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**David Di Giantomasso**
**Clive N. May**
**Rinaldo Bellomo**

# Norepinephrine and vital organ blood flow

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D. Di Giantomasso · R. Bellomo (✉)
Department of Intensive Care and
Department of Medicine,
Austin and Repatriation Medical Centre,
Heidelberg, Victoria 3084, Australia
e-mail: rinaldo.bellomo@armc.org.au
Tel.:. +61-3-94965992
Fax: +61-3-94963932

C.N. May
Howard Florey Institute, Parkville,
Melbourne, Australia

**Abstract** *Objective:* To test whether norepinephrine (NE) infusion at 0.4 μg $kg^{-1}$ $min^{-1}$ adversely affects regional blood flow in the normal mammalian circulation. *Design and setting:* Randomized cross-over experimental animal study in a university-affiliated physiology institute. *Subjects:* Six merino ewes. *Interventions:* Staged insertion of transit-time flow probes around the ascending aorta and circumflex coronary, superior mesenteric and left renal arteries. In conscious animals with chronically embedded flow probes randomization to either 6 h of placebo (saline) or drug (NE at 0.4 μg $kg^{-1}$ $min^{-1}$). *Measurements and results:* Compared to placebo, NE significantly increased mean arterial pressure (84.4 vs. 103.8 mmHg), heart rate (61.0 vs. 74.6 bpm) and cardiac output (3.76 vs. 4.78 l/min). These changes were associated with an increase in coronary blood flow (24.2 vs. 37.4 ml/min) and renal blood flow (215.2 vs. 282.0 ml/min) but no change in mesenteric blood flow. The increase in renal and coronary blood flow was associated with an increase in regional conductance (regional vasodilatation), while mesenteric conductance fell (mesenteric vasoconstriction). Urine output (91±17 vs. 491±360 ml/h) and creatinine clearance (61±18 vs. 89±12 ml/min) increased during NE infusion. *Conclusions:* NE infusion does not induce vital organ ischaemia in the normal mammalian circulation. Furthermore, it results in a significant increase in coronary and renal blood flow with a concomitant improvement in urine output and creatinine clearance.

**Keywords** Norepinephrine · Vasoconstriction · Blood pressure · Cardiac output · Coronary circulation · Renal circulation

## Introduction

Norepinephrine (NE) is a potent vasoactive agent often used to treat hypotension in the setting of systemic vasodilatation as in septic shock [1, 2, 3, 4, 5]. It is also used in the absence of vasodilatation to maintain cerebral perfusion pressure in the setting of intracranial hypertension [6, 7, 8, 9]. Under these circumstances, increasing blood pressure might increase cerebral blood flow. However, controversy remains about the use of NE because of concerns that, especially in the absence of pre-treatment vasodilatation, NE infusion might also cause vital organ ischaemia, particularly to kidney and gut [10, 11, 12, 13, 14]. Unfortunately, all studies conducted so far have been either very short term in nature, performed immediately after an extremely invasive surgical preparation, or carried out using indirect measures of blood flow. No studies have assessed the effect of prolonged NE infusion on vital organ blood flow using chronically embedded flow probes, which allow continuous measurement of blood flow in animals that have fully recovered from surgery. Such studies would allow a more complete and accurate assessment of the effect of NE on regional blood flow. Accordingly, using a chronically instrumen-

