Electronic Supplementary Material:
Plots from each dog experiment (n=8) showing the relationship between mean arterial pressure and renal blood flow (indexed to weight) in control (black dots) and bacteremic (white dots) conditions.
Materials and methods (supplementary)

Anaesthesia and maintenance of homeostasis

Anaesthesia was induced with intramuscular ketamine (5mg/kg) and xylazine (2mg/kg) and maintained with inhaled halothane (0.5-1.5%) in oxygen, the inhaled dose being adjusted to prevent spontaneous movement. The trachea was intubated with an endotracheal tube and the lungs were mechanically ventilated to a tidal volume of 10-12 ml/kg at a rate of 15-20 breaths/min using a Manley ventilator. Intravenous access was secured in the forelimb and used to administer intravenous drugs and fluids, warmed normal saline at 2 ml/kg/h. The femoral artery and left internal jugular vein were canulated and used to measure artery blood pressure (MAP) and central venous pressure (CVP), respectively. Body temperature was maintained by covering the dog with an insulated blanket.

Placement of flow probes

A left thoractomy via the fourth intercostal space was performed to expose the heart and great vessels. The pericardium was incised longitudinally to expose the aortic root. The ascending aorta was separated from pulmonary artery by blunt dissection using a finger. The free fat that surrounded the aorta was carefully removed. A snug fitting flow probe, either 16 or 20 mm A-series ultrasonic flow probe (Transonic Systems Inc., Ithaca, NY, USA) was placed around the ascending aorta and ultrasonic gel applied. The probe cable was run posteriorly to exit the thorax. The pericardium was closed with sutures, a chest drain to underwater seal inserted, the collapsed lung re-expanded and the chest wall closed. A longitudinal flank incision was made to expose the left kidney. Retroperitoneal dissection was performed to isolate the renal artery. A 4 mm R-probe (Transonic Systems Inc) was placed on renal artery and ultrasonic gel applied. The flank incision was closed.
Blood flow and pressure measurements

The A-series flow probe used a high precision four crystal array. The smaller R-series flow probe used a smaller single crystal. The probes were connected via a cable to a T106 flowmeter (Transonic Systems Inc.) which also processed the transduced arterial blood pressure wave. The blood pressure system was kept patent with a 10ml/h saline infusion. The CVP was measured intermittently using this system. The T106 meter has only one cable input, so aortic and renal blood flows were measured alternately. Data from the flowmeter was transferred to a laptop computer where it was displayed in real–time and stored at 10-second intervals using the data acquisition program WinDaq (DataQ Instruments, OH, USA).

Induction of bacteraemic shock

Bacteraemic shock was induced by injecting intravenously a bolus of $2 \times 10^9$ colony–forming units of *Escherichia coli* bacteria (JM 109 strain) provided by the microbiology laboratories at the Chinese University of Hong Kong. The onset of established bacteraemic shock was determined by a decrease in MAP to 60 mmHg, which usually occurred after 1 h.

Circulatory management

The MAP during the bacteraemic shock was maintained at around 60 mmHg and the CVP between 8-12 mmHg by infusing intravenously 100 ml aliquots of normal saline. NA was delivered by syringe pump. Infusion rates of 0.1, 0.2, 0.3, 0.4 and 0.5 µg/kg/min were used. In part I NA was infused for 5 minutes and the peak or trough effects recorded. In part II NA was infused for 30 minutes to achieve a steady state and data recorded for the final 5 minutes.
**Part I: Validity of the model**

In four dogs, weight 18-27 kg, the reliability of the bacteraemic shock model was assessed over a 4 hour period. The anaesthetized dog was surgically prepared and allowed to stabilize for 30 minutes. Pre-bacteraemic haemodynamic measurements were recorded. Bacteraemic shock was induced and after 1 hour a set of baseline followed by NA response haemodynamic data were recorded. NA was infused for 5 minutes at 0.4 \( \mu \)g/kg/min. This dose was chosen because it restored the MAP back to the pre-bacteraemic level. Hourly baseline and noradrenaline response data were then recorded for the next 4 hours. The dog was killed at the end of the experiment.

**Part II: NA dose-response**

In eight dogs, weight 15-25 kg, the haemodynamic response to an increasing dose of NA, 0.1 to 0.5 \( \mu \)g/kg/min, was tested under both normal (non-bacteraemic) and bacteraemic conditions. The anaesthetized dog was surgically prepared and allowed to stabilize for 30 minute. In the first phase normal (non-bacteraemic) conditions were tested. Pre-infusion baseline data was recorded for 5 minutes. NA was infused at a rate of 0.1 \( \mu \)g/kg/min for 30 minutes and data collected. The infusion was then stopped for 30 minutes to allow the MAP to return to the baseline before the next NA dose was started. The NA infusion was increased by 0.1 \( \mu \)g/kg/min and the procedure repeated until data for all five doses of NA had been collected. In the second phase bacteraemic conditions were tested. The dog was made bacteraemic and shock developed over 1 hour. The five doses of NA were then tested as above. The whole experiment took 8-10 hours to complete and the dog was then killed.
**Measured parameters**

The following haemodynamic variables were recorded: MAP, CVP, cardiac output (CO), heart rate (HR) and renal artery blood flow (RBF). Systemic vascular resistance (SVR) was calculated from the standard equation SVR=(MAP-CVP)x80/CO (dyne.s/cm\(^5\)). The CO and RBF were indexed to the dog’s weight. The percentage of circulating blood perfusing the kidneys was also estimated by dividing the CO by 2xRBF (both kidneys). The total fluid input and urine output during each phase of the study were also recorded. These data were divided by time to give an hourly rate.

**Data analysis and statistics**

Haemodynamic data from the study were stored on the laptop computer and later transferred to Microsoft Excel for analysis. Data was averaged over each 5 minute collection period. For the NA data from part I the peak and trough values were used. The percentage changes from the baseline for each haemodynamic variable following induction of bacteraemia and NA administration were also calculated.

Statistical analysis was performed using StatView for Windows (SAS Institute Inc. Cary. NC. USA.). The changes in each haemodynamic parameter following the onset of bacteraemia and NA administration were compared using the student t-test. Normality of the data was assumed. The effects on serial measurements, such as hourly interval data in part I and dose-response data in part II, were compared within and between groups (part II only) using analysis of variance for repeated measures. Bonferroni Dunn was used for post-hoc analysis. Results were presented as mean±SD. P<0.05 was considered statistically significant.