

VASOPRESSORS AND INTESTINAL MUCOSAL PERFUSION

Studies in Cardiac Surgical and Critically Ill Patients

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*To my family
Maria, Amanda and Matilda*

ABSTRACT

During trauma, surgery and critically illness, splanchnic ischemia and reperfusion damage may threaten the barrier function of the intestinal mucosa, leading to bacterial translocation, immune activation and subsequent development of systemic inflammatory response syndrome. Detection, prevention and treatment of intestinal mucosal hypoperfusion are therefore important for prevention of complications in critically ill patients. In this thesis, the intestinal mucosal perfusion, measured by laser Doppler flowmetry, has been studied during and after cardiac surgery and in critically ill patients with vasodilatory shock, with focus on the effects of vasopressor treatment.

The intestinal mucosal perfusion was evaluated postoperatively in eighteen cardiac surgery patients. Elevation of the systemic perfusion pressure with norepinephrine induced no change in intestinal mucosal perfusion, whereas the combination of norepinephrine and dopamine caused increased mucosal perfusion. Furthermore, the differential effects of phenylephrine, a pure α_1 -adrenoceptor agonist, and norepinephrine, which has both α_1 -constricting and β_1 -dilating properties, were investigated postoperatively in ten patients. Intestinal mucosal perfusion was not altered by the vasopressors, whereas both drugs increased the global splanchnic oxygen extraction. This increase was more pronounced with phenylephrine, indicating a more pronounced global splanchnic vasoconstriction, compared to norepinephrine.

In ten critically ill patients with multi organ failure and norepinephrine-dependent vasodilatory shock, the effects of norepinephrine-induced variations in perfusion pressure on global splanchnic and intestinal mucosal perfusion were evaluated. The intestinal mucosal perfusion and the global splanchnic oxygenation were not altered despite a change in mean arterial pressure from 60 to 90 mmHg.

The autoregulation of intestinal mucosal perfusion during cardiopulmonary bypass was tested in ten cardiac surgery patients. Variations in perfusion pressure induced by alterations in cardiopulmonary bypass flow rate revealed an intact autoregulatory capacity of the intestinal mucosa. Vasodilation with prostacyclin increased jejunal mucosal perfusion and abolished the autoregulatory capacity of the mucosa. The amplitude and frequency of the cyclic oscillation of the mucosal perfusion (vasomotion) increased with increasing perfusion pressure.

In conclusion: Intestinal mucosal perfusion is not affected by clinical relevant doses of the vasopressors norepinephrine and phenylephrine, in postoperative patients and critically ill patients with vasodilatory shock. Phenylephrine causes a more pronounced global splanchnic vasoconstriction compared to norepinephrine. Addition of dopamine increases intestinal mucosal perfusion during norepinephrine infusion. Autoregulation of intestinal mucosal perfusion is intact during cardiopulmonary bypass.

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ABBREVIATIONS

ANOVA	analysis of variance
AL	arterial lactate concentration
CI	cardiac index
CPB	cardiopulmonary bypass
CVP	central venous pressure
DA	dopamine
HvL	hepatic vein lactate concentration
JMP	jejunal mucosal perfusion
JMHt/JMHct	Jejunal mucosal haematocrit
LDF	laser Doppler flowmetry
MAP	mean arterial pressure
NE	norepinephrine
PAOP	pulmonary artery occlusion pressure
PHE	phenylephrine
PaO ₂	arterial oxygen tension
PaCO ₂	arterial carbon dioxide tension
PvO ₂	venous oxygen tension
PHvO ₂	hepatic vein oxygen tension
RBCvelocity	red blood cell velocity
SVI	stroke volume index
SVRI	systemic vascular resistance index
SaO ₂	arterial oxygen saturation
SIRS	systemic inflammatory response syndrome
SvO ₂	mixed venous oxygen saturation
SHvO ₂	hepatic vein oxygen saturation
SOFA score	sequential organ failure assessment score

LIST OF PUBLICATIONS

This thesis is based on following original papers, which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

- I Effects of norepinephrine alone and norepinephrine plus dopamine on human intestinal mucosal perfusion.
Nygren A, Thorén A, Ricksten S-E.
Intensive Care Med. 2003 Aug; 29(8): 1322-8.

- II Vasopressors and intestinal mucosal perfusion after cardiac surgery: norepinephrine vs. phenylephrine.
Nygren A, Thorén A, Ricksten S-E.
Crit Care Med 2006; 34(3): 722-29.

- III Effects of norepinephrine-induced variations in perfusion pressure on intestinal mucosal perfusion in vasodilatory shock after cardiac surgery
Nygren A, Thorén A, Ricksten S-E.
Manuscript, submitted Mars 3, 2006

- IV Autoregulation of human jejunal mucosal perfusion during cardiopulmonary bypass
Nygren A, Thorén A, Houltz E, Ricksten S-E.
In press 2006, Anesthesia & Analgesia

INTRODUCTION

Resuscitation of critically ill patients and perioperative management of trauma and surgical patients include detection, prevention and treatment of global as well as local hypoxia. Monitoring of systemic haemodynamic variables may reveal disturbances in global oxygen delivery and/or uptake. On the other hand, various forms of circulatory shock may induce redistribution of perfusion in different parts of the body, for instance away from the splanchnic area, which will not be detected by measurement of systemic haemodynamics. Splanchnic ischemia and reperfusion damage threaten the mucosal barrier function of the intestine leading to bacterial translocation, immune activation and subsequent development of the systemic inflammatory response syndrome -SIRS. Detection, prevention and treatment of mucosal hypoperfusion are therefore important for prevention of complications in critically ill patients. In this thesis the intestinal mucosal perfusion has been studied during and after cardiac surgery and in critically ill patients, with focus on the effects of vasopressor treatment.

The Intestine

Anatomical and physiological considerations

The visceral organs receive 30% of cardiac output via three main arteries. The celiac trunc supplies the ventricle, liver, spleen, pancreas and duodenum. The superior mesenteric artery supplies jejunum, ileum and proximal and transversal part of colon while the inferior mesenteric artery supplies the distal part of colon, sigmoideum and rectum. The veins draining blood from the intestine accompany the arteries emptying into the portal vein, which also collects blood from the spleen, pancreas and gallbladder. Two-thirds of the liver is perfused with nutritious blood with low oxygen content from the portal vein and one-third with arterial blood from the hepatic artery. Blood from both the portal vein and hepatic artery passes into liver sinusoids and drains into central veins. The central veins drain the blood into the hepatic veins.

The portal blood flow is the major intrinsic regulator of the hepatic arterial tone. Changes in hepatic arterial flow act to buffer the impact of portal flow alterations on total hepatic blood flow. This response is called “the hepatic buffer response” and acts to maintain the hepatic blood flow at a constant level [1].

The intestinal wall of the gastrointestinal canal is composed of four different layers. The mucosa and submucosa are responsible for absorption and

excretion. The muscularis, with an inner circular and outer longitudinal muscle layer, induces propulsive and non-propulsive motion of the intestine. Jejunum, the proximal 2/5 of the small intestine is thicker with more mucosal folds and richer vascularisation than the distal part, the ileum. The total area of the inner surface of the jejunum is increased by 5-8 mm high folds, plica circulares, containing mucosa and submucosa, and finger like projections, villi, with a length of 0.5-1.5 mm. The villi are composed of an epithelial layer with an underlying lamina propria, arterioles and venous plexa, and centrally placed lymphatic capillaries, lacteals. The intestinal villi, and attending microvilli, from the duodenum to the ileum, augment the mucosal absorption surface. Cells proliferate in the crypts migrating towards the tip of the villi where they finally are exchanged.

The innervation of the intestinal wall is complex and consists of three main systems. 1) The enteric nervous system with two interconnecting plexa -the submucosal nerve plexus and the myenteric nerve plexus. Mucosal receptors include mechanoreceptors sensitive to wall stretch and chemoreceptors that sense intestinal contents. The plexa are responsible for peristaltic and propulsive contractions. 2) Parasympathetic activity mainly increases the activity of intestinal smooth muscle. 3) Sympathetic noradrenergic activity generally decreases smooth muscle activity and increases sphincter tone. Sympathetic activity also induces vasoconstriction.

Migrating motor complexes

The migrating motor complex (MMC) is an interdigestive program of motor, secretion and perfusion activity starting in antrum of the ventricle or proximally in the intestine, migrating distally towards the terminal ileum. MMC is characterized by three phases: phase 1: intestinal quiescence, with less than two contractions/min, phase 2: with irregular contractions followed by phase 3: with a period of intense regular contractions more than 10-12/min [2]. The rhythm of the MMC is generated by the enteric nervous system, but the start of the cycle, migration, speed and duration of the phases are modulated by external nerves and hormones such as motilin [3]. During sepsis the pattern of MMC is disturbed or absent [4]. The standard technique for measurement of intestinal motility is manometry. Laser Doppler flowmetry detects motion artefacts corresponding to MMC phase 3 movements providing an indirect sign of MMC [5].

The intestinal mucosa

The barrier function

The gastrointestinal mucosa creates a barrier between the inside of the body and the potentially harmful microorganisms in the lumen of the intestine. It also provides protection against acid from the ventricle, bile acids, digestive enzymes and endotoxins.

The preepithelial defence consists of a combination of protective factors. The mucus forms a protective viscous layer. IgA-antibodies, that bind to and aggregate bacteria to prevent them from adhering to the epithelial cells [6]. Bicarbonate secretion, that buffers and protects against gastric acid and acidic microbial metabolites [7]. Under normal conditions, anaerobic organisms cover the lower small intestine and colon, limiting overgrowth and colonization of other more harmful bacteria [8]. The propulsive motion of the intestine also clears the mucosal surface from microorganisms and debris.

The epithelial barrier consists of enterocytes with tight junctions further limiting penetration of harmful agents. The epithelial layer has a capacity of rapid restoration of superficial damage by a process of cell migration and reepithelization. Cell death, apoptosis, and the renewal also forms a part of epithelial protection sacrificing challenged cells [9]. The turnover rate of epithelial cells is impaired during SIRS [10, 11].

At the subepithelial level, lymph vessels and veins prevent the accumulation of harmful agents and transport toxins to the liver for detoxification. The enteric wall is also rich in leucocytes in the mucosa, submucosa and lymph nodes.

Mucosal perfusion

Each villus is perfused through a central arteriole with a surrounding venous plexus. A critical feature of the vasculature of the villus is the close approximation, less than 20 μm , of the main arteriole in the core to the peripherally located capillaries and venules [12, 13], which leads to a progressive lowering of pO_2 and increasing osmolarity towards the tip of the villus. The countercurrent flow reduces the pO_2 to 2.0-3.3 kPa at resting conditions, whereas it decreases to below 0.7 kPa during glucose exposure or reduced perfusion pressure [14]. Precapillary mucosal arterioles act as resistance vessels and are the site of local metabolic and neurogenic control of mucosal blood flow. Precapillary sphincters control both number of perfused capillaries and distribution of perfusion within the intestinal wall. The tone of the postcapillary resistance vessels, venules and veins determine the capillary hydrostatic pressure, pooled blood volume and rate of fluid exchange across

the capillary wall. The blood flow in the mucosa/submucosa constitute approximately 65-90% of total intestinal blood flow during resting conditions [15]. The villi and crypts accounts for 25-35% and 20-30% respectively of total intestinal blood flow [16].

Metabolic regulation of perfusion

During food processing and absorption the oxygen requirements can increase up to 100% [17]. The increased oxygen requirement is matched by a combination of an increase in blood flow and an increase in oxygen extraction [17, 18]. The metabolic control of perfusion predicts that oxygen delivery to tissue, not flow, is the controlled variable. Any condition causing imbalance between tissue O₂ supply and O₂ demand will increase the production of K⁺, H⁺, osmolality and adenosine locally, causing relaxation in arteriolar and precapillary sphincter smooth muscle.[16] However experiments with hypoxia induces only a slight increase in villus perfusion suggesting that hypoxia is not the major determinant of metabolic control. Submucosal hyperosmolarity by increased sodium concentration accounts for a substantial part of the signal for vasodilation during absorption [14, 19].

Myogenic mechanisms and autoregulation of perfusion

The intestinal vascular bed characteristically displays a marked autoregulation of blood flow. Under normal conditions, a decrease in arterial pressure induces a redistribution of flow toward the mucosa due to the pressure flow autoregulation [20]. The autoregulation is defined as the ability to maintain constant blood flow despite changes in perfusion pressure within a range of 50 and 150 mmHg and is achieved by contractions and relaxation of the small precapillary resistance vessels, arterioles, due to the effect of stretch on smooth muscle activity (Bayliss-effect). This constancy of capillary pressure as a result of autoregulation is functionally important since the huge fenestrated capillary area of the mucosa would otherwise imply a considerable risk of rapid oedema formation [15].

Auoregulatory escape

The response to α_1 -stimulation are quite similar whether the stimulation is due to direct nerve stimulation, reflex activation or infusion of α_1 -adrenergic agonists [21]. Increased activity in sympathetic nerves induces a marked initial constriction of resistance vessels and a decrease in blood flow reaching its peak within 40 seconds after start of stimulation. The peak vasoconstrictor response gradually subsides despite continued nerve stimulation to reach a perfusion steady state level within 2-3 minutes. When the nerve stimulation is stopped, the intestinal perfusion exhibits a hyperaemic phase when blood flow increases above the control level. This pattern is called "autoregulatory escape from

sympathetic stimulation” [22, 23]. Local factors, capable of antagonizing the vasoconstriction in arteriolar smooth muscles e.g. adenosine, and not opening of arteriovenous anastomoses, are responsible for this phenomenon [24, 25]. The autoregulatory escape phenomenon is even more pronounced in the villus part of the intestinal wall [26]

Vasomotion

The arterioles supplying blood to the capillary network exhibit rhythmic oscillations in vascular tone, independent of external influences such as cardiac, intestinal peristaltic, or respiratory cycles. This phenomenon of periodic diameter variations is referred to as *vasomotion* and is a natural property observed in most microcirculatory vascular beds [27]. The mechanism for vasomotion is believed to be due to intermittent calcium release from the sarcoplasmic reticulum leading to cyclic smooth muscle depolarization of the blood vessels via activation of chloride channels [27]. Cyclic microcirculatory blood flow variations have previously been described in the human jejunal mucosa [28], but not the serosa further emphasizing potential differences between the characteristics of intestinal perfusion between measurements sites [29]. The frequency of vasomotion in human jejunal mucosa is usually between 1.9 and 5 cycles/min [28, 30]. Jejunal mucosal vasomotion has also been observed experimentally as variations in jejunal mucosal tissue oxygenation and microvascular haemoglobin oxygen saturation using a Clark-type surface oxygen electrode and with tissue reflectance spectrophotometry, respectively [29, 31]. The pattern of vasomotion varies considerably between both species and vascular beds and may be affected by vasoactive agents [32] or changes in blood pressure, haematocrit, or oxygen tension [33].

