (<2 h).[16] Only three studies have assessed renal function during sustained (>24 h) sepsis, the condition typically seen in critically ill humans. In the first, Cumming *et al.*[36] induced sepsis in sheep by cecal ligation and perforation. These authors found a 70% decrease in glomerular filteration rate but had no control animals and did not measure RBF or renal vascular conductance directly. Instead of measuring RBF via flow probes, radioactive labelled *para*-aminohippurate was used to determine the renal plasma flow. Particularly in the septic setting, this technique might not be sufficiently accurate.[37,38] Nonetheless, in this study, renal plasma flow did not decrease.[36] The second and third studies, by Weber *et al.*,[39,40] were also uncontrolled in design and sepsis was induced by continuous endotoxin infusion. In both studies, only two animals survived to be assessed at 48 h. In both studies, however, once a hyperdynamic state had developed after 24 h and in those animals that were still alive, RBF increased[39] and renal vascular resistance decreased.[40]

Our findings are important because there is a widely proposed paradigm that, in sepsis, renal ischemia occurs owing to renal vasoconstriction and a consequent decrease in RBF.[12–14] Contrary to this paradigm, we found that septic ARF in our sheep occurred in the setting of marked renal vascular vasodilatation and a marked increase in RBF. Given that 90% of RBF is delivered to the glomeruli, in order for such renal vascular vasodilatation to occur, both afferent and efferent arteriolar vasodilatation should logically occur. We found that in this setting CC, a surrogate of glomerular

filtration rate, decreased. Glomerular filteration rate is mostly dependent upon intraglomerular pressure. The relationship between afferent and efferent arteriolar tone controls such pressure. Thus, it is physiologically logical to expect glomerular filteration rate to decrease if the efferent arteriole dilates more than the afferent arteriole. We speculate that this might have happened in our animals. This theory is supported by the finding that the filtration fraction in the sepsis group decreased significantly despite an increase in renal plasma flow. Nonetheless, it is not possible to know whether the loss of CC seen in our animals is indeed secondary to such hemodynamic changes alone, whether other factors played a role or even whether such hemodynamic changes represent an epiphenomenon. However, a decrease in the fractional excretion of sodium, a marker for relatively intact tubular function, was seen over time compared to the control period. This significant decrease in FeNa has also been described in septic humans.[41] Similarly, decreased fractional excretion of urea nitrogen, another marker of relatively preserved tubular function,[42] was also observed during sepsis in our animals.

The dramatic increase in RBF in sepsis might have been associated with intrarenal shunting and a change in intrarenal blood flow distribution.[43] Thus, ischemia to the medulla might have occurred despite increased global RBF. However, in a recent study, using laser Doppler flow probes, no significant change in the intrarenal distribution of blood flow could be demonstrated in sepsis.[22] Similarly, studies using microspheres could not detect any significant change in intrarenal blood flow distribution in sepsis.[44–46] It is possible that medullary ischemia might yet occur in the setting of hyperemia because oxygen consumption increases more than oxygen delivery. This would require a greater than threefold increase in renal oxygen consumption. When renal oxygen consumption has been measured during experimental sepsis, it has been found to be only mildly increased,[47,48] whereas oxygen extraction remained unchanged.[39] Furthermore, a recent study of renal ATP in sheep with bacteremic septic shock found no decrease in high-energy phosphate compounds during sepsis.[49]

Our study has several limitations. First, it is neither randomized nor double-blinded in design. However, it is controlled and the changes are so dramatic that it is inconceivable that they would represent an alpha error. Furthermore, the physiological changes are objective and not subject to bias. Second, we did not measure renal oxygen consumption, which would have been important in the interpretation of the changes in organ blood flow. However, measurement of regional oxygen consumption requires an acute preparation, because we have found that it is difficult to maintain the patency of chronically implanted venous cannulae and our goal was to study awake animals to minimize confounding variables. Third, our model does not completely reproduce severe human sepsis. For example, severe human sepsis is associated with an attributable mortality approaching 30%. However, whereas only one of the experimental animals died (15% mortality), two more were extremely ill at the time of euthanasia and would have likely died in the next 12 h. Fourth, no antibiotics were given to more closely simulate the human situation. Furthermore, only a few conditions in humans (e.g. endocarditis) are associated with almost constant bacteremia. In most other septic states, bacteremia is episodic. All of these differences between our model and human sepsis must be taken into account in the interpretation of our findings. To our knowledge, however, this is the first study to describe a model of ARF induced by hyperdynamic sepsis that mimics so many aspects of severe Gram-negative sepsis in humans: tachycardia, tachypnea, fever, leukopenia, hypotension, oliguria, high CO, and peripheral vasodilatation all sustained for 48 h and with significant mortality. Finally, we did not study renal histopathology. However, this was not the focus of the present investigation, in which we aimed to assess the effect of sustained sepsis on RBF, vascular conductance, and renal function.

Conclusion

In conclusion, we have studied the effects of sustained Gram-negative bacteremia and sepsis on RBF, renal vascular conductance, and renal function. In addition to generalized peripheral vasodilatation with increased CO and decreased MAP, we found that such sepsis induced renal vasodilatation accompanied by a striking increase in RBF. Despite this marked increase in RBF, however, CC decreased significantly and serum creatinine increased fourfold. Our findings provide *proof of concept* that ARF can occur in mammals in the setting of hyperemia and highlight the need for renewed interest in investigations directed at measuring blood flow and renal vascular conductance in critically ill septic patients who develop ARF.

