The Effect of Norepinephrine and Dobutamine on Bladder Epithelial Oxygen Tension*

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Study objectives: To assess the effects of two contrasting vasoactive agents (dobutamine [DOB] and norepinephrine [NE]) on (1) global and regional cardiorespiratory variables, (2) acid base status, and (3) bladder epithelial oxygen tension (BEOT), a putative marker of organ perfusion.

Design: Measurement of aortic blood flow (ABF) and renal blood flow (RBF), mean arterial blood pressure, arterial blood gases, and BEOT were made during infusion of placebo and varying doses of DOB and NE.

Setting: Medical school laboratory.

Subjects: Eighteen anesthetized, spontaneously breathing, male Sprague-Dawley rats divided into three groups.

Interventions: Two groups were allocated to receive escalating doses of DOB (to 40 μg/kg/min) or NE (to achieve a 50% change in any hemodynamic variable). The drug therapy was then discontinued for 15 min and restarted at the previous maximum dose. A third group received 0.9% saline solution at the same infusion rate (16 mL/kg/h).

Measurements and results: There was a dose-related increase in mean blood pressure with NE and fall with DOB. Compared with control values, NE had no effect on ABF but decreased RBF significantly whereas DOB significantly increased ABF but had no effect on RBF. Base excess and BEOT decreased significantly and in parallel with both agents, more so with NE.

Conclusions: Despite their different macrocirculatory effects, DOB and NE both produced a significant but reversible fall in BEOT and a metabolic acidosis. BEOT shows potential as a monitor of the effectiveness of organ perfusion.

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ABF=aortic blood flow; BEOT=bladder epithelial oxygen tension; DOB=dobutamine; NE=norepinephrine; PtO2=tissue oxygen tension; RBF=renal blood flow

Key words: bladder epithelial oxygen tension; dobutamine; hemodynamics; norepinephrine; rat, tissue oxygen tension

Despite the current wide array of monitoring equipment, the clinician is given little insight into the adequacy of regional perfusion. Heart rate and blood pressure are coarse and sometimes misleading guides to circulatory status while measurement of global variables such as mixed venous oxygen saturation, lactate, and acid base status are not always reflective of organ perfusion. Tonometric derivation of gastric intramucosal pH has been advanced as a measure of splanchnic perfusion and appears to be a better predictor of outcome than standard variables. However, little evidence supports the use of gastric intramucosal pH as a treatment end point. Furthermore, the technology is unwieldy and prone to methodologic error which has prevented this technique from gaining significant clinical acceptance.

There is considerable body of work suggesting that tissue oxygen tension (PtO2) monitoring could be a valuable adjunct to standard monitoring techniques.

PtO2 reflects the balance between supply and demand and therefore has the potential to assess adequacy of perfusion under the prevailing circumstances. Subcutaneous oxygen tension has been shown experimentally to be a sensitive indicator of early blood loss; it has been used clinically to assess postoperative hypovolemia and was more sensitive than clinical evaluation based on standard hemodynamic measures and urine output. Conjunctival PO2 used in the early assessment of trauma has also been shown to be a reliable indicator of the severity of trauma. We have previously described how a miniature polarographic oxygen electrode (Continucath; Biomedical Sensors Ltd; High Wycombe, England) in contact with the bladder epithelium responded rapidly and in parallel with base deficit to control hemorrhage and resuscitation in a rat model.

There remains considerable controversy over the use and choice of inotropes and vasopressors, particularly in sepsis. Little is known about the effects of these agents on tissue oxygen availability and regional blood flow. We therefore decided to compare the effects of dobutamine (DOB) and norepinephrine (NE) on hemodynamics and blood gas variables in the rat and to compare these with concurrent changes in
bladder epithelial oxygen tension (BEOT).