Patophysiological considerations

The mucosal layer is sensitive to decreased oxygen delivery as the mucosa already at physiological conditions balances on the limit to hypoxia [34]. The countercurrent exchange of oxygen will progressively decrease the pO_2 and increase the osmolarity during low flow state such as shock or inadequate volume resuscitation leaving the villus tip hypoxic.

In the vessels, red blood cells tend to accumulate in the centre of the flowing stream. Consequently, the blood along the side of the vessels has a lower haematocrit. Branches leaving the side of the vessel at right angles may receive a disproportionate amount of this erythrocyte-poor blood. This “plasma-skimming phenomenon” may explain why the haematocrit of capillary blood regularly is 25% lower than whole body haematocrit [35]. Intestinal tissue haematocrit is significantly lower in the mucosa than in the submucosa, the ratio is in experimental studies not changed by nervous vasoconstriction [36].

Restoration of flow after an ischemic event causes an ischemia-reperfusion injury. Tissue ischaemia leads to depletion of cellular energy stores and accumulation of toxic metabolites. Formation of oxygen derived cytotoxic products is critical in ischemia-reperfusion injury. Xanthine oxidase is the rate-limiting enzyme of nucleic acid degradation. During ischaemic conditions oxidation of xanthine to hypoxanthine is enhanced by xanthine oxidase instead of xanthine dehydrogenase. Xanthine oxidase generate toxic superoxide radical O_2^- and other reactive metabolites [37]. The intestine is especially vulnerable since the gut is rich in xanthine oxidase [38]. These metabolites may damage membrane lipids, nucleic acids, enzymes and receptors with impaired cellular function, eventually leading to necrosis. This injury of the enterocytes and leucocytes triggers local, as well as systemic, inflammatory response with subsequent release of pro-inflammatory substances. Neutrophils are also a source of cytotoxic enzymes and reactive oxygen metabolites as NADPH oxidase in neutrophils reduces O_2 to O_2^- . The radical oxygen metabolites also attracts polymorph nuclear leucocytes to the intestinal microvasculature, promoting adherence to the endothelium resulting in endothelial injury and increased microvascular permeability [37].

Sepsis and splanchnic perfusion

Septic shock is characterized by profound vasodilation and an increase in cardiac output. The underlying pathophysiology has not yet been fully elucidated, but it is generally accepted that hypotensive shock is related to the release of proinflammatory mediators, resulting in vasodilation and vasoplegia. The final common pathway of most inflammatory cascades is production of nitric oxide (NO). Under physiologic conditions, NO is produced from L-arginine by a calcium-dependent, rate-limited constitutive NO synthase, cNOS. cNOS is shear stress sensitive and mainly responsible for regulation of local vascular tone. Under septic conditions, inducible NO synthase (iNOS), with a maximum turnover rate that is only limited by substrate availability, is expressed. This enzyme is part of the non-specific host defence and thrives to produce cytotoxic amounts of NO. NO produced by ubiquitously expressed iNOS, causes general vasodilation rather than local vasodilation [39]. The vasoconstrictive response to α_1 -adrenergic agonists is lower in sepsis and the dosages of α_1 -adrenergic catecholamines needed to achieve an increase in MAP, are much higher in septic than in non-septic state [40]. NO synthase inhibition by L-NAME in septic vasodilatory animals can restore the decreased NE response in sepsis [41], suggesting that NO release attenuates the effects of NE. The number of α_1 -adrenergic receptors on the cell surface is reduced during severe sepsis [42] and α_1 -mediated calcium influx is reduced leading to less contractile response in sepsis [43].

The ratio between global splanchnic blood flow and cardiac index may be normal or even elevated in septic patients ranging from 23% to 31% [44-46],

compared to 21% -25% in non-septic postcardiac surgery patients [28, 47], and in healthy volunteers [48]. Under different conditions of low cardiac output, the global splanchnic perfusion is reduced in proportion to the reduction in systemic blood flow in non septic animals [49] and subjects [48].

The liver is believed to be relatively well protected against hypoperfusion because of the hepatic buffer response [50]. During sepsis, splanchnic tissue oxygenation may be at risk due to elevated metabolic demand despite the increase in splanchnic blood flow [51].

Regional changes of perfusion are possible mechanisms for protecting more vulnerable areas. Thus, in experimental hyperdynamic sepsis, the blood flow in the superior mesenteric artery is preserved or even increased while a reduction of blood flow in the celiac trunk occur [52].

The intestinal mucosal perfusion during hypodynamic experimental porcine septic shock remain virtually constant despite a reduction in regional blood flow by 50% [53, 54]. Redistribution of microcirculatory blood flow away from the muscularis layer toward the mucosa is an important regulatory mechanism to maintain blood flow to the intestinal mucosa during hypodynamic septic shock [55]. In early septic shock, autoregulation of blood flow in the intestinal wall is largely intact [53].

Data on intestinal mucosal perfusion in patients with vasodilatory shock and multiple organ failure are not available.

Vasoactive drugs and splanchnic perfusion

Adrenergic agents may have significant effects on splanchnic perfusion and oxygen extraction capabilities in septic and non-septic conditions. Norepinephrine is the recommended agent and commonly used agent for treatment of hypotension in volume-resuscitated hyperdynamic septic shock [56, 57], and to correct hypotension in the vasodilatory shock syndrome after cardiac surgery with cardiopulmonary bypass [58-61]. Norepinephrine has α_1 -agonistic as well as β_1 - and β_2 -agonistic properties and elevates systemic perfusion pressure mainly by an increase in systemic vascular resistance but also to some extent by an increase in cardiac output in patients with septic shock [62]. Splanchnic blood flow seems to be well maintained during vasopressor therapy with norepinephrine in these patients [63-65]. It has been shown in man that there is no consistent association between global splanchnic blood flow and local intestinal mucosal perfusion evaluated by laser Doppler flowmetry or gastric mucosal perfusion assessed by gastric tonometry [28]. The lack of correlation between intestinal mucosal perfusion and splanchnic blood flow may thus indicate that global measurements of oxygen delivery

across the whole splanchnic region do not necessarily reflect the degree of oxygenation or perfusion of the mucosal layer [28], the probably most vulnerable portion of the intestinal wall [34]. The fact that norepinephrine does not seem to jeopardize global splanchnic perfusion in patients with septic shock does not necessarily mean that vasopressor therapy with norepinephrine is harmless in terms of intestinal mucosal perfusion as norepinephrine might redistribute blood flow away from the mucosa. The effect of norepinephrine on human intestinal mucosal perfusion has not been evaluated neither in septic nor non-septic patients.

In septic shock patients, Reinelt et al studied the effects on splanchnic perfusion of the pure α_1 -receptor agonist phenylephrine. Replacement of norepinephrine with phenylephrine caused a lowered global hepato-splanchnic perfusion while hepato-splanchnic metabolism remained unaltered [66]. The balance between the β_2 -dilating and the α_1 -constricting properties of norepinephrine could explain why splanchnic blood flow is maintained during norepinephrine in sepsis. The presence and magnitude of this potential β_2 -mediated vasodilatory action of norepinephrine or phenylephrine on the intestinal mucosa has not been elucidated in man.

The use of epinephrine in septic shock is not recommended [57], as it has been shown that epinephrine decreases splanchnic perfusion when compared to norepinephrine or dopamine alone [67] or when compared to a combined infusion of norepinephrine and dobutamine [68]. Dopamine increases cardiac output, oxygen delivery and splanchnic blood flow in hyperdynamic sepsis in man [45]. The splanchnic blood flow, expressed as a fraction of cardiac output, is increased by dopamine [69, 70], suggesting that dopamine redistributes flow to the splanchnic region. In postoperative patients, dopamine induces a more pronounced intestinal mucosal vasodilation than dobutamine [71], suggesting that dopaminergic receptors are important for the catecholamine-induced increase in splanchnic blood flow. The effect of norepinephrine in combination with dopamine on human intestinal mucosal perfusion is not yet evaluated.

In patients with volume-resuscitated vasodilatory shock the restoration of adequate perfusion pressure to a level that allows appropriate organ perfusion is the end-point of vasopressor therapy. The optimal perfusion pressure with respect to systemic, regional or local perfusion is, however, not yet established.

Cardiopulmonary bypass and splanchnic perfusion

Splanchnic oxygen delivery decreases during hypothermic cardiopulmonary bypass (CPB) due to haemodilution-induced decrease in arterial oxygen

content and a decreased [72, 73] or unchanged [74, 75] splanchnic blood flow. Splanchnic ischemia during CPB has been suggested to be a causal factor for the development of the systemic inflammatory response syndrome and multiple organ failure after cardiac surgery. The latter is speculated to be due to disruption of intestinal mucosal barrier function and translocation of endotoxins and microorganisms leading to a release of proinflammatory cytokines that contribute to organ ischemia-reperfusion injury [76-78]. This hypothesis has been supported by the results of studies on gastric mucosal perfusion during CPB in humans. Using the laser Doppler flowmetry (LDF) technique, it has repeatedly been shown that gastric mucosal perfusion decreases during CPB in humans [79, 80] also when systemic oxygen delivery was deliberately maintained at pre-bypass levels. Furthermore, it has been shown in an animal model that intestinal tissue perfusion during CPB is primarily dependent on CPB flow rate [81]. A linear relationship between CPB flow rate and intestinal tissue perfusion over a wide range of CPB flow rates was described, indicating a severely disturbed autoregulatory control of intestinal tissue perfusion [81]. This impairment of the intestinal autoregulatory control of blood flow, could to some extent explain how systemic hypotension might induce intestinal ischemia during CPB.

Using the LDF technique, it has been shown that the jejunal mucosal perfusion increases during mild hypothermic CPB in man [30, 82]. It is of importance to further characterize the behaviour of the human vascular bed of the intestinal mucosa during CPB with focus on the autoregulatory capacity of the intestinal mucosa.

AIMS

The overall aims of the investigations were:

To evaluate the intestinal mucosal microcirculatory effects of commonly used vasoactive agents, norepinephrine, phenylephrine and dopamine in patients. The first two studies were designed to evaluate the pharmacological effects of these agents in uncomplicated post-cardiac surgery patients. The third study was designed to evaluate whether the dose of norepinephrine was of importance for intestinal and global splanchnic perfusion in critically ill patients with severe vasodilatory shock, or not. The fourth investigation was performed to study the autoregulatory capacity of the human intestinal mucosa during cardiopulmonary bypass.

The specific aims were:

To evaluate the effect of norepinephrine alone and norepinephrine combined with dopamine on jejunal mucosal perfusion, gastric mucosal - arterial pCO₂ gradient and global oxygen demand/supply relationship after cardiac surgery

To evaluate the potential differential effects of norepinephrine an α_1 -, β_1 - and β_2 -receptor agonist, to the pure α_1 -agonist, phenylephrine, on jejunal mucosal perfusion, red blood cell velocity and mucosal haematocrit, gastric mucosal - arterial pCO₂ gradient and global oxygen demand/supply relationship after cardiac surgery

To study the effects of norepinephrine induced variations in mean arterial pressure on jejunal mucosal perfusion gastric mucosal - arterial pCO₂ gradient and global oxygen demand/supply relationship in patients with vasodilatory shock.

To investigate the autoregulatory capacity of the jejunal mucosa during non-pulsatile cardiopulmonary bypass in patients undergoing heart surgery.

MATERIALS AND METHODS

Ethical issues

All studies were approved by the Ethics Committee of the University of Göteborg. Informed consent was obtained from each patient. In paper III informed consent was obtained from the closest relative.

Patients and anaesthesia

Paper I-II

Postoperative patients after uncomplicated coronary artery bypass grafting were included in these studies. All patients underwent surgery for coronary artery disease and had left ventricular ejection fraction >50%. Eighteen patients with a mean age of 68 years were included in study I. In study II ten patients with a mean age of 66 years were included. The patients were premedicated with oral flunitrazepam (1mg), intramuscular morphine (5mg) and scopolamine (0.2mg). Anaesthesia was induced with thiopentone, 3-5 mg/kg, fentanyl, 5-7 µg/kg followed by pancuronium 0.1mg/kg and maintained by fentanyl 2-4 µg/kg and enflurane. Anaesthesia was maintained by propofol during cardiopulmonary bypass. Sedation was maintained postoperatively with infusion of propofol 4.8 ± 2.3 mg/kg/h in study I, and 3.4 ± 0.6 mg/kg/h in study II.

Paper III

Ten patients, nine male and one female, with a mean age of 71 ± 6 years (range 60-77) with vasodilatory shock and multiple organ failure with or without sepsis after cardiac surgery were included. SOFA score was >9 in all patients (range 9-15). Four patients had septic shock and six were studied early after surgery and considered to have post-cardiotomy vasodilatory shock. The following inclusion criteria were used: a) MAP < 70 mmHg despite optimal preload as assessed by right- and left- sided cardiac filling pressures and transoesophageal echocardiography, b) the need for norepinephrine to obtain a mean arterial pressure of ≥ 70 mmHg, c) cardiac index > 2.5 L/min/m² and d) the need for mechanical ventilation. All patients were sedated with fentanyl (43 ± 6 ng/kg/min) and midazolam (1.7 ± 0.2 µg/kg/min) during the study.