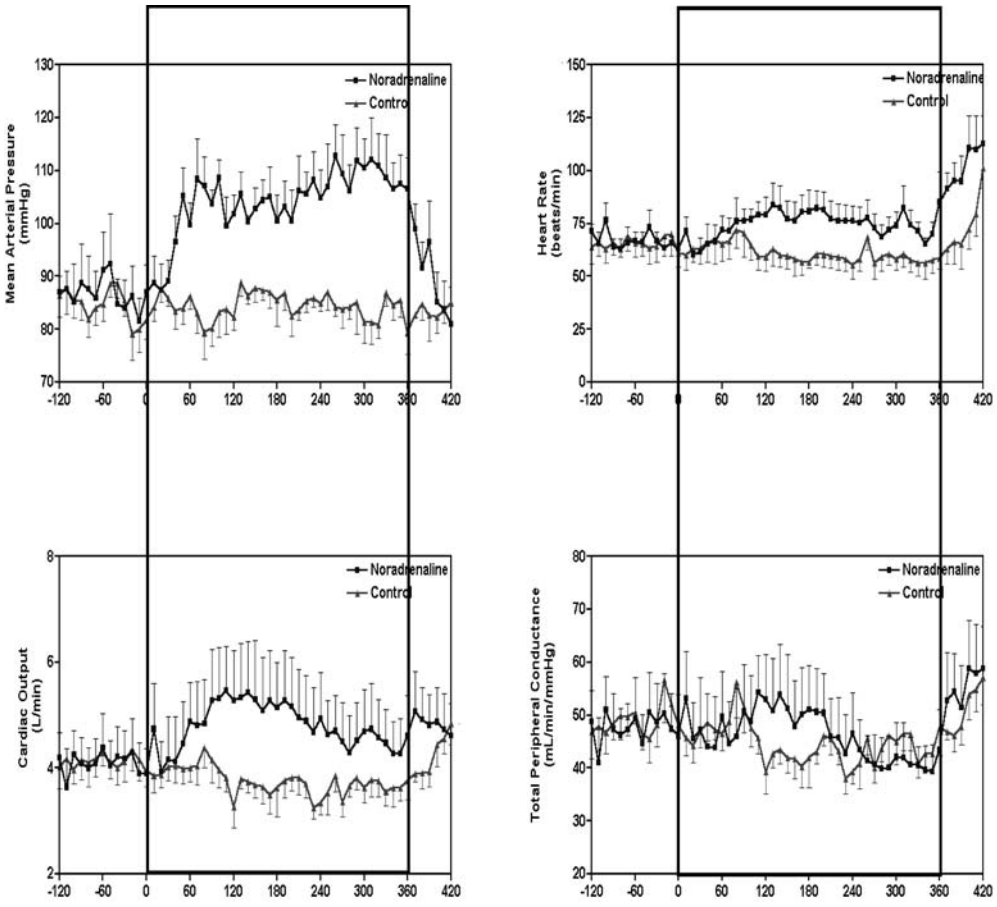


**Fig. 1** The effect of intravenous infusion of NE 0.4 μg kg$^{-1}$ min$^{-1}$ on central haemodynamic parameters. *X axis* Time (in minutes); *area enclosed by squares* period during which noradrenaline was infused. This resulted in a significant increase in mean arterial pressure, heart rate and cardiac output ($p<0.05$)

ted sheep model we investigated the effect of the intravenous administration of 0.4 μg kg$^{-1}$ min$^{-1}$ NE on central and regional haemodynamics in the normal mammalian circulation.

## Materials and methods

### Animal preparation

This study was approved by the local institutional animal ethics committee. Seven Merino ewes weighing between 35 and 45 kg were procured for chronic instrumentation. The animals underwent three separate operative procedures for the placement of flow probes. Anaesthesia was induced with sodium thiopentone (15 mg/kg) for endotracheal tube placement (cuffed size 10). Maintenance anaesthesia was by means of oxygen/air/isoflurane (0–2%). Fractional inspired oxygen was altered to maintain $PaO_2$ at approx. 100 mmHg and ventilation controlled to maintain $PaCO_2$ at approx. 40 mmHg. Anaesthesia was essentially the same for each operative procedure.

The first procedure was oophorectomy and carotid loop creation. After induction of anaesthesia as described above, the animals underwent oophorectomy. During the same sitting both carotid arteries were exteriorized and covered with skin to form bilateral carotid loops. The sheep were allowed at least 2 weeks to recover.

The second procedure was performed approximately two to 3 weeks later. After induction of anaesthesia a left-sided thoracotomy was performed. The pericardium was opened to expose the heart and great vessels. A transit time flow probe (Transonics Systems, Ithaca, N.Y., USA) was placed on the circumflex artery and an electromagnetic flow probe (In Vivo Metrics, Healdsburg, Calif., USA) placed on the ascending aorta.

After an appropriate recovery period (approximately 2 weeks) the third procedure was performed. After induction of anaesthesia as described above a left-sided flank incision was made and retroperitoneal dissection performed to expose the superior mesenteric and left renal arteries. Transit time flow probes (Transonics Systems) were placed on these arteries (6 and 4 mm, respectively). Following this procedure the animals were allowed to recover for approximately 3 weeks. The use of chronically implanted transit time flow probes has been previously validated [15].