**Materials and Methods**

Approval for this study was obtained from the Home Office (according to the Animals [Scientific Procedures] Act 1986). The experiments were performed on an anesthetized, spontaneously breathing, male Sprague-Dawley rat model. The animals were given free access to food and water until the time of surgery. Anesthesia was established with an intraperitoneal injection of thiobutabarbital, 60 mg/kg, and the animals were placed on a heated operating table to maintain core temperature. Neck dissection was performed to allow placement of vascular lines using polyethylene tubing of 0.9-mm external diameter stretched over a heat source to reduce the diameter of the ends. A right jugular venous line for infusion of fluid and drugs and a left carotid arterial line for continuous monitoring of blood pressure (pressure transducer MX860; Medex; Haslington, UK; and Monitor 78353A; Hewlett Packard; Bracknell, UK) and intermittent sampling for blood gas analysis (165 µL heparinized capillary tube samples; processed by ABL4; Radiometer; Copenhagen, Denmark) were placed. A tracheostomy (2.08-mm external diameter polyethylene tube) was sited and cut to a length approximating anatomic dead space to secure the airway and allow tracheal toilet. A 1-mL bolus of 0.9% saline solution was given after placement of these lines followed by a continuous infusion of 4 mL/h/250 g of body weight.

A midline laparotomy was performed to gain access to the abdominal vasculature and bladder. Doppler flow probes were placed on the left renal artery (1 mm, J-reflector [1RB]) and on the infrarenal abdominal aorta (2 mm, J-reflector with sliding gate [2SB]) and connected to a flow monitor (T206; monitor and probes from Transonics; Ithaca, NY). Two cannulas (1.57-mm outside diameter) were inserted surgically into the bladder, via the laparotomy, through an incision in the avascular area at its dome. One cannula allowed free drainage of urine to ensure that the bladder was empty and the other was used to allow insertion of the oxygen electrode (active length, 10 mm; diameter, 0.35 mm). The electrode was inserted until a 15-mm length was seen through the bladder wall, thus ensuring close contact with the bladder epithelium. The two cannulas were secured with a ligature close to the incision in the bladder. The electrode was calibrated before insertion by immersing it in degassed saline solution for 30 min. A sample of the saline solution was then put through the blood gas analyzer and the electrode was calibrated to this value after temperature compensation (correction factor x1.04°C). This procedure was repeated after each experiment to check for electrode drift. After instrumentation, the animals were left to stabilize until three consistent hemodynamic measurements at 5-min intervals were obtained.

The animals were divided into three groups, DOB treated, NE treated, and control. Six rats were included in each group. DOB infusion was started at 5 µg/kg/min and the dose doubled until 40 µg/kg/min was reached. The drug therapy was then stopped before being restarted at 40 µg/kg/min. NE infusion was started at 1 µg/kg/h and doubled until a 50% change was observed in any monitored hemodynamic variable. The drug therapy was then stopped and restarted at the previous maximum dose. Changes of dose were made every 10 min except for a 15-min interval between stopping and restarting the drug therapy. These protocols for administering the drugs were chosen as they were believed to reflect the clinical usage of the two agents. The infusion rate was kept constant at 4 mL/h/250 g of body weight throughout the experiment by changing the concentration of the drugs. The control animals were treated in the same way except that they received only 0.9% saline solution.

To prevent excessive blood loss through repeated sampling, blood gas samples were only taken at the end of the following periods: stabilization, alternate dose escalation, maximum dose, after the drug infusions were stopped, and 10 min after restarting. Blood gas sampling and recording of other variables were performed on the control animals at the same time points as the experimental animals. As the NE doses required to achieve the desired hemodynamic endpoints varied, the control values for the two groups differ slightly despite coming from the same group of animals.

Statistical analysis was performed by repeated measures analysis of variance using a standard computer package (Statview 4). Results are expressed as means ± SEM.

**Results**

The results are represented graphically in Figures 1 and 2. For the purposes of clarity, only the results from the midrange and maximum doses are presented. The average weight of the rats used was 219 g (range, 150 to 260 g). The maximum dose of NE given was 32 µg/kg/h in two rats, 64 µg/kg/h in one rat, and 128 µg/kg/h in three rats.