Paper IV

The study included ten patients, five male and five female, with a mean age of 75 years (range 51-84) undergoing elective cardiac valve surgery with or without coronary artery bypass grafting. Exclusion criteria were known diabetes mellitus, laboratory evidence of liver disease and carotid artery stenosis. Anaesthesia was maintained prior to CPB with an intravenous infusion of propofol 200-600 mg/h until the LDF catheter was positioned, and was then maintained with a combination of fentanyl (total dose, including the induction dose, $7.9 \pm 1.5 \mu\text{g/kg}$) and isoflurane. During CPB, anaesthesia was maintained by propofol (200-400 mg/h).

Systemic haemodynamics

Cardiac output was measured by the thermodilution technique, which is regarded as the clinical golden standard for estimation of cardiac output. The method applies the indicator-dilution principle, using cold saline as the indicator. The centrally injected volume of cold saline mixes with the blood in the right heart and results in a change in blood temperature over time recorded by a thermistor at the tip of the catheter in the pulmonary artery. Cardiac output was automatically calculated with a modified Stewart-Hamilton equation by the monitoring device. (Vigilance, Baxter Healthcare)

The pulmonary artery was catheterized with a 7 F pulmonary artery catheter (Baxter Healthcare, Irving, CA, USA). The correct position in the right or left pulmonary artery was confirmed by fluoroscopy. Cardiac output was measured in triplicate by 10-ml ice-cold saline injections randomly injected unrelated to the respiratory cycle. Pulmonary artery occlusion pressure (PAOP) as well as central venous pressure (CVP) were recorded at the time of the measurement of cardiac output. Heart rate (HR), cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI) were subsequently calculated. Body surface area (BSA) was calculated as $\text{BSA} = \text{weight}^{0.425} \times \text{height}^{0.725} \times 0.007184 \text{ (m}^2\text{)}$

All patients received a percutaneously inserted radial or femoral artery catheter (20G, 45mm, Becton Dickinson, Swindon, UK) and a 3 lumen central venous catheter (I-III) (7 F 20 cm Arrow, Reading, PA, USA). For measurements of invasive pressures mid-line axillary level was considered as the reference point. Arterial, venous and pulmonary artery pressures were continuously measured and stored into the Perisoft software using the analog output signal from the monitoring device (Marquette). The signal was digitalized by an analog-to-digital converter (Perimed Järfälla Sweden).

Samples of arterial and mixed venous blood were drawn simultaneously for analysis of haemoglobin (Hb), haematocrit (Hct), arterial (SaO₂) and mixed venous oxygen saturation (SvO₂), arterial (PaO₂) and mixed venous oxygen pressure (PvO₂) and arterial pH (pHa). Analyses were performed with automated blood gas analyzer (Synthesis 25, Instrumental Laboratories, Milano, Italia papers I and II, and ABL 725, Radiometer Copenhagen in papers III and IV)

Global oxygen delivery index (paper III) was calculated as the product of CI and arterial oxygen content (CaO₂). CaO₂ was calculated as $1.39 \times \text{Hb} \times \text{SaO}_2 + \text{dissolved oxygen} (\text{PaO}_2 \times 0.031)$. Global oxygen consumption was calculated as the difference between arterial and mixed venous oxygen content multiplied by cardiac index.

In paper IV, the CPB flow rate was delivered by the CPB device (Jostra HL20) using the analog output signal digitally converted and continuously recorded in the Perisoft software.

Splanchnic perfusion

Laser Doppler flowmetry

The laser Doppler instrument uses near-infrared monochromatic light to illuminate the mucosal tissue through an optic fibre. By collecting and analyzing the Doppler shifted and backscattered light, an estimation of perfusion can be made. The light is diffusely scattered into a hemisphere-shaped volume of the tissue in direct contact with the emitting optic fibre. The depth and radius of the hemisphere studied is depending on properties of the tissue and the equipment used. Light scattered into tissue containing blood vessels will meet moving blood cells. Depending on the speed and direction of the moving blood cells, a shift in the frequency of the reflected backscattered light will occur –the Doppler shift. The backscattered light is thus a summation of a variety of frequencies depending on angle and speed of the moving cells, and the non-changed frequency from static tissue. The mean change in frequency is approximately linearly related to the mean velocity of the moving cells in the tissue. The intensity of the reflected light at a certain frequency representing the mean Doppler frequency is linearly related to the volume fraction of moving red cells in the tissue –the mucosal haematocrit.

For measurement of jejunal mucosal perfusion in the four studies a laser Doppler flow meter was used (Periflux PF 4001, Perimed, Järfälla Sweden) which generates a red light with a wavelength of 780 nm. A custom made two-probe laser Doppler catheter (Perimed Järfälla Sweden) was made by the use of a nasogastric tube with a diameter of 5 mm. Each probe consists of three

triangular placed optical fibres with a diameter of 150 μm and a fibre centre separation of 200 μm . The two probes are incorporated in the catheter and placed at 23 and 123 mm from the tip of the catheter. One fibre emits light and the other two receives the Doppler shifted and backscattered light.

For measurements of jejunal mucosal perfusion, a time constant of 0.2 s and a bandwidth of 20-25 kHz were used and the sampling frequency was 32 Hz. Calibration of the probe was performed as recommended by the manufacturer at 0 PU on a plastic disc for optical zero and at 250 PU using motility standard latex solution.

Jejunal mucosal perfusion (JMP) is defined as number of red blood cells (RBC) $\times \text{area}^{-1} \times \text{time}^{-1}$. The laser Doppler equipment used in the present study has the ability to separately analyze the two components of the JMP: jejunal mucosal haematocrit (JMht), defined as the number of RBC $\times \text{volume}^{-1}$, and red blood cell velocity, defined as $\text{length} \times \text{time}^{-1}$. The JMP is thus the product of the JMht and RBC velocity. All the JMP, JMht and RBC velocity values presented study were calculated from periods of intestinal quiescence. (Figure 1)

In paper I, III and IV, JMP is calculated as the mean of the two probes during periods of intestinal quiescence. In paper II one probe was used. The variables RBC velocity and JMht were measured in paper II, III and IV. The amplitude and frequency of the cyclic oscillation in JMP were studied in paper IV.

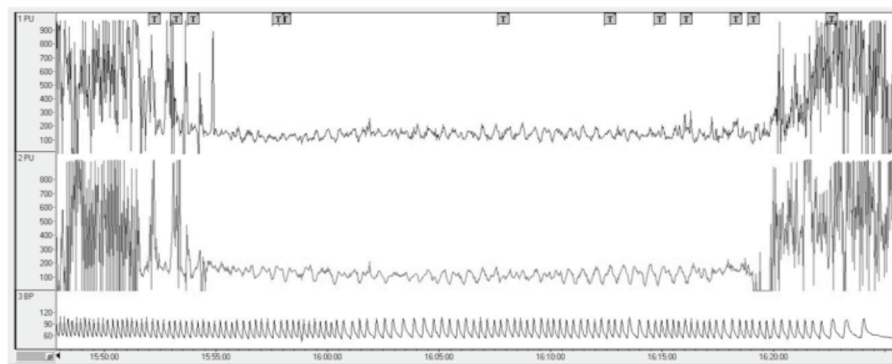


Figure 1 A representative, 40 minute, registration of the two laser Doppler flow probes (1PU, 2PU) during intestinal quiescence in a postoperative patient. The third registration represents arterial pressure (BP), subjected to interference artefacts due to the sampling frequency of 32 Hz. Artefacts in JMP at the beginning and end of the registration is due to peristalsis caused by the migrating motor complex (MMC), Note the cyclic oscillation in JMP (vasomotion).

Tonometry (paper I-III)

Gastric mucosal $p\text{CO}_2$ was measured every 10 min by using a standard tonometry nasogastric tube (TRIP, NGS tonometry catheter, Tonometrics, Helsinki, Finland) connected to an automated gas analyzer (Tonocap TC-200, Datex, Helsinki, Finland). The correct position of the tube was confirmed by fluoroscopy and continuous suction was applied to drain the stomach of air and gastric juice. The semi-permeable air-filled silicon balloon equilibrates with the mucosal $p\text{CO}_2$ within ten minutes and since there is a linear relation between $p\text{CO}_2$ and tissue content of CO_2 under stable conditions, changes in gastric $p\text{CO}_2$ reflect the relation between $p\text{CO}_2$ production (metabolism) and perfusion. The gastric mucosal - arterial $p\text{CO}_2$ gradient is calculated as the difference between arterial and gastric mucosal $p\text{CO}_2$.

Measurements of splanchnic oxygen extraction

One of the hepatic veins was catheterized via the right jugular vein with a 7 F pulmonary artery catheter (Baxter Healthcare, USA) during fluoroscopic guidance. The catheter was inserted into a wedge position and then withdrawn 1-2 cm. Drawing blood samples from the tip of the catheter was at all times easy to perform for analysis of hepatic venous oxygen saturation and lactate concentration.

Blood gas analyses were performed with automated blood gas analyzer (Synthesis 25, Instrumental Laboratories, Italy). Splanchnic oxygen extraction was calculated as: $\text{Splanchnic O}_2 \text{ extraction} = (\text{SaO}_2 - \text{SHvO}_2) / \text{SaO}_2$. Increase in oxygen extraction is caused by either increased oxygen utilization by increased metabolism and/or decreased oxygen supply by decreased perfusion. The splanchnic oxygen- mixed venous oxygen gradient is the difference between SHvO_2 and SvO_2 . A change in this gradient indicates a change in distribution of perfusion to or from the splanchnic region.

Measurements of splanchnic lactate extraction

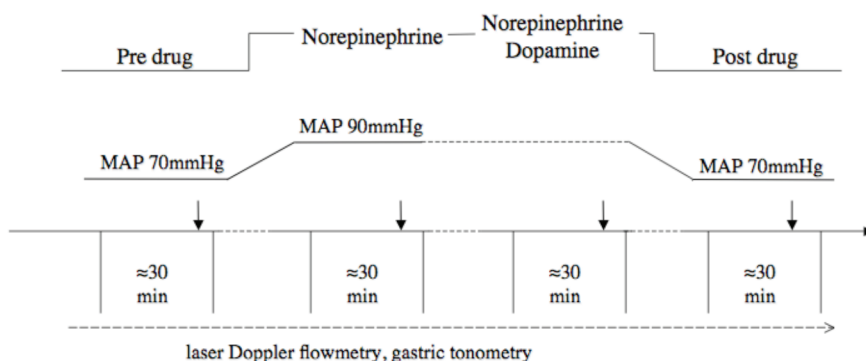
Lactate concentrations were determined in arterial (AL) and hepatic venous (HvL) blood using an enzymatic method (YSI 2300 Stat Plus, YSI, Yellow Springs, Ohio, USA). The blood samples were immediately centrifuged, pipetted and the plasma was frozen if not immediately analyzed. Splanchnic lactate extraction was calculated from standard formulae: $\text{Splanchnic lactate extraction} = (\text{AL} - \text{HvL}) / \text{AL}$.

Experimental procedures

Paper I

The protocol consisted of four study periods (figure 2): 1) a pre drug control period at a stable MAP level of approximately 70 mmHg, 2) norepinephrine infusion at an infusion rate needed to reach a target MAP of approximately 90 mmHg, 3) during steady state norepinephrine infusion, a low-dose dopamine was started with a target dose of 3 µg/kg/min and 4) post drug control measurements were performed after a washout period of 120 min. Each of the four periods consisted of a 30-min measurement period preceded by a 20–30-min period for dose titration (period 2 and 3). JMP was continuously recorded during the four periods and mean JMP was calculated during intestinal quiescence. Gastric mucosal pCO₂ was measured every 10 min. Systemic haemodynamics were measured and samples for blood gas analysis, lactate, and haemoglobin concentrations were drawn at the end of each measurement period.

Figure 2

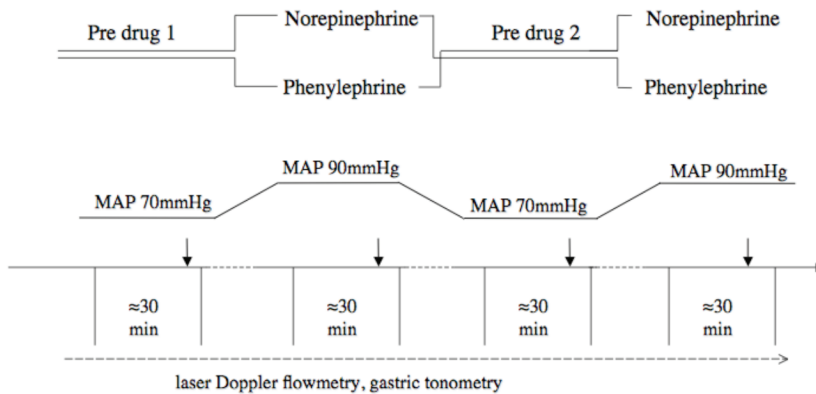


Paper II

Each patient received sequentially and randomly both norepinephrine and phenylephrine in a crossover study design (Figure 3). The infusion rate of each vasopressor was titrated to a target MAP of 90 mmHg. The protocol thus consisted of four periods: 1) a predrug control period at a stable MAP of 65–75 mmHg; 2) infusion of the first vasopressor; 3) a second predrug control period after a washout period of 60 minutes; 4) infusion of the second vasopressor. Each of the four periods consisted of a 30 minutes measurement period preceded by a 10–20 minute period for dose titration (period 2 and 4).