The transit time flow probes were connected to a Transonics T201CDS flowmeter via a four-channel sequential scanner (TM04). The electromagnetic flow probes were activated by a Biotronex flow metre (Biotronex, Kensington, Md., USA). The output voltage of the EMF metre was reset to zero using an autozero circuit during a portion of diastole when blood flow in the ascending aorta is assumed to be zero. A separate circuit measured the first differential of the upstroke of systole (d$F$/d$t$) at each beat. Approximately 1 month after implantation the electromagnetic flow probes were calibrated in vivo against thermodilution over a range of cardiac output values. Dobutamine (Dobutrex, Lilly, West Ryde, NSW, Australia) was used to increase cardiac output from approximately 4–9 l/min.

The day before experimentation a tygon catheter (inner diameter 1.0 mm, outer diameter 1.7 mm) was inserted into the carotid artery and advanced 20 cm towards the heart for measurement of

arterial pressure. Under local anaesthesia two polythene catheters (inner diameter 1.2 mm, outer diameter 1.7 mm) were placed 25 cm into the jugular vein for the measurement of central venous pressure and for infusion. The arterial and one venous cannula were connected to pressure transducers (TDXIII, Cobe, Lakewood, Colo, USA) tied to the wool on the sheep's back. A correction factor was added in the data collection program to compensate for the height of the transducer above the heart. A urinary catheter was inserted for urine flow measurements and sample analysis. Analogue signals (mean arterial pressure, central venous pressure, cardiac output, d$F$/d$t$, regional flows) were collected using a PC 486 data acquisition system using custom software written at the Howard Florey Institute. Data were collected at 100 Hz for 10 s at 10-min intervals throughout the experimental protocol.

### Protocol and measurements

The following day, after a 2-h observation period, sheep were randomized to either placebo (vehicle) or NE infusion. The period of intervention began immediately after the period of observation. The animals received either intravenous NE (0.4 μg kg$^{-1}$ min$^{-1}$) or the vehicle (as placebo) at the same infusion rate for 6 h. Intravenous normal saline was administered at a rate that replaced urinary fluid loss. Mean arterial pressure, cardiac output, heart rate, coronary flow, mesenteric flow, and renal flow were measured continuously and recorded every 10 min. Urinary flow was measured continuously and urine sampled 2-hly for analysis (Model 3CII Osmometer, Advanced Instruments, Needham Heights, Mass., USA). Arterial blood samples were collected for analysis of serum urea, creatinine and electrolytes (Beckman, Brea, Calif., USA) at 0, 30, 60, 180, and 360 min during the observation period. At the end of 6 h the infusion was stopped. Animals were allowed to recover. The various catheters were removed. After an appropriate period of recovery (10–14 days) the animals were crossed over to the other arm of the study.

### Statistical analysis

Data are presented as means ±standard error of the mean. Comparisons of haemodynamics, biochemistry, and regional blood flows between the control period and the NE period were performed using the area under the curve method, as described by Matthews et al. [16] and the Wilcoxon signed rank test. A level of $p<0.05$ was considered statistically significant.

## Results

Infusion of NE at 0.4 μg kg$^{-1}$ min$^{-1}$ caused a significant increase in mean arterial pressure (from 84.4±2.4 to 103±6.7 mmHg), heart rate (from 61±4.1 to 74.6±6.3 beats/min) and cardiac output (from 3.76±0.24 to 4.78±0.43 l/min, $p<0.05$ for all changes). Myocardial contractility (assessed by d$F$/d$t$) was also significantly increased (from 852±22.1 to 1060±104 ml/s, $p<0.05$; Fig. 1). There were no significant changes in total peripheral conductance or stroke volume.

NE increased coronary conductance by 28% (from 0.28±0.02 to 0.36±0.03, $p<0.05$) and coronary blood flow by 54% (24.2±1.9 to 37.4±4.2 ml/min, $p<0.05$; Fig. 2). NE infusion caused mesenteric vasoconstriction as shown by the 18% decrease in mesenteric conductance (from 7.27±0.45 to 5.92±0.61, $p<0.05$; Fig. 3) that prevented any increase in blood flow (611.2±28.2 vs. 619.8±45 ml/min, NS) due to increased perfusion pressure. In contrast, NE infusion induced a 7% increase in renal conductance (from 2.56±0.13 to 2.75±0.17 ml mmHg$^{-1}$ min$^{-1}$, $p<0.05$), which together with the increase in perfusion pressure resulted in a 30% increase in renal blood flow (from 215.2±7.6 to 282±22 ml/min, $p<0.05$; Fig. 4).