All control values remained stable throughout the course of the experiment with the exception of abdominal aortic blood flow (ABF). Compared with controls, there was a significant and reversible rise in mean arterial blood pressure with NE and a significant, reversible fall with DOB. There was no change from
control in ABF with NE. However, DOB maintained ABF significantly higher than control values throughout the experiment. However, no change in renal blood flow (RBF) was seen with DOB but a significant, reversible fall was seen with NE.

All the animals had a respiratory acidosis at the start of the experiment, which remained stable in the control animals. Arterial pH dropped significantly and reversibly with NE but no significant change was seen in the DOB-treated animals, but fell significantly and reversibly with NE. There was a significant, reversible fall in base excess on exposure to DOB although not significantly more than control. In contrast, PaCO₂ remained steady with NE until discontinuation when a large and reversible fall in PaCO₂ occurred. PaO₂ was unchanged from control in the DOB-treated animals, but fell significantly and reversibly with NE. There was a significant, reversible fall in base excess on exposure to DOB and a much larger but only partially reversible fall with NE. BEOT dropped early and significantly on exposure to both agents and mirrored changes in base excess. Highly statistically significant changes occurred in BEOT with infusions of both drugs, although more so with NE.

**DISCUSSION**

This study forms part of an ongoing evaluation of BEOT monitoring as an index of organ perfusion. The oxygen electrode (Continucath) is available as a clinical intra-arterial continuous Po₂ monitor; its in vitro and in vivo performance has been well validated with the response being linear and accurate through and beyond the physiologic range. In the present study, electrode contact with the bladder wall was assured visually and contamination by atmospheric oxygen prevented by the retaining ligature and the 2-cm length of cannulas containing urine. The rapid response of the measured Po₂ value (within 30 s) in an animal producing only 1 to 2 mL/min of urine and unpublished experiments that have yielded identical results despite dividing the ureters allows us to conclude that the oxygen tension of the bladder epithelium is being measured. The ureters are not divided routinely in order to minimize the extent of the potentially disruptive surgery required.

DOB and NE are vasoactive agents commonly used in critically ill patients to augment either systemic flow or pressure and thereby improve organ perfusion. These two agents were selected because of their different pharmacologic profiles, noradrenaline being primarily an α-agonist with vasoconstrictor and minimal inotropic effects while DOB is primarily a β₁-agonist with inotropic and vasodilating properties. The drugs were infused into a group of healthy anesthetized instrumented animals as a prequel to the evaluation of their systemic and regional circulatory effects on a rat model undergoing various hemodynamic insults.

The hypertensive response to NE was predictable while the fall in BP with DOB could be explained by β-adrenergic-mediated vasodilation. NE had no effect on ABF but a detrimental effect on RBF whereas DOB, despite augmenting ABF, produced no improvement in RBF. These actions on ABF must be interpreted in the light of a falling ABF in the control group that we have found to be a feature of the anesthetic technique used. Notwithstanding this falling control value, the different effects of the two agents on ABF (taken as representative of cardiac output) are clear and in keeping with their known mechanisms of action. This could be due to preferential redistribution of cardiac output to muscle beds, possibly reflecting different levels of adrenoreceptor activity and concentration in different tissues. Thus, even at a macrocirculatory level, regional variations in flow were seen which, if reproduced in the clinical situation, would pass unrecognized. This serves to underline the implicit peril in assuming that measurement of global changes are representative of changes occurring at organ level, let alone any additional and unmonitored.

![Diagram of Norepinephrine and Dobutamine](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21724/ on 06/26/2017)
microcirculatory effects.