JMP, JMht and RBC velocity were continuously recorded during the four periods and mean values were calculated during intestinal quiescence. Gastric mucosal $p\text{CO}_2$ was measured every 10 minutes and the mean value for each sampling period was calculated. Systemic haemodynamics was measured and samples for blood gas analysis, lactate and haemoglobin concentrations were taken at the end of each period.

Figure 3

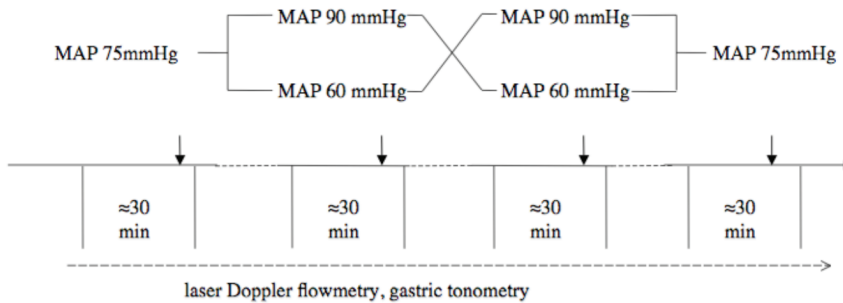


Paper III

After entering into the study, the patient's norepinephrine dose was adjusted to attain a MAP of 75 mmHg. Vascular pressures as well as jejunal mucosal perfusion were continuously measured for 30 minutes. The infusion rate of norepinephrine was then randomly increased or decreased to obtain a 30 min sampling period at a MAP of 60/90 mmHg and a 30 min period at a MAP of 90/60 mmHg. (Figure 4) Thereafter, a post-intervention period of 30 min at a MAP 75 mmHg was obtained. The inotropic medication was not changed during the experimental procedure.

JMP, RBC velocity and JMht were continuously recorded during the four periods and mean values were calculated during intestinal quiescence. Gastric mucosal $p\text{CO}_2$ was measured every 10 min and the mean value for each 30-min period was calculated. Systemic haemodynamics were measured and samples for blood gas analysis, lactate, and haemoglobin concentrations were performed at the end of each measurement period.

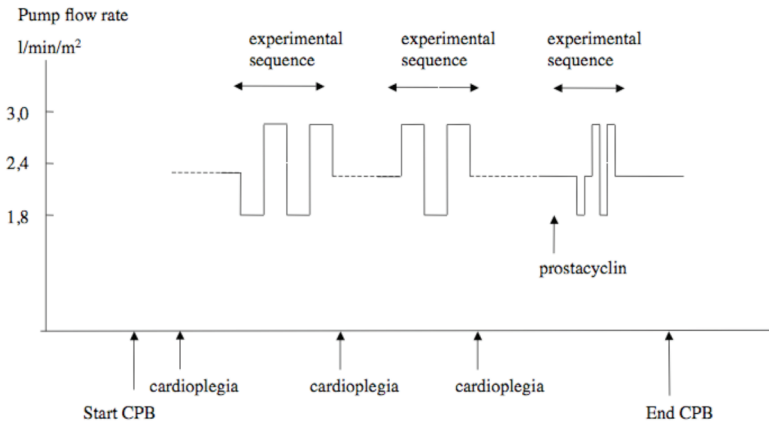
Figure 4



Paper IV

At a body temperature of 34°C and a CPB flow rate index of 2.4 L/min/m², MAP, JMP, JMHt and RBC flow velocity, as well as CPB flow rate were continuously recorded (baseline). Approximately 5 minutes after the first administration of cardioplegia, 15-20 minutes after start of CPB, the patients were subjected, in random sequence, to 3-min periods of low CPB flow rate (1.8 L/min/m²), standard CPB flow rate (2.4 L/min/m²) and high CPB flow rate (3.0 L/min/m²) (Figure 5). In each patient, this CPB flow rate variation procedure was performed 1-3 times, depending on the duration of the operation. Thereafter, at a CPB flow rate of 2.4 L/min/m², systemic vasodilation was induced by an intravenous injection of prostacyclin 10 µg (Flolan®, GlaxoSmith Kline) and then the maximal change in MAP and JMP were recorded. During the prostacyclin-induced vasodilation, the CPB flow rate was again randomly altered, as described above, but now only for periods of 30 seconds at each CPB flow rate. Intravenous injections of prostacyclin were repeated 1-2 times depending on the duration of the surgical procedure. (Figure 5)

Figure 5



Statistics

Paper I

A Kolmogorov-Smirnov test for goodness-of-fit to normal distribution was performed and normality was obtained for all main measurements.

Analysis of variance for repeated measurements (ANOVA) followed by post-hoc single-degree of freedom comparisons (contrast analysis) were used to evaluate the effects of norepinephrine alone vs. control and the effects of norepinephrine + dopamine vs. norepinephrine and for comparing control and post drug control periods. A linear regression analysis was performed to evaluate the relationship between the individual norepinephrine dose and absolute changes in splanchnic oxygen extraction, jejunal mucosal perfusion, and the gastric mucosal - arterial $p\text{CO}_2$ gradient. The group was arbitrarily divided into two subgroups depending on cardiac index at baseline (< 2.4 L/min/m² or ≥ 2.4 L/min/m²). A Mann Whitney test was performed to test difference between the groups with regard to dose of norepinephrine.

Paper II

As in paper I, a Kolmogorov-Smirnov test for goodness of fit to normal distribution was performed and all main measurements showed normal distribution. A two-way ANOVA followed by contrast analysis were used to evaluate: a) the effects of each vasopressor vs. their respective control (within-group comparison), b) the effects of phenylephrine vs. those of norepinephrine (between-group comparison) and c) for comparing the control periods preceding norepinephrine to the control period preceding

phenylephrine. To evaluate the effect of time on various variables, a paired t-test was performed on the first and the second predrug control period.

Paper III

Analysis of variance for repeated measurements (ANOVA) as well as linear trend tests were used to evaluate the effects of norepinephrine-induced variations in perfusion pressure on measured variables. Pre- and post-intervention values were compared using a paired Student's t-test.

Paper IV

Student's paired t-tests were performed for comparing PaO_2 , PaCO_2 , mixed venous oxygen tension (SvO_2), haematocrit and body temperature before and after the experimental procedure and to evaluate the effects of prostacyclin on JMP and MAP. ANOVA followed by contrast analysis was used to evaluate the effects of variations in CPB flow rate on MAP, SVRI, SvO_2 , JMP, JMHT, RBC flow velocity, and vasomotion frequency and amplitude. Mean values for each patient were obtained at each CPB flow rate if more than one CPB flow rate variation procedure was performed. A correlation within subject analysis [83] was also performed to evaluate a potential correlation between MAP and JMP during CPB flow variations, without and with prostacyclin

RESULTS

Paper I

Systemic haemodynamics (Figure 6): Norepinephrine (NE) at an infusion rate of 50 ± 26 ng/kg/min was needed to increase MAP from 70 to 90 mmHg. SVRI increased by 33%. Cardiac filling pressures increased slightly while CI, HR or SVI did not change. Addition of dopamine caused an increase in CI (27%), SVI (10%) and HR (16%) with no change in MAP, while SVR decreased (23%). There was a slight increase in temperature and cardiac index accompanied by systemic vasodilation over time during the postoperative recovery.

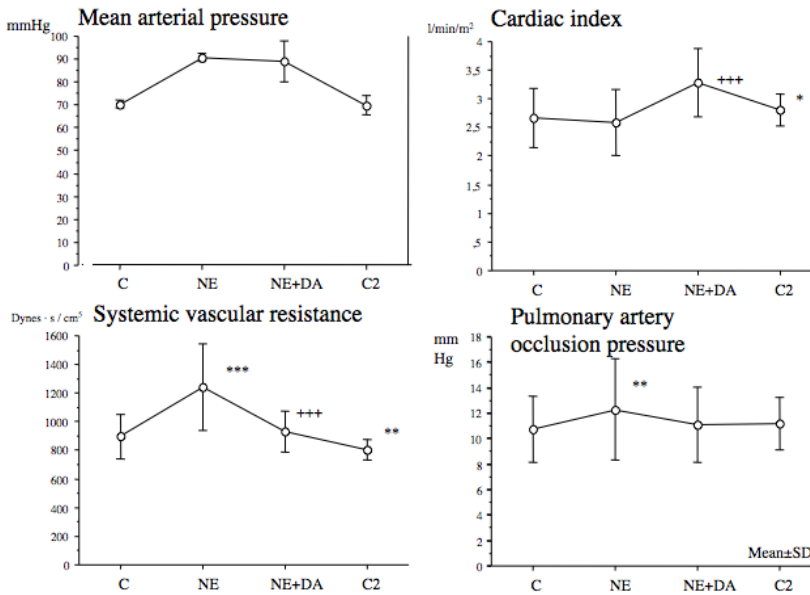


Figure 6 Systemic effects of norepinephrine (NE) and norepinephrine in combination with dopamine (DA). C=control period.

* $p=0.05$ vs. control, ** $p<0.01$ vs. control, *** $p<0.001$ vs. control

Splanchnic perfusion: (Figure 7) The increase in SVRI and the subsequent increase in MAP caused by norepinephrine did not cause any change in JMP. Splanchnic O_2 extraction increased, indicating a global splanchnic vasoconstriction.

In the subgroup of patients ($n=9$) with the lowest cardiac index, ($CI < 2.4$, mean $CI=2.1 \pm 0.2$ L/min/m²) norepinephrine induced a significant increase in splanchnic O₂ extraction from $36 \pm 4\%$ to $43 \pm 11\%$ ($P < 0.05$), which was not seen in the subgroup of patients ($n=9$) with high baseline cardiac index ($CI > 2.4$, mean $CI=2.8 \pm 0.4$ L/min/m²) ($42 \pm 9\%$ to $42 \pm 10\%$, n.s.). A linear regression analysis revealed a positive correlation between the individual dose of norepinephrine and the absolute increase in splanchnic oxygen extraction ($r=0.78$, $P < 0.0001$), (Figure 8). The dose-dependent increase in splanchnic oxygen extraction was obvious in those who had the lowest cardiac ($r=0.84$, $p < 0.01$), and could not be seen in the group of patients with high cardiac index ($r=0.11$, n.s.). Patients with high cardiac index tended to need less norepinephrine (39 ± 8 ng/kg/min), than those with low cardiac index (60 ± 33 ng/kg/min) ($p=0.064$) to reach the target MAP. There was no relation between individual dose of norepinephrine and change in JMP. (Figure 9)

Addition of dopamine caused a systemic as well as intestinal mucosal vasodilation. Splanchnic O₂ extraction decreased indicating splanchnic vasodilation.

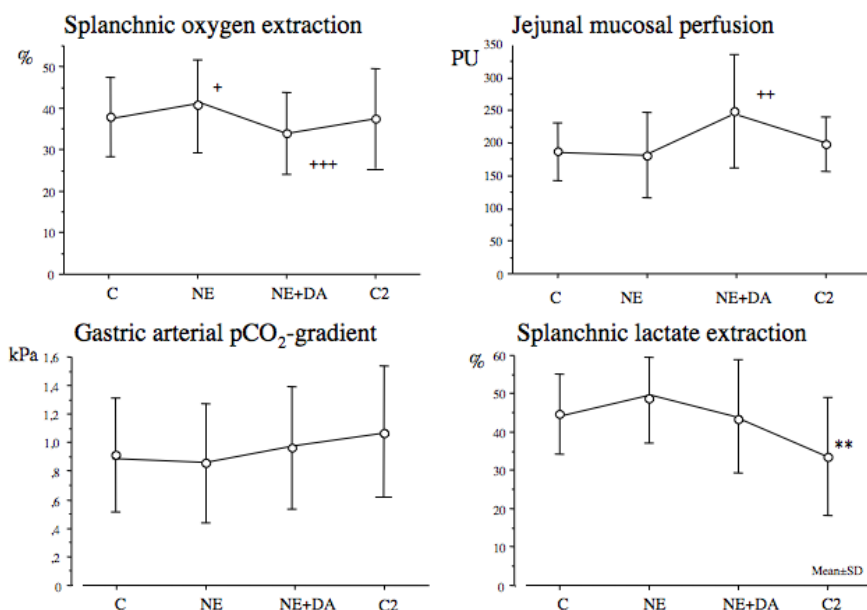


Figure 7 Splanchnic perfusion during infusion of norepinephrine (NE) and infusion of norepinephrine plus low dose dopamine (DA). C=control period.

* $p = 0.05$ vs. control, ** $p < 0.01$ vs. control, *** $p < 0.001$ vs. control

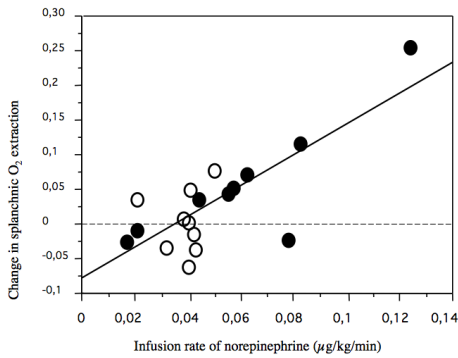


Figure 8 A linear regression analysis relating the individual dose of norepinephrine to the norepinephrine-induced change in splanchnic oxygen extraction. There was a significant relation between individual dose of norepinephrine and change in splanchnic oxygen extraction. Filled circles represent patients with the lowest Cardiac index ($CI < 2.4 \text{ L/min/m}^2$).

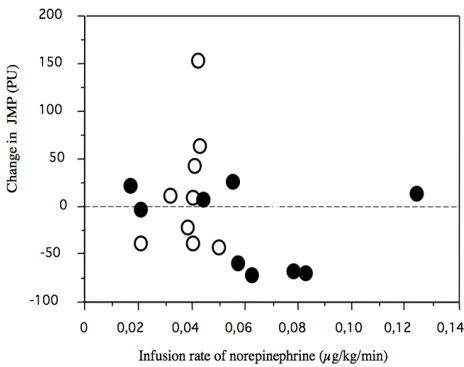


Figure 9 A linear regression analysis relating the individual dose of norepinephrine to the change in JVP. There was no significant relation between individual dose of norepinephrine and change in JVP. Filled circles represent patients with the lowest cardiac index ($CI < 2.4 \text{ L/min/m}^2$).