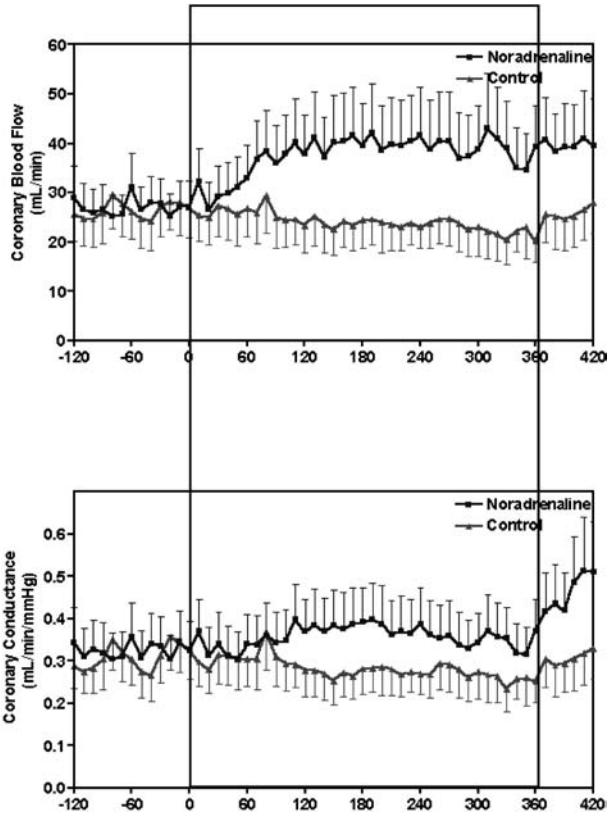


**Fig. 2** The effect of intravenous infusion of NE 0.4 μg kg$^{-1}$ min$^{-1}$ on coronary blood flow and conductance. *X axis* Time (in minutes); *area enclosed by squares* period during which noradrenaline was infused. This resulted in a significant increase in both parameters ($p<0.05$)

Associated with the increase in renal blood flow there was a 540% increase in urine output during NE infusion (491±360 vs. 91±17 ml/h, $p<0.05$). Creatinine clearance also increased by 46% (89±12 vs. 61±18 ml/min, $p<0.05$). There were no changes in plasma lactate levels (0.6±0.2 vs. 0.7±0.2 mmol/l, NS).

## Discussion

NE has long been thought to cause vasoconstriction of several regional beds, especially mesenteric and renal, such that during its infusion vital organ blood flow may

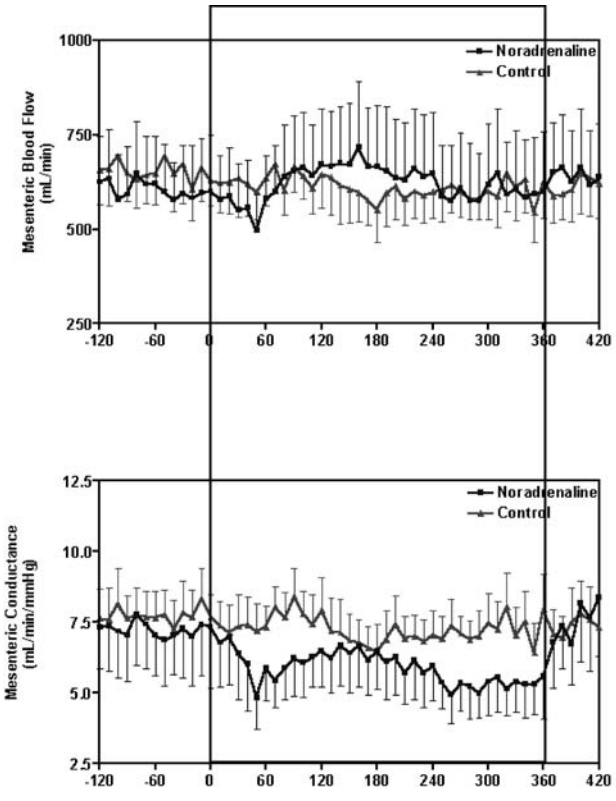


**Fig. 3** The effect of intravenous infusion of NE 0.4 μg kg$^{-1}$ min$^{-1}$ on mesenteric blood flow and conductance. *X axis* Time (in minutes); *area enclosed by squares* period during which NE was infused. This resulted in a significant decrease in mesenteric conductance ($p$<0.05)