The changes in arterial oxygen and carbon dioxide tensions are difficult to explain. The baseline hypercapnia can be attributed to the anesthetic technique while catecholamine-induced alterations in metabolic rate and oxygen consumption would affect carbon dioxide production. In the previously reported exsanguination model, the animal hyperventilated in response to the increasing metabolic acidosis. Despite breathing room air, there was a significant rise in PaO2 that could not be explained by the concomitant fall in PaCO2 and change in the alveolar air equation. In this study, DOB induced similar changes, though these were not significantly different from controls. However, NE induced a consistent, significant, and reversible fall in PaO2, while the PaCO2 fell transiently only when the infusion was stopped. This may be related to ventilation/perfusion changes, to hypoventilation, or to a reduction in mixed venous Po2; however, this is not clear from the data collected in these experiments. Changes in PaO2 and BEOT showed a similar pattern with NE but no relationship with DOB. These findings are in contradistinction to those seen during hemorrhage when the PaO2 rose despite a fall in BEOT.

Both DOB and NE induced a metabolic acidosis, the etiology of which is uncertain. The increase in base deficit with both agents, albeit significantly greater with NE, may be reflective of alterations in flow at a microcirculatory level causing regional hypoperfusion, though the contribution of catecholamine-induced increases in metabolic rate and accelerated aerobic glycolysis remains open to question. The concordance between this acidosis and the fall in PtO2 (as measured by the bladder oxygen probe) suggests that cellular hypoxia may be at least partly responsible as there appears to be an imbalance between oxygen supply and demand at tissue level. The rapid response time of the BEOT reading (changes are seen within 30 s of a maneuver) is highly indicative that the probe is responding to changes in the epithelium rather than urine. We did not measure lactate in order to avoid excessive blood sampling and reduction in hematocrit and oxygen delivery. Standardized base deficit has been shown to be as, if not more, useful than lactate in shock states; furthermore, lactate release from skeletal muscle is induced by catecholamines in the presence and absence of hypoxia. Further work is being undertaken using 31P magnetic resonance spectroscopy to assess cellular energetics and intracellular pH in this model and allow further interpretation of the cause of the metabolic acidosis seen in these animals.

It is apparent from animal and human studies that conventional monitoring does not accurately represent perfusion at organ level. A monitor of the adequacy of tissue perfusion at a local level, which is simple to insert and operate, minimally invasive, reliable, sensitive, and specific would be highly desirable. Newer techniques include gut tonometry, which has several limitations and challenged assumptions; unpublished studies from our institution have found interobserver variations, the potential for operator error, dependence on gastric pH, and interference from enteral feed. The use of arterial bicarbonate as a measure of tissue bicarbonate for this technique has also been questioned. The base deficit is a sensitive marker of metabolic acidosis and as such is an indicator of inadequate tissue perfusion. However, it can be affected by extraneous sources of alkali (eg, bicarbonate therapy, hemofiltration replacement fluid), by renal and hepatic dysfunction, and by metabolic compensation for hypercapnia. It is a global variable and is prone to dilution if the area of tissue ischemia is regionalized and relatively small. Arterial lactate is similarly affected and the significance of this measurement is further complicated by the balance between lactate production and utilization by organs such as liver and brain. It is further recognized that hyperlactatemia can be produced in the absence of cellular hypoxia by catecholamines, accelerated proteolysis and aerobic glycolysis (accompanying critical illness), and by decreased levels of the active form of pyruvate dehydrogenase seen in sepsis.

Tissue oxygen tension monitoring has been identified as a sensitive indicator of hypoperfusion, in particular to hypovolemia. It has not gained widespread clinical acceptance as methods have been either unwieldy (eg, implantation of tonometers) or esthetically unattractive (eg, conjunctival). Insertion into tissue will induce local trauma and inflammation with secondary hyperemia, and this may possibly produce misleading data. The location may also be significant; for example, skeletal muscle blood flow behaves differently to abdominal visceras. The bladder epithelial site may overcome these problems; it is minimally invasive and atraumatic, especially in the context of the critically ill patient or the patient undergoing major surgery who would routinely receive a urethral catheter, and provides continuous, 'hands-off' and direct monitoring. Whether this site is representative of 'vital organ' perfusion requires further investigation, though the results of these studies provide encouragement.

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