MATERIALS AND METHODS

Animal preparation

The institutional Animal Ethics Committee approved this study. Seven female Merino ewes weighing between 34.2 and 47.3 kg were procured for chronic instrumentation. The sheep were held and studied in metabolic cages, with free access to food and water. The animals underwent two separate operative procedures. For all procedures, anesthesia was induced with sodium thiopentone (15 mg/kg) for endotracheal tube placement (cuff size 10). Maintenance anesthesia was by means of oxygen/air/isoflurane (1–2%). Fractional inspired oxygen was altered to maintain PaO_2 at approximately 100 mm Hg, and ventilation was controlled to maintain $PaCO_2$ at approximately 40 mm Hg.

First, a left-sided thoracotomy was performed. The pericardium was opened, and a transit time flow probe (20 mm; Transonics Systems, Ithaca, NY, USA) was placed around the pulmonary artery to measure CO. After 2 weeks recovery, a left-sided flank incision was made and a retroperitoneal dissection was performed to expose the left renal artery. A transit time flow probe (4 mm; Transonics Systems, Ithaca, NY, USA) was placed around the renal artery.

During the same operative procedure, one carotid artery was isolated and a skin flap was sutured around it to create a single carotid artery loop that facilitates subsequent arterial cannulation. The animals were allowed to recover for 2 weeks before experimentation.

The transit-time flow probes were connected to flow meters (Transonics Systems, Ithaca, NY, USA). Before starting the experiment, a Tygon catheter (Cole-Parmers; Boronia, Australia; i.d. 1.0 mm, o.d. 1.7 mm) was inserted into the carotid loop to measure arterial pressure. Two internal jugular venous polyethylene catheters (Critchley, Silverwater, Australia; i.d. 1.2 mm, o.d. 1.7 mm) were placed to measure CVP and for infusion. The cannulae were connected to pressure transducers (TDXIII, Code, Lakewood, CO, USA) tied to the wool on the back. A correction factor was added in the data-acquisition program to correct for the height of the transducers above the heart (Labview National Instruments Cooperation 11 500 N Mopac Expwy, Austin, TX, USA). A urinary catheter was inserted for measurement of urine volume and for sample collection.

Analog signals of MAP, CVP, CO, and RBF were collected using a PC with a customized data-acquisition system (Labview National Instruments). Data were recorded at 100 Hz for 10 s at every minute throughout the experimental protocol. Total peripheral conductance (CO/MAP) and renal vascular conductance (RVC) (RBF/MAP) were calculated.

Protocol and measurements

We conducted a sequential study with seven animals. During the experimental periods, MAP, CVP, CO, RBF, and heart rate were measured continuously. Initially, all animals were examined during the baseline period. This consisted of a 12-h period without any intervention and a 48-h period with fluid administration only (normal saline 1 ml/kg/h). After a week, the sepsis period was performed. Again, after a 12-h period without any intervention, a 48-h sepsis period was induced by an intravenous bolus of live *E. coli* (3.9×10^9 colony-forming units in 15 ml saline) followed by a continuous infusion of 3.5×10^8 colony forming units per/h. During the sepsis period, fluid was administered at the same rate as in the baseline period to prevent hypovolemia.

Urinary output was measured and urine sampled every 90 min. Arterial blood samples were obtained for analysis of hematological variables, electrolytes, creatinine (SYNCHRON LX® System Beckmann Coulter Inc., Fullerton, CA, USA), and urea nitrogen (SYNCHRON LX® System Beckmann Coulter Inc., Fullerton, CA, USA) every 12 h. The urine collected for the corresponding 12-h periods was used to also measure electrolytes, creatinine, and urea nitrogen (SYNCHRON LX® System Beckmann Coulter Inc., Fullerton, CA, USA).

The CC ($\text{creatinine}_{\text{urine}}/\text{creatinine}_{\text{plasma}} \times \text{urine}_{\text{volume}}/\text{time}$), the fractional excretion of sodium ($\text{sodium}_{\text{urine}}/\text{sodium}_{\text{plasma}} \times \text{creatinine}_{\text{plasma}}/\text{creatinine}_{\text{urine}} \times 100$), and the fractional excretion of urea nitrogen ($\text{urea nitrogen}_{\text{urine}}/\text{urea nitrogen}_{\text{plasma}} \times \text{creatinine}_{\text{plasma}}/\text{creatinine}_{\text{urine}} \times 100$) were calculated.

The filtration fraction (FF) was calculated using the CC, the mean RBF for the corresponding period, and the hematocrit (HCT) according the following formula: $\text{FF} = \text{CC}/\text{RBF} \times (1-\text{HCT})$.

No fluid boluses, inotropic support, mechanical ventilation, or antibiotics were administered. The animals were conscious and not sedated for the duration of the experiment. At the end of the septic period, the sheep were killed using intravenous administration of sodium pentobarbitone (150 mg/kg).

Statistical analysis

Data are presented as mean $\pm$ s.d. In the control and the sepsis period, mean values for each hour were compared using two-way repeated measures analysis of variance. The control and septic period values for central and renal hemodynamics and renal functional variables were compared using the Wilcoxon ranked sign test. A $P < 0.05$ was considered statistically significant.

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