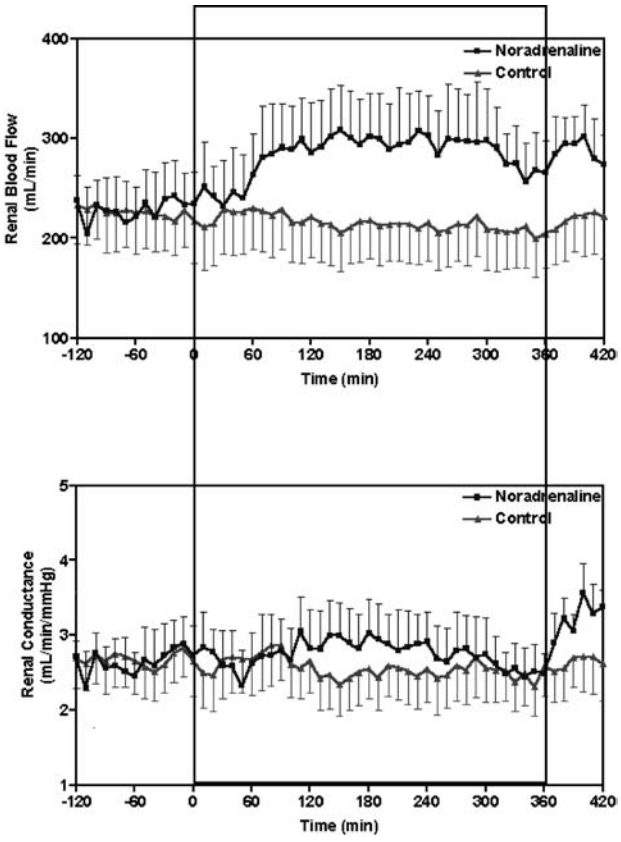


**Fig. 4** The effect of intravenous infusion of NE 0.4 μg kg$^{-1}$ min$^{-1}$ on renal blood flow and conductance. *X axis* Time (in minutes); *area enclosed by squares* period during which noradrenaline was infused. This resulted in a significant increase in both parameters ($p$<0.05)

become compromised. These concerns are based on studies performed with extremely high doses of NE infused directly into the renal artery [12, 13], other short-term studies based on acute invasive or indirect measurements [10, 11, 17, 18] or studies using microsphere technology [19], which allow assessment of regional circulations only at a particular moment in time. Despite the limitations and questionable clinical relevance of such studies NE has developed a reputation as a dangerous drug [20]. Thus its use has been shunned or markedly delayed in situations in which its effect on blood pressure might prove beneficial [4], especially in the absence of pre-treatment vasodilatation. It is possible that these fears are unjustified and lead to unwarranted delays in the restoration of a physiologically desirable vital organ perfusion pressure. To address these concerns we conducted a controlled animal study in which we sought to overcome the problems induced by confounding variables and by the technical limitations of previous studies.

Our study led to several clinically relevant findings. First, the infusion of NE at 0.4 μg kg$^{-1}$ min$^{-1}$ resulted in an increase in mean arterial pressure, cardiac output, myocardial contractility and heart rate. These findings have also been reported in humans and are consistent with the known combined α and β effects of this drug [4]. These findings occurred in an experimental setting in which mean arterial pressure was increased from 84 to 104 mmHg, a pressure increase of a magnitude often pursued in patients with an intracranial pressures between 15 and 25 mmHg. Thus our observations appeared clinically relevant and allowed us to assess changes in regional blood flow in a context that reasonably mimics the systemic circulation of patients receiving pressor therapy to maintain cerebral perfusion pressure. It is in this context that we found that during NE infusion renal and coronary blood flow *increased* and mesenteric blood flow was *unchanged*. It is interesting to note that the peak effect of NE on systemic haemodynamics (esp. blood pressure) appeared to occur 60–90 min after the initiation of drug infusion. The cause of this delay is unknown. However, previous work [21] suggests that much of the pressor effect of NE is mediated by angiotensin II production secondary to a β-receptor dependent increase in renin release.