Paper II

Systemic haemodynamics (Figure 10): Norepinephrine at an infusion rate of $0.052 \pm 0.009 \mu\text{g/kg/min}$ (range $0.021\text{--}0.124 \mu\text{g/kg/min}$) and phenylephrine at an infusion rate of $0.50 \pm 0.22 \mu\text{g/kg/min}$ (range $0.21\text{--}0.94 \mu\text{g/kg/min}$) were used to elevate the MAP from 70 to 90 mmHg. Norepinephrine and phenylephrine induced an increase in SVR by 40% and 46% respectively. CVP and PAOP increased while CI, stroke volume and heart rate did not change by the drugs

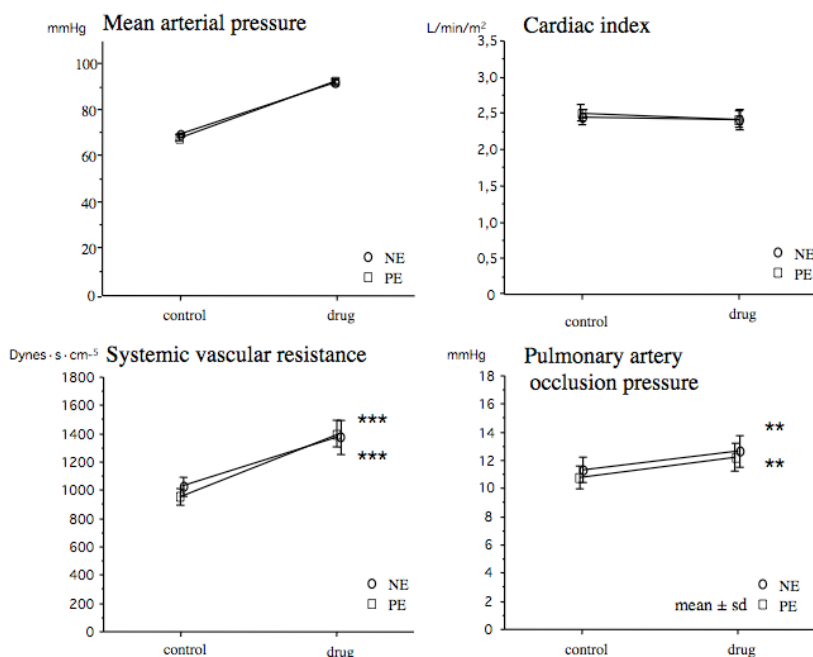


Figure 10 Systemic haemodynamic changes during infusion of norepinephrine (NE) and phenylephrine (PHE). ** $p < 0.01$ vs. control, *** $p < 0.001$ vs. control

Splanchnic perfusion: (Figure 11) An individual recording of JMP, JMHT and RBC velocity and MAP during infusion of norepinephrine is provided in figure 12. Neither JMP, nor the two variables RBC velocity and JMHT were affected by the vasopressors. Splanchnic oxygen extraction increased with both drugs. PHE caused a significantly greater increase in splanchnic oxygen extraction than norepinephrine ($p < 0.05$). There was a tendency for an increase in splanchnic lactate extraction with both vasopressors (ANOVA $p = 0.059$). None of the vasopressors induced individual lactate production. No apparent difference in response to vasopressors between patients with or without

previous hypertension was observed in JMP, gastric mucosal - arterial $p\text{CO}_2$ difference or splanchnic oxygen extraction. An individual registration of JMP, JMht and RBC velocity and MAP during infusion of norepinephrine is provided in figure 12

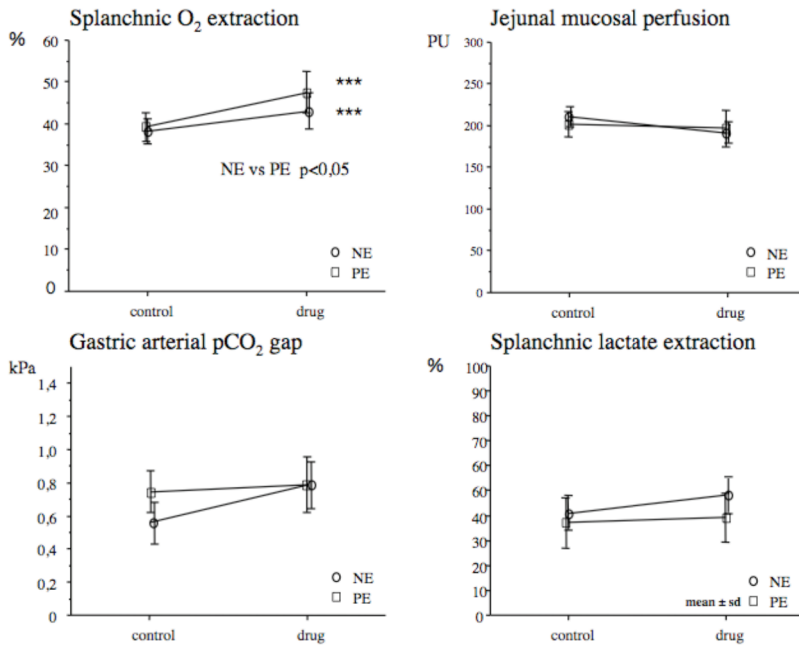


Figure 11. Splanchnic perfusion during norepinephrine (NE) and phenylephrine (PHE) infusion. Splanchnic oxygen extraction increased with both drugs, the increase was significantly more pronounced with phenylephrine ($p < 0.05$) *** $p < 0.001$ vs. control

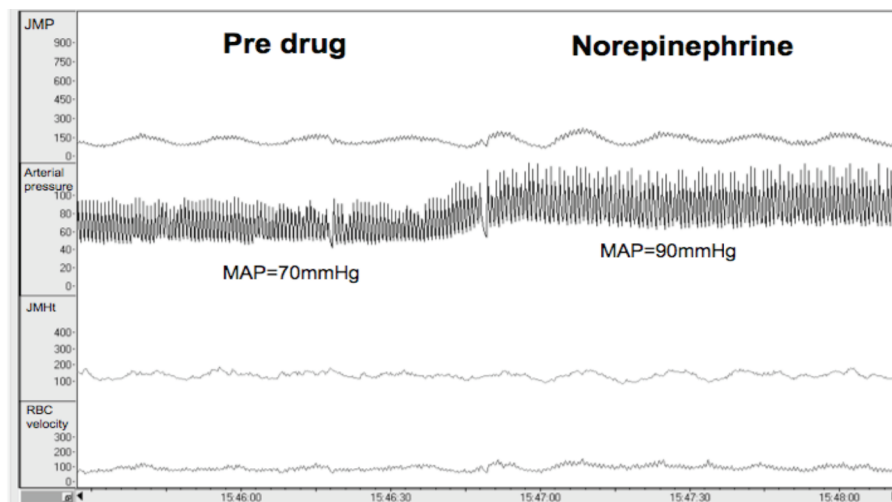


Figure 12 This figure shows an individual recording of JMP, arterial pressure, JMHt and RBC velocity during norepinephrine infusion to increase MAP from 70 to 90 mmHg. Note that the level of JMP, JMHt and RBC velocity is not changed. However, there is an increase in vasomotion amplitude and frequency, which could be a part of the intestinal mucosal autoregulatory response.

Paper III

Systemic haemodynamics (Table 1): The norepinephrine-induced elevation in MAP (from low to high) was accompanied by a significant increase in systemic vascular resistance index (39%), cardiac index (12%), stroke volume index (11%), global oxygen delivery (21%) mixed venous oxygen saturation (6%), central venous pressure (16%) and pulmonary artery occlusion pressure (36%), while global oxygen extraction decreased. There were no significant changes in heart rate or global oxygen consumption. Haemoglobin and haematocrit increased significantly with norepinephrine (7.8%, 7.3% respectively). Arterial lactate tended to increase with increasing norepinephrine infusion rates. Body temperature was unchanged during the experimental procedure ($37.8 \pm 1.0^\circ\text{C}$ to $37.9 \pm 1.0^\circ\text{C}$). Pre-and post-intervention values of the various systemic variables did not differ significantly.

	Target MAP			ANOVA	Linear trend test
	Low	medium	high		
Infusion rate of NE ($\mu\text{g/kg/min}$)	0.25 \pm 0.24	0.37 \pm 0.21	0.55 \pm 0.39	-	-
Mean arterial pressure (mmHg)	62 \pm 3	76 \pm 2	91 \pm 2	-	-
SVRI ($\text{dynes}\cdot\text{s/cm}^5/\text{m}^2$)	1456 \pm 269	1764 \pm 306	2018 \pm 327	0.0001	0.0001
Cardiac index (L/min/m^2)	2.7 \pm 0.3	2.9 \pm 0.4	3.1 \pm 0.5	0.0076	0.0021
CVP (mmHg)	12.9 \pm 2.5	13.6 \pm 2.5	15.0 \pm 2.0	0.0002	0.0001
PAOP (mmHg)	16.8 \pm 4.8	19.0 \pm 4.2	22.9 \pm 4.1	0.0006	0.0002
Stroke volume index (ml/m^2)	29 \pm 7	31 \pm 7	32 \pm 8	0.056	0.021
Heart rate (bpm)	97 \pm 13	95 \pm 11	98 \pm 13	0.38	0.44
Systemic O_2 delivery index (mL/min/m^2)	374 \pm 49	422 \pm 54	452 \pm 74	0.0002	0.0001
Systemic O_2 consumption index (mL/min/m^2)	127 \pm 15	131 \pm 19	135 \pm 15	0.22	0.09
Systemic oxygen extraction (%)	34.7 \pm 7.2	31.5 \pm 5.9	30.6 \pm 7.7	0.0015	0.0006
Mixed venous oxygen saturation (%)	63.2 \pm 6.8	66.7 \pm 6.1	67.2 \pm 7.9	0.0007	0.0004
Haemoglobin (g/L)	102 \pm 13	108 \pm 13	110 \pm 13	0.0001	0.0001
Haematocrit (%)	31.5 \pm 3.9	33.1 \pm 4.0	33.8 \pm 4.0	0.0001	0.0001

Table 1 Systemic effects of norepinephrine-induced variations in mean arterial pressure (MAP) in patients with vasodilatory shock

Splanchnic perfusion (Table 2): Increasing doses of norepinephrine did not affect JMP or its components JMHT or RBC velocity. Neither gastric-arterial mucosal pCO₂ gradient nor gastric mucosal pH was affected by variations in norepinephrine infusion rate. Splanchnic oxygen extraction, hepatic venous oxygen saturation and mixed venous – hepatic venous oxygen saturation gradient were not significantly affected by increasing doses of norepinephrine. Hepatic vein lactate or splanchnic lactate extraction were not affected by variations in norepinephrine dose while arterial lactate tended to rise. Pre- and post-interventional values of the various splanchnic variables did not differ significantly

	Low	Target MAP medium	high	ANOVA	Linear trend test
JMP (PU)	276±68	294±74	278±57	0.36	0.85
JMHT (AU)	298±57	281±47	273±46	0.20	0.08
RBC velocity (AU)	96±17	105±19	107±14	0.21	0.11
Gastric mucosal – arterial pCO ₂ gradient (mmHg)	2.2±0.8	2.0±0.7	2.1±0.9	0.38	0.62
Splanchnic O ₂ extraction (%)	71.2±18.4	70.4±18.5	68.3±20.1	0.32	0.15
Hepatic venous O ₂ saturation (%)	28.0±17.9	28.9±18.2	29.3±19.5	0.61	0.34
Mixed venous–hepatic venous O ₂ gradient (percent unit)	35.2±13.5	37.8±14.2	37.9±14.2	0.098	0.054
Arterial lactate (mmol/l)	1.43±0.53	1.54±0.56	1.57±0.52	0.084	0.034
Hepatic vein lactate (mmol/l)	1.02±0.58	1.01±0.66	1.08±0.61	0.79	0.59
Splanchnic lactate extraction (%)	32±18	38±21	34±25	0.56	0.68

Table 2 Splanchnic effects of norepinephrine-induced variations in mean arterial pressure (MAP) in patients with vasodilatory shock.

Paper IV

Seventeen sequences of variation in CPB flow rate were performed in the ten patients. In six patients we were able to repeat the CPB flow rate variation procedure at least once. The autoregulatory response to flow rate variations did not differ between the first and the subsequent CPB flow variation. MAP and SvO₂ increased while SVRI decreased with higher CPB flow rates. JMP, JMHt, and RBC flow velocity were unchanged during the variations in CPB flow rate index. In all patients, SvO₂ was $\geq 70\%$ at a CPB flow rate of 1.8 L/min/m². Individual data on the relation between changes in MAP and changes in JMP are seen in Figure 13a. There was no significant within-subject correlation between MAP and JMP ($r=0.06$ $p=0.58$).

Cyclic oscillation in JMP (vasomotion) was seen in all patients during CPB and was present during $72 \pm 18\%$ of the recorded time. (Figure 14) Both vasomotion frequency and amplitude increased with higher CPB flow rates.

Six patients received 13 bolus doses of prostacyclin at a CPB flow rate index of 2.4 L/min/m². Prostacyclin abolished the vasomotion waves (an individual registration is shown in figure 15) while JMP increased from 192 ± 53 to 277 ± 70 PU ($p < 0.05$) despite a reduction in MAP from 59 ± 12 to 45 ± 10 mmHg ($p < 0.05$). During prostacyclin-induced vasodilation, CPB flow rate variations caused changes in perfusion pressure within a range of 30-69 mmHg. A within-subject positive correlation between MAP and JMP ($r=0.66$, $p < 0.0001$) was demonstrated during prostacyclin-induced vasodilation, indicating that JMP was pressure-dependent (Figure 13b).

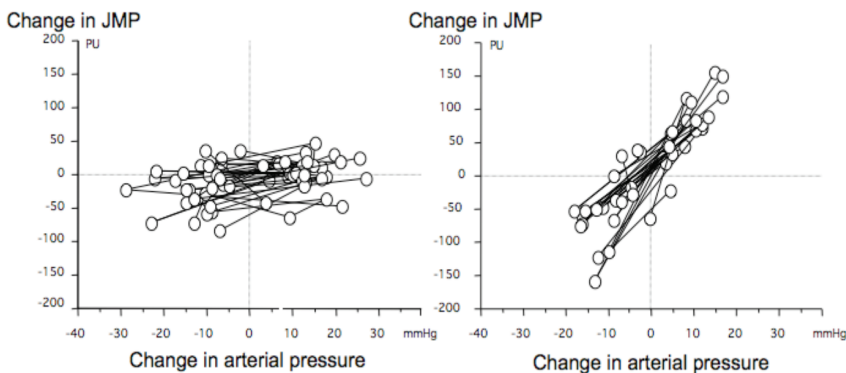


Figure 13 a) without prostacyclin

b) with prostacyclin

The figure shows the individual changes in JMP for each change in arterial pressure induced by changes in CPB flow. a) Without prostacyclin and b) during prostacyclin induced vasodilation. Note that in a) there are no obvious changes in JMP at a certain change in arterial pressure indicating an intact autoregulation and in b) JMP is pressure-dependent

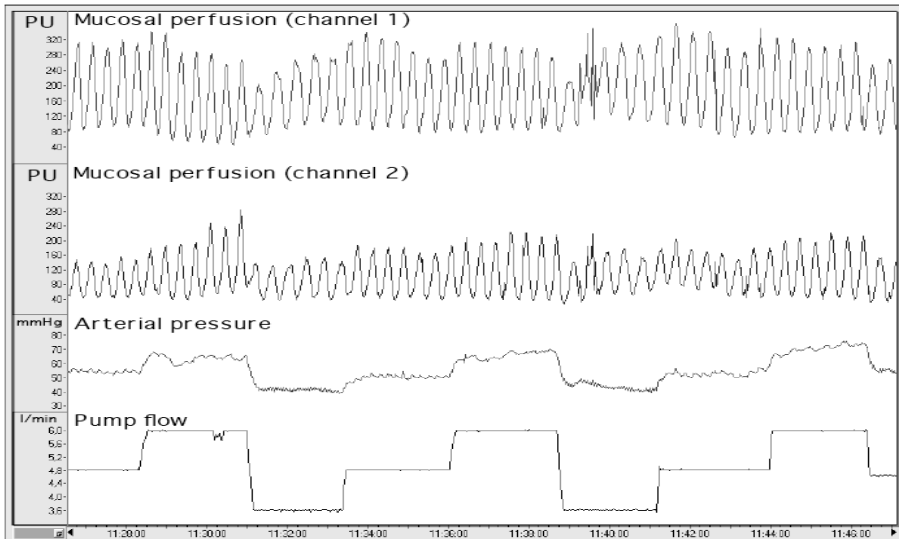


Figure 14 This 20 minute registration shows how variations in CPB flow affect arterial pressure and JMP. Note that arterial pressure increases with increasing CPB flow while the level of JMP is not changed. The cyclic oscillation has a higher amplitude and frequency during high CPB flow and pressure.

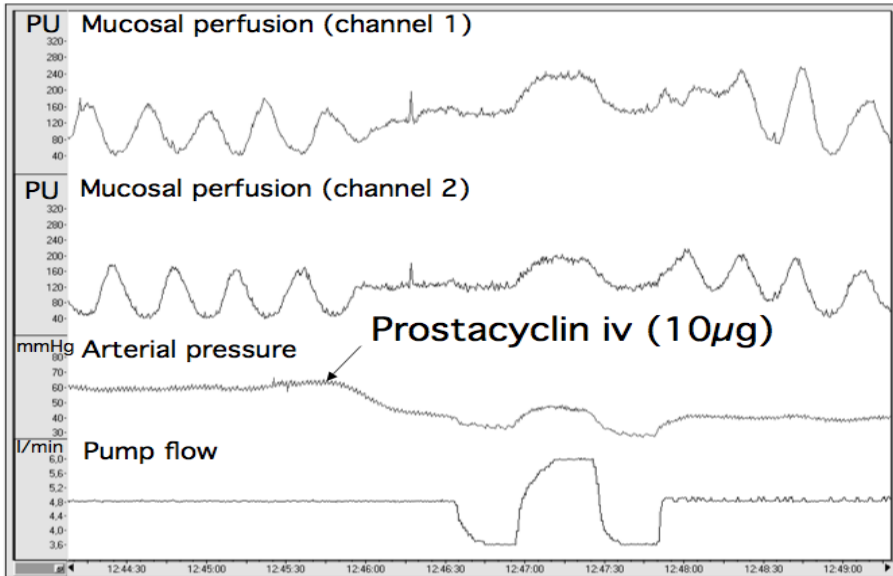


Figure 15 This individual registration shows the effects of one intravenous injection of prostacyclin, 10 µg, on JMP and arterial blood pressure, during CPB. Typical cyclic oscillations of JMP are seen prior to prostacyclin injection. Prostacyclin induced a systemic vasodilation, blunted the cyclic oscillations of JMP and increased JMP. During the influence of prostacyclin, variation in CPB flow rate induced parallel changes in arterial pressure and JMP.

Effects of vasopressors on haemoglobin and haematocrit (I-III)

There was a highly significant increase in haemoglobin (7.8%) and haematocrit (7.3%) with increasing infusion rates of norepinephrine (III). In paper I (unpublished data) norepinephrine caused an increase in haemoglobin by 4.0% (112 ± 12 - 117 ± 11 g/l, $p=0.0021$ t-test). In paper II (unpublished data) phenylephrine caused an increase in haemoglobin concentration by 5.0% (112 ± 14 - 117 ± 13 g/l, $p=0.0046$ t-test) and norepinephrine by 5.1% (113 ± 14 - 118 ± 12 g/l, $p=0.0019$ t-test).

GENERAL DISCUSSION

Methodological and experimental considerations

Ethical issues

Papers I and II were pharmacological studies on the effects of norepinephrine and phenylephrine on splanchnic perfusion in patients undergoing routine cardiac surgery. One could argue that elevation of blood pressure from 70 to 90 mmHg would increase the risk of reoperation because of postoperative bleeding in these patients. The highest acceptable systolic blood pressure level was, however, 150 mmHg during vasopressor infusion, which is our upper limit for clinical routine care of this patient group. None of the patients reached this upper limit and no patient was subjected to reoperation.

The optimal perfusion pressure with respect to systemic, regional or local perfusion is not yet established in patients with septic or postcardiotomy vasodilatory shock. We therefore considered it ethically justified, in paper III to vary mean arterial blood pressure between 60 and 90 mmHg, by adjusting the infusion rate of norepinephrine, in the critically ill patients with vasodilatory shock.

In paper IV, we investigated the jejunal mucosal capacity to autoregulate perfusion during non-pulsatile CPB (34°C). It could be argued that lowering CPB flow rate to 1.8 L/min/m² for 3-minute periods could have jeopardized organ perfusion in the present study. We consider this less likely as mixed venous oxygen saturation was $\geq 70\%$ in all patients at a CPB flow rate of 1.8 L/min/m². Pre bypass values of cardiac index and mixed venous oxygen saturation, at a body temperature of 35-36°C, were 2.1 ± 0.4 and $67 \pm 15\%$, respectively.

Population size

The population size was based on previous data on mucosal perfusion in postoperative patients. A statistical power analysis with a power of 0.80 and a significance level of 0.05, revealed a sample size of 8-10 to detect a 30 % change in JMP, which was regarded as significant.

Study design

In patients studied postoperatively (I, II) the recovery phase is dynamic with spontaneous changes in metabolism, body temperature and haemodynamics. We did not include a time-control group, but instead a comparison between the pre- and post-intervention study period was performed. One cannot therefore, completely rule out time-dependent changes influencing the results. In previous postoperative studies on cardiac surgical patients, mucosal perfusion was, however, shown not to be time-dependent [28, 71]. In papers I and II, there were no detected changes over time in the main variables studied. A crossover design (II, III) diminishes the influence of time-dependent effects, but have the limitations of possible carry over effects of the drug.

In paper IV, the autoregulatory capacity of the jejunal mucosa was studied at several occasions in some patients. One could argue that the autoregulatory capacity of the jejunal mucosa changes over time. On the other hand, the autoregulatory response to flow rate variations did not differ between the first and the subsequent CPB flow variation. The effects of prostacyclin on intestinal mucosal perfusion was studied only during the influence of bolus doses of prostacyclin, and not during a continuous steady-state infusion, which we were not able to obtain due to time restraint. However, the vasodilatory response to bolus prostacyclin lasted at least 90 seconds in all patients, during which time we were able to decrease/increase CPB flow rate from baseline.

Laser Doppler flowmetry

Laser Doppler flowmetry is an established method for measurement of mucosal, cutaneous and tissue perfusion both in experimental and in clinical situations [84]. In cardiac surgery patients, laser Doppler flowmetry has been used for measurement of gastric mucosal perfusion [79, 80, 85], and intestinal mucosal perfusion both during [30, 82], and after CPB [28, 71]. Laser Doppler flowmetry does not provide absolute blood flow values, but the laser Doppler flowmetry values correlate strongly to simultaneously obtained absolute blood flow values obtained by the total venous outflow technique both in humans [86], and in experimental settings [87]. Furthermore, the LDF values from the mucosal side of the jejunum correlate strongly with simultaneously obtained absolute mucosal blood measurements by hydrogen gas clearance and microsphere techniques [88] as well as electromagnetic flow probe technique [89]. There is also a high correlation between fluorescein flowmetry and laser Doppler flowmetry measured in human ileal mucosa [90]. One advantage of the LDF technique is that it is possible to measure mucosal perfusion continuously, whereas the drawback is that measurements can be performed only at a local site and during intestinal quiescence, because peristalsis causes motion artefacts. Other limitations are potential transposition

of the probe and loss of contact with the mucosa. However, intestinal motion is a smaller problem during anaesthesia compared to awake subjects [91] and the occurrence of peristalsis during CPB or sepsis is even more uncommon [4].

The measuring depth of the flow probe is dependent on both instrumental factors - fibre diameter, fibre separation and the wavelength of the light used and biophysical properties of the investigated tissue such as absorption and scattering of light. Studies on the influence of different probe designs, estimated the measuring depth to be less than 2.4mm for a probe with fibre diameter of 120 μ m, fibre separation 250 μ m and a wavelength of 633nm [92]. In our studies, a higher wavelength (780nm) and a wider fiber diameter (150 μ m) was used, suggesting a somewhat larger penetration depth, despite a shorter fibre separation (200 μ m). The thickness of human jejunal mucosa and submucosa is approximately 1.7-4.0 mm [93]. However, since the tissue volume under study is a hemisphere, most of the signal originates from the superficial, mucosal layers.

The endoluminal positioning of the catheter was performed during fluoroscopic guidance. Gastrointestinal motility is essential for proper positioning of the catheter in the jejunum. The perioperative use of opioids decreases gastric motility. Gastric motility was enhanced with cisapride (I and II) and erythromycin (III). Cisapride has an onset of 30 to 60 minutes and a plasma half time of 10 hours after oral administration. Theoretically, cisapride could therefore increase the problem with motion artefacts. Motility artefacts during the measurement period 6-10 hours after administration of cisapride was, however, not considered a problem. The postoperative patients had a fasting pattern of regular MMC with an interval of 30-40 min between each MMC. In these study populations, MMC was visually present in all postoperative subjects (I, II), while seen in only 5/10 septic patients (III) and not present during CPB (IV).

Paper III was performed after the withdrawal of cisapride from the market [94, 95]. Instead erythromycin 0.1-0.5g was infused during positioning of the jejunal catheter in five of the ten patients, in whom placement of the catheter was difficult. The effect of erythromycin is almost immediate and gastric emptying was observed visually by fluoroscopy only a few minutes after start of infusion. Erythromycin stimulates the motilin receptor, augmenting antroduodenal motility, particularly the aboral propagation mediated by phase III of the MMC [96]. The protocol started approximately three ours after administration and there were no obvious differences between those who received erythromycin and those who did not, with respect to JMP or the pattern of observed MMC-associated changes in the laser Doppler signal.

Gastric tonometry

The theoretical background for the use of tonometry is the assumption that CO_2 accumulates in the tissue during poor perfusion. The air in the balloon on the tip of the catheter, calibrates with within 10 minutes through the semipermeable silicon membrane with the gastric mucosal tissue pCO_2 [97]. Because there is a linear relation between gastric pCO_2 and tissue content of CO_2 under stable conditions, changes in gastric pCO_2 reflect the relation between pCO_2 production (metabolism) and perfusion. Gastric mucosal - arterial pCO_2 gradient is therefore taken to reflect the relationship between metabolism (CO_2 production) and perfusion [98]. This technique based on gastric tonometry has been used as a surrogate technique for the assessment of hepato-mesenteric perfusion.

There are several limitations with this method. 1) Changes in gastric mucosal perfusion do not always reflect intestinal perfusion, due to the different sources of arterial supply to the stomach and the intestines (celiac trunk vs. superior and inferior mesenteric arteries) [99, 100]. 2) Bicarbonate ion contents in intestinal regurgitation content may interfere with intraluminal carbon dioxide concentration. 3) Increased gastric mucosal perfusion may lead to increased gastric acid output and subsequent buffering by duodenal bicarbonate could cause an increase in pCO_2 gradient [101]. To reduce the effects of alkaline regurgitation and gastric juice, a continuous suction was applied to the lumen of the catheter. All patients (III) were treated for clinical reasons with proton pump blocker to reduce gastric acidity. 4) Oxygenated haemoglobin has a lower affinity to carbon dioxide than deoxygenated haemoglobin, the Haldane effect. When venous oxygen saturation increases as a result of increased blood flow, changes in venous blood pCO_2 and carbon dioxide content may differ because of the Haldane effect. The Haldane effect may also explain increases in gastric mucosal - arterial pCO_2 gradient despite major increases in splanchnic blood flow. Furthermore, whenever major changes in mucosal tissue oxygen extraction are likely to occur, an increase in the gastric mucosal - arterial pCO_2 gradient may be explained in part or completely by the Haldane effect, and may therefore not reflect worsening of perfusion [102]. 5) The method cannot differ changes in perfusion from changes in metabolism.

In healthy volunteers, the gastric mucosal - arterial pCO_2 gradient is less than 1.0 kPa [103], and ~3.3-4.6 kPa is considered to be the critical level above which anaerobic gastric mucosal metabolism might occur [104]. In paper I and II, pCO_2 gradient was approximately 0.7-1.0 kPa and in paper III 2.0 ± 0.9 , suggesting a well preserved balance between oxygen demand and supply. None of the patients in paper I-III had a pCO_2 gradient > 3.5 kPa.

Global splanchnic oxygenation

Interpretation of changes in hepatic venous oxygen saturation must be done with caution since a change in portal blood flow results in a reciprocal change in hepatic artery flow –the hepatic buffer response [105]. The hepatic buffer response is suggested to be mediated by adenosine, which is constantly released in the liver sinusoids. Decreased portal flow reduces the washout of adenosine, which subsequently causes vasodilation and increased hepatic artery flow [106]. The hepatic buffer response is impaired during early sepsis and during low cardiac output, when celiac trunk blood flow may not increase sufficiently to compensate for an acute decrease in portal flow [99]. The hepatic artery expresses both α_1 -constricting and β -dilating adrenergic receptors. Studies on septic experimental shock have suggested a less pronounced hepatic arterial vasoconstriction by norepinephrine compared to phenylephrine [107, 108]. This could at least partly explain, the more pronounced increase in splanchnic oxygen extraction with phenylephrine seen in paper II.

Splanchnic lactate extraction

Lactate is formed from glucose via pyruvate. Lactate dehydrogenase, NADH and hydrogen are essential for formation of lactate. During insufficient oxygen supply, pyruvate is accumulated in the cytosol due to decreased Krebs cycle metabolism. An increased lactate/pyruvate ratio may reveal anaerobic tissue conditions. Lactate is eliminated primarily by the liver. Arterial lactate concentration is dependent on the balance between lactate production and uptake from different organs. The muscles are the main producer of arterial lactate both under resting and working conditions [109]. The capacity of the liver to metabolize lactate is dependent on both systemic lactate concentration and liver perfusion [110]. Increasing lactate levels induces higher liver lactate metabolism [111]. The capacity of the liver to maintain lactate clearance remains normal until perfusion decreases below 25% of normal values [112]. After cardiac surgery lactate metabolism may be influenced by several factors as hypothermia, incipient SIRS [113], oxygen supply demand mismatch [114] and blood flow redistribution [115]. Interpretation of splanchnic lactate extraction should be performed carefully since increased portal lactate levels originating from the gut may be not detected [116]. Splanchnic lactate extraction is also a flow-dependent variable. The increase in lactate extraction seen with vasopressor infusion and the decrease seen with dopamine (I) can thus be explained by reciprocal changes in splanchnic blood flow.

Effect of vasopressors on splanchnic circulation (I, II)

Neither intestinal mucosal perfusion nor gastric mucosal - arterial $p\text{CO}_2$ gradient were changed by norepinephrine when used to increase mean arterial blood pressure by 30%. Norepinephrine caused, however, an increase in global splanchnic oxygen extraction, a direct measure of splanchnic oxygen demand-supply relationship. Furthermore, a highly significant positive correlation between the individual dose of norepinephrine and absolute increase in global splanchnic oxygen extraction was demonstrated, particularly in patients with low baseline cardiac index. Such an increase in splanchnic oxygen extraction by norepinephrine is likely to be caused by a decrease in splanchnic blood flow, as splanchnic blood flow is closely and inversely correlated to splanchnic oxygen extraction in man after cardiac surgery [28]. Those patients with the lowest baseline cardiac index needed higher infusion rates of norepinephrine and were thus more likely to respond with a more pronounced increase in splanchnic oxygen extraction (decrease in splanchnic blood flow). One could therefore speculate that the lack of effect of norepinephrine on jejunal mucosal perfusion might be explained by a redistribution of intestinal blood flow to the mucosa during vasopressor therapy in postoperative patients.

Alternatively, the lack of effect of norepinephrine on intestinal or gastric mucosal perfusion, in spite of a dose-dependent increase of the global splanchnic oxygen demand-supply relationship, could, at least partly, be explained by a counteraction of the norepinephrine-induced α_1 -agonistic vasoconstriction by a β_2 -mediated vasodilation of the gastrointestinal mucosa. To evaluate the presence and the magnitude of this potential β_2 -mediated vasodilatory action on the gastrointestinal mucosa, we compared the effects of norepinephrine to those of the pure α_1 -agonist phenylephrine (II). It was found that neither intestinal mucosal perfusion nor gastric mucosal -arterial $p\text{CO}_2$ gradient was changed by any of the vasopressors. The lack of effect of norepinephrine on mucosal perfusion can thus not be explained by β_2 -mediated counteraction on α_1 -agonistic vasoconstriction.

An increase in splanchnic oxygen extraction and mixed venous-hepatic vein oxygen saturation gradient might, however, also be explained by an increase in splanchnic oxygen consumption, mainly mediated by β_2 -adrenoceptors [118, 119]. On the other hand, norepinephrine is a 80 times less potent β_2 receptor stimulator compared to epinephrine, suggesting that norepinephrine is unlikely to have clinically relevant metabolic effects [117]. This is further supported by the fact that norepinephrine did not affect systemic oxygen consumption (I-II unpublished data, III). Furthermore, norepinephrine with its β_2 -agonistic properties does not increase splanchnic oxygen consumption in

patients with septic shock [63, 64]. Data on the effects of phenylephrine on splanchnic oxygen consumption are scarce. Reinelt et al compared the effects of phenylephrine to those of norepinephrine at an identical cardiac index and mean arterial pressure in six patients with hyperdynamic septic shock and found no significant difference in splanchnic oxygen consumption between the vasopressors [66].

The finding that phenylephrine caused a more pronounced increase in splanchnic oxygen extraction and mixed venous-hepatic vein oxygen saturation gradient, compared to norepinephrine, suggests that phenylephrine induces a more pronounced global splanchnic vasoconstriction, with a redistribution of global splanchnic blood flow away from the gastrointestinal territory, compared to norepinephrine. From a global splanchnic point of view one should therefore be cautious in the use of or even avoid phenylephrine for treatment of normovolemic hypotension after cardiac surgery. Our data support the results from Reinelt et al who demonstrated in septic patients that splanchnic blood flow decreased by 40% when norepinephrine was substituted for the pure α_1 -agonist phenylephrine at identical levels of mean arterial pressure and cardiac index [66].

Our data are in line with experimental studies on dogs demonstrating that norepinephrine (200 ng/kg/min) did not change ileal mucosal perfusion [120] and studies on normal anesthetized pigs showing that incremental infusion rates of norepinephrine or phenylephrine, to increase MAP by 15-70%, caused no changes in jejunal microvascular blood flow, mucosal tissue oxygen tension or microvascular haemoglobin oxygen saturation [121]. In endotoxin shock models, norepinephrine induced no adverse effects on intestinal mucosal perfusion [122, 123], or even attenuated mucosal acidosis [123] when used to maintain MAP at pre-shock levels. In a normodynamic porcine model of endotoxin shock it was demonstrated that norepinephrine maintained intestinal mucosal blood flow at the expense of the muscularis blood flow and that mucosal tissue ATP levels were higher than in the endotoxin treated animals not receiving norepinephrine [55].

The absence of vasopressor-induced reduction in gastrointestinal mucosal perfusion could at least partly be explained by the so-called "autoregulatory escape" phenomenon (see introduction). It has been shown that both the muscularis and the mucosal circulation exhibit the ability to escape an α_1 -mediated vasoconstrictor influence, but that the propensity to escape is greater in the mucosa than in the muscularis [89, 124], particularly in humans [124].

Neither norepinephrine nor phenylephrine did affect the gastric mucosal - arterial $p\text{CO}_2$ -gradient suggesting that the vasopressors did not alter the regional gastric mucosal relationship between blood flow and metabolism.

However, changes in gastric mucosal - arterial $p\text{CO}_2$ -gradient must be interpreted by caution after cardiac surgery. It has been demonstrated that the physiology of the gastric mucosal - arterial $p\text{CO}_2$ -gradient during therapeutic interventions after cardiac surgery is complex and that changes in splanchnic blood flow or oxygen delivery induced by catecholamine therapy, may not be associated by changes in the gastric mucosal - arterial $p\text{CO}_2$ -gradient [125]. It has previously been shown that there is a lack of association between gastric mucosal - arterial $p\text{CO}_2$ gradients and jejunal mucosal perfusion, assessed by laser Doppler flowmetry, after cardiac surgery [28]. In other words, changes in gastric and intestinal mucosal perfusion might not occur in parallel. This inconsistent relationship could be explained by the fact that laser Doppler flowmetry measures perfusion while gastric tonometry reveals the relationship between gastric mucosal CO_2 production and perfusion or by the presence of uneven flow distribution within jejunal and/or gastric mucosal tissues.

The fact that mucosal perfusion remained constant in spite of the increase in perfusion pressure during infusion of norepinephrine or phenylephrine, suggests that intestinal vascular resistance increased. This increase in vascular resistance can be attributed to a myogenic autoregulatory response related to the rise in perfusion pressure and not necessarily to the vasoconstrictor effect of the vasopressor itself [126, 127].

Low doses of norepinephrine and phenylephrine induced a substantial increase in MAP (30%). Obviously, the results of the present study cannot immediately be transposed to patients with septic shock or to patients with severe post-cardiotomy vasodilatory shock, requiring considerably higher doses of vasopressors. However, these relatively low infusion rates of vasopressors, have been shown in other clinical trials on post-cardiac surgery patients to induce an increase in MAP of similar magnitude, as observed in the present study [128, 129].

Effects of norepinephrine plus dopamine on splanchnic perfusion (I)

When a low-dose of dopamine was added to the continuous norepinephrine infusion, cardiac index increased (33%) and splanchnic oxygen extraction decreased indicating a concomitant increase in splanchnic blood flow. This was accompanied by a 32 % increase in jejunal mucosal perfusion. These results confirm previous findings in postoperative patients of a 20-27% increase in jejunal mucosal perfusion with low doses of the dopaminergic agents dopexamine ($0.7\mu\text{g/kg/min}$) and dopamine ($2.7\mu\text{g/kg/min}$), in striking contrast to the only 7% increase with dobutamine when cardiac index was

increased by 25% by each agent in a randomized blinded cross-over study [71]. Thus, the results of the present and the previous study [71], suggest that dopaminergic agents should preferably be used in cardiac surgical patients who may suffer from intestinal mucosal hypoperfusion. It has been demonstrated in animal studies that dopamine may redistribute jejunal blood flow to the mucosa and submucosa from the serosal and muscular layers and that this mucosal vasodilatation is mediated by dopamine-1 (DA₁) receptors [130, 131]. Furthermore, dopamine improves jejunal mucosal tissue oxygenation and microvascular haemoglobin oxygen saturation in anaesthetized normal as well as endotoxemic pigs [32, 132]. In humans the effects of dopamine on gastric mucosal perfusion have been evaluated by using the endoluminal laser Doppler flowmetry technique [85, 133, 134] and the results of these studies are controversial. Karzai et al found that dopamine at a dose of 6 µg/kg/min increased gastric mucosal perfusion by 66% during cardiopulmonary bypass whereas dobutamine at the same dose did not affect gastric mucosal perfusion [85, 133]. In striking contrast, Nevière et al showed that in septic patients 5 µg/kg/min of dopamine caused a 28% decrease in gastric mucosal perfusion, whereas the same dose of dobutamine increased gastric mucosal perfusion by 32% [134]. It has recently been shown that dopamine increases both splanchnic blood flow and oxygen consumption after uncomplicated cardiac surgery [135]. In the present study, dopamine did not affect the gastric mucosal - arterial pCO₂-gradient, which could be explained by a proportional increase in both gastric mucosal blood flow and metabolism.

Splanchnic oxygenation in septic and non-septic state (I-III)

Systemic oxygen extraction in the vasodilatory shock group was comparable to that of the control group, indicating that systemic oxygen delivery matched the significantly higher systemic oxygen consumption in the former group. On the other hand, splanchnic oxygen extraction was considerably higher in the vasodilatory shock group, indicating a global splanchnic oxygen demand-supply mismatch compared to controls. This is also supported by the higher gastric mucosal - arterial pCO₂ gradients, considered to reflect the relationship between gastric mucosal metabolism (CO₂ production) and blood perfusion [102, 136]. In previous reports on norepinephrine-dependent hyperdynamic septic shock, with mean values of cardiac index ranging from 3.7 to 4.3 L/min/m², splanchnic oxygen extraction has been reported to range from 44% to 71% [45, 66, 137]. The relatively high levels of splanchnic oxygen extraction (70%) in the present study is most likely explained by a combination of a high splanchnic oxygen uptake, as suggested by the high systemic oxygen consumption and a splanchnic oxygen delivery, which did not meet the high splanchnic oxygen demand. Such an inappropriately low

splanchnic oxygen delivery may be explained by the relatively low systemic oxygen delivery in these patients with heart disease, undergoing complicated cardiac surgery, when compared to hyperdynamic septic patients, devoid of primary heart disease [45, 66, 137]. Alternatively, it could be explained by the splanchnic vasoconstrictive effects of high doses of norepinephrine administered to these patients, causing a redistribution of blood flow away from the splanchnic territory. On the other hand, JMP was higher (see below) in the vasodilatory shock group, suggesting that this mechanism is less likely to explain the high splanchnic oxygen extraction in the vasodilatory shock group.

Intestinal mucosal perfusion in septic and non-septic state (I-III)

Quantitatively, the impaired global splanchnic as well as gastric oxygen demand-supply relationship was associated with a 61% higher jejunal mucosal perfusion in the vasodilatory shock group compared to postoperative controls. This was most likely a manifestation of a generalized excessive vasodilation seen in these patients, in turn caused by extreme generation of endogenous vasodilators such as nitric oxide and prostaglandins or activation of the ATP-sensitive potassium channels in vascular smooth muscle cells, promoted by e.g. lactic acidosis [60, 138]. The cause of vasodilatory shock in these postoperative patients were presumably multifactorial: prolonged cardiopulmonary bypass, cardiogenic, haemorrhagic or septic shock, which all may have a final common pathway of severe peripheral vasodilation after correction of the initial problem [60].

The level of intestinal mucosal perfusion as well as the pattern of cyclic vasomotion differed when comparing postoperative and septic patients (Fig 16 and 17). Qualitatively, JMP behaved differently in the vasodilatory shock group when compared to controls. A pulse-synchronous JMP signal was seen in all patients but the JMP signal exhibited an irregular variation in perfusion reflecting an irregular variation in mucosal arteriolar diameter in the vasodilatory shock patients, in contrast to controls, as can be seen in Figures below. The vast majority of the postoperative patients exhibited cyclic oscillations of the JMP signal (vasomotion), which was seen in only three of ten vasodilatory shock patients. The pattern of vasomotion varies considerably between both species and vascular beds and may be affected by vasoactive agents [32] or changes in blood pressure, haematocrit, or oxygen tension [33]. In addition it has been shown that spontaneous arteriolar vasomotion ceases in animals made endotoxinemic by injection of E-coli lipopolysaccharide [139].

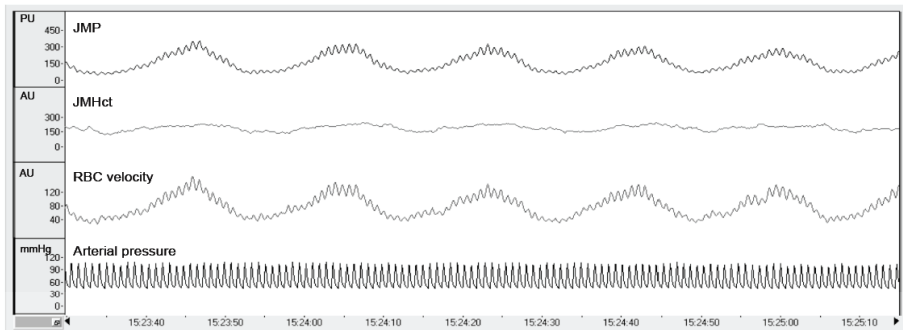


Figure 16 This registration shows jejunal mucosal perfusion, jejunal mucosal haematocrit and red blood cell velocity in a non-septic postoperative patient during 1,5 min. Note that heart synchronous flow alterations are visible in the mucosa. The typical cyclic oscillation pattern – vasomotion, at a frequency of approximately 3.5 cycles/min is present.

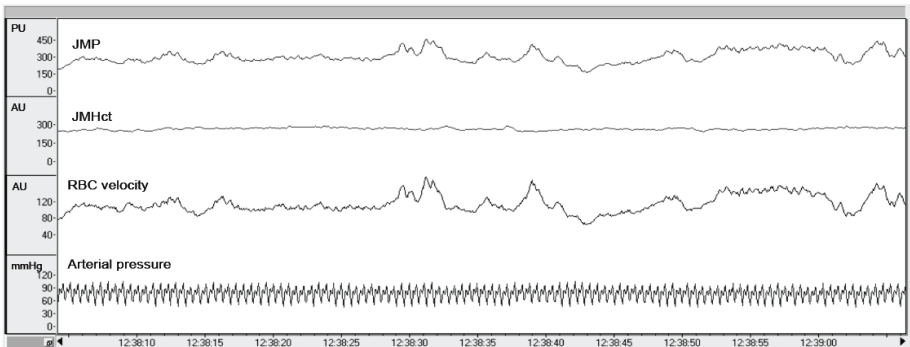


Figure 17 This one-minute registration shows jejunal mucosal perfusion, jejunal mucosal haematocrit and red blood cell velocity in a patient with vasoplegic shock. There is no obvious vasomotion. Heart synchronous flow alterations are present. The arterial pressure curve shows twin peaks due to an intra aortic balloon pump.

Norepinephrine, perfusion pressure and vasodilatory shock (III)

Norepinephrine elevates systemic perfusion pressure mainly by an increase in systemic vascular resistance but also to some extent by an increase in cardiac output in patients with septic shock [62]. In patients with volume-resuscitated vasodilatory shock the restoration of adequate perfusion pressure to a level that allows appropriate organ perfusion is the end-point of vasopressor therapy. The optimal perfusion pressure with respect to systemic, regional or local perfusion is, however, not yet established. Neither intestinal mucosal perfusion

nor gastric mucosal - arterial $p\text{CO}_2$ gradient was changed when target MAP was increased from 60 to 90 mmHg by a more than 100% increase in the norepinephrine dose and a 40% increase in systemic vascular resistance index. Furthermore, increasing doses of norepinephrine did not seem to redistribute blood flow away from the splanchnic territory, as indicated by the lack of significant change in the mixed venous –hepatic venous oxygen gradient.

Increasing doses of norepinephrine did not cause any change in hepatic venous oxygen saturation or splanchnic oxygen extraction, indicating that in patients with vasodilatory shock, the global splanchnic demand/supply relationship is maintained during norepinephrine-induced alterations in perfusion pressure. This could be explained by the, for this group of patients with severe heart disease, relatively high levels of cardiac index. In a paper I on uncomplicated post-cardiac surgery patients, it was shown that norepinephrine caused a dose-dependent increase in splanchnic oxygen extraction in patients with a cardiac index $< 2.4 \text{ L/min/m}^2$, which could not be seen in patients with high cardiac index ($> 2.4 \text{ L/min/m}^2$). In other words, norepinephrine-induced variations in MAP within a range of 60-90 mmHg do not seem to jeopardize the global splanchnic oxygen demand/supply relationship in patients with vasodilatory shock. A further support of this finding is the lack of effect of norepinephrine on hepatic vein lactate levels or splanchnic lactate extraction.

Norepinephrine increased cardiac index and systemic oxygen delivery by 12% and 21%, respectively. These results confirm the data from two previous studies showing that cardiac index increased by approximately 20% when increasing MAP by norepinephrine in patients with septic shock, due to the β_1 -stimulatory effect of norepinephrine [140, 141]. The relatively lower effect of norepinephrine on cardiac index increase in the present study could be explained by a lower myocardial contractile reserve in our patients and higher afterload sensitivity due to the nature of their primary disease. Thus, in the present study, pulmonary artery occlusion pressure increased by 36% when afterload was increased by norepinephrine, while in the above cited studies, pulmonary artery occlusion pressure was not affected by increased afterload [140, 141].

Five patients in paper III received milrinone, which is a potent vasodilator. One could argue that the need for norepinephrine in these patients was a pharmacological consequence of milrinone treatment and not because of vasodilatory shock. The milrinone doses were low to moderate and the infusion rates of norepinephrine at a target MAP of 75 mmHg did not differ between those patients who received and those who did not receive milrinone. Four patients had an identified source of infection (pneumonia or urosepsis) and were considered to have a septic vasodilatory shock, while the remaining six patients were considered to have a postcardiotomy vasodilatory shock [58-61]. It is not immediately obvious that these two subgroups should have the same

splanchnic response to variations in norepinephrine dose. However, as can be seen from Fig. 1-3 in paper III, there were no obvious differences in global and regional splanchnic vascular responses to norepinephrine between the two subgroups

Autoregulation of intestinal mucosal perfusion (IV)

In paper IV, the autoregulation of the JMP during mild hypothermic CPB in patients undergoing elective cardiac surgery, was evaluated. Neither JMP nor its composite variables, JMHT and RBC flow velocity, were significantly affected by flow-induced variations in MAP within the pressure range of 50-75 mmHg. These data indicate that intestinal mucosal autoregulation is maintained during CPB in man.

Our results are in contrast to previous experimental studies evaluating regional splanchnic circulation during CPB. Mackay et al and O'Dwyer et al [142, 143] both evaluated the effects of variations in CPB flow rate on regional blood flow in pigs using microsphere technique. These investigators found that splanchnic blood flow was pressure-dependent, indicating impaired autoregulation. Bastien et al [81] evaluated the importance of systemic flow for intestinal perfusion, as measured by laser Doppler flowmetry (LDF), during mild hypothermic CPB in rabbits. They found a linear relationship between CPB flow rate and perfusion of gastric, ileal, jejunal, and hepatic regions, further indicating impairment of intestinal autoregulation during CPB. In the latter experiment, intestinal perfusion was measured via the serosal side of the intestinal wall rather than from the lumen, as in our study. It is possible that LDF recordings from exterior of the intestine reflect blood flow to the serosa/muscularis layers rather than the actual mucosa thus explaining, at least in part, the discordant findings between this study and prior animal experiments.

Ohri et al [79] and Sicsic et al [80] have shown that significant *gastric* mucosal hyperperfusion, assessed by the laser Doppler flowmetry technique, occurs during CPB in man. In contrast, it has previously been shown that *intestinal* mucosal perfusion increases during CPB in man [30, 82]. This increase in JMP was accompanied by an increase in red blood cell velocity and the lack of changes in JMHT, in spite of a decrease in systemic oxygen delivery and systemic haemodilution. That is, data obtained from measurements of gastric mucosal perfusion during CPB may not necessarily be extrapolated as representative of intestinal mucosal perfusion. In paper IV, we have extended our prior studies of the intestinal microcirculation during CPB and demonstrating that intestinal mucosal autoregulation is maintained during variations in MAP caused by changes in CPB flow rate. Thus, these results

from humans suggest that intestinal mucosal perfusion is not compromised during CPB. These results further suggest that, the previously described disruption of intestinal mucosal barrier function and translocation of endotoxins and microorganisms during CPB [78, 144] might not necessarily be explained by intestinal mucosal hypoperfusion.

In the present study, vasomotion amplitude increased in parallel to increased systemic perfusion and vice versa, which could be explained by the myogenic mechanism, by which vascular smooth muscle contracts as tension is increased (see Figure 14). Changes in vasomotion amplitude to variations in arterial blood pressure could thus be one mechanism by which the intestinal mucosa autoregulates perfusion. In Figure 18 it can be seen that the vasomotion amplitude of JMP also increases with increasing arterial pressure caused by bolus injections of phenylephrine, indicating that an increase in perfusion pressure stimulates the myogenic autoregulatory response [126, 127].

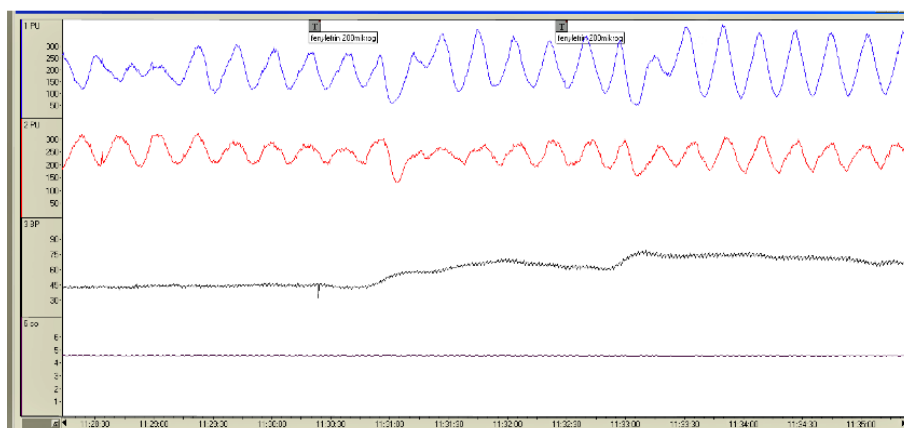


Figure 18 This figure shows jejunal mucosal perfusion on the two first curves, arterial pressure on the third and CPB flow in the fourth. At constant CPB flow at 2,4 L/min/m², two injections of phenylephrine were administered i.v. Arterial pressure increases as a result of vasoconstriction. Mucosal perfusion remains at the same mean perfusion level. Note the change in vasomotion amplitude when perfusion pressure is increased.

Prostacyclin (Figure 15) induced a 25% decrease in mean arterial pressure during CPB but JMP increased by 45%, indicating a pronounced prostacyclin-induced arteriolar vasodilation. This vasodilation could also to some extent be attributed to a myogenic, autoregulatory response to the fall in systemic pressure. During prostacyclin injection intestinal perfusion became pressure-dependent. Furthermore, vasomotion was abolished in all patients with prostacyclin, suggesting that increased intracellular cAMP in vascular

smooth muscle cells inhibits intestinal mucosal vasomotion. One mechanism behind the prostacyclin-induced inhibition of vasomotion could be hyperpolarization of the cell membrane, which would block spontaneous depolarization set up by the sarcoplasmic reticulum basic oscillator. It could also be a direct effect of cAMP on the sarcoplasmic reticulum by influencing intracellular calcium availability, uptake and/or release [27]. The prostacyclin-induced change from non pressure-depedent to pressure-dependent intestinal mucosal perfusion suggests an indirect evidence of presence of autoregulation prior to vasodilation.

Effects of vasopressors on haemoglobin and haematocrit (I-III)

In papers I-III, norepinephrine increased haemoglobin and haematocrit significantly. In mammals there