The increase in renal blood flow was approximately 30% in magnitude and was statistically significant. It was also associated with an increase in urine output and creatinine clearance.

The increase in renal blood flow was associated with a 7% increase in regional conductance (decreased renal vascular resistance), indicating that increased perfusion pressure was not the only cause of increased flow. These findings have important clinical implications because they suggest that, when infused at clinically relevant doses, NE increases both renal blood flow and glomerular filtration rate (GFR) even in the absence of pre-treatment vasodilatation. The above observations may be surprising to some but are in accord with previous findings in animals. For example, in dogs, intravenous NE (0.1–0.4 μg $kg^{-1}$ $min^{-1}$) increased renal blood flow and GFR [21]. These findings were recently supported by another investigation of the effect of NE on renal and hepatic blood flow [22] and are consistent with other experimental and clinical reports [23, 24, 25, 26, 27]. Finally, the increase in renal blood flow was associated with marked polyuria and a significant increase in creatinine clearance, suggesting a beneficial effect of either NE or increased perfusion pressure or both on GFR.

Mesenteric blood flow was unchanged during NE infusion. However, mesenteric vascular resistance increased by approximately 20%. These findings are consistent with the previously held view that NE induces mesenteric vasoconstriction [19] and are supported by other experimental observations [17, 18, 19]. Although NE induces mesenteric vasoconstriction, this effect is offset by an increase in perfusion pressure, such that the aggregate result is a maintained mesenteric blood flow. Importantly, no increase in plasma lactate was seen.

Coronary blood flow was increased by approximately 50%. This increase was partly explained by an increase in coronary conductance (25% increase), the remainder being accounted for by the increase in perfusion pressure. Such coronary vasodilatation may represent a response to the increase in cardiac work induced by β-receptor stimulation. Our findings, however, indicate that NE is unlikely to induce coronary hypoperfusion when infused to augment mean arterial pressure as in our study.

Our study has several limitations. We studied normal animals. It is possible that, had we induced intracranial hypertension, our findings would have been different. However, the induction of intracranial hypertension would have required the killing of all animals, which given the nature of the preparation was logistically undesirable. Furthermore, it would have also required changing the preparation from awake to unconscious animals, thus introducing many other confounding variables. In most patients NE is given in the setting of vasodilatory shock. Our findings may not be relevant to such patients. On the other hand, if NE does not induce vital organ hypoperfusion in the normal mammalian circulation, it would appear unlikely that it would do so in a vasodilated circulation. Nonetheless, we are currently conducting such studies. We did not measure any dose response relationship between NE and regional flows. However, we selected the typical dose reported in the literature and studied its effects over a relatively prolonged period. We did this because the limited duration of studies of vasoactive drug effects is one of the major deficiencies in previous investigations, and we considered it our most important priority to ensure that we would study the effect of prolonged steady state administration (the more common clinical situation).

Our assessment of organ function was partial. However, the assessment of renal function beyond GFR is very difficult and of uncertain clinical significance, the assessment of gut permeability in a ruminant is of questionable relevance to humans, and the assessment of myocardial pressure-volume loops requires a highly invasive method. We did not measure organ oxygen consumption. Such information 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 chronic cannulation in the sheep induces venous thrombosis. We are currently conducting acute studies to elucidate this aspect of organ perfusion. The liver is also a vital organ, but hepatic blood flow was not measured. However, given its dual blood supply, it is unlikely that hepatic flow would have been decreased in the presence of adequate mesenteric flow. In one of the sheep the flow probe was placed on an artery before the division into separate coeliac and mesenteric arteries. This blood flow increased, which suggests that hepatic arterial blood flow should also not decrease.

In conclusion, NE infusion at 0.4 μg $kg^{-1}$ $min^{-1}$ resulted in a significant increase in mean arterial pressure, cardiac output, heart rate and myocardial contractility. Furthermore, coronary blood flow increased in association with coronary vasodilatation, renal blood flow also increased with an improvement in urine output and GFR, while mesenteric blood flow remained constant. These findings support the view that NE infusion at clinically relevant doses does not induce hypoperfusion or dysfunction of vital organs in the normal mammalian circulation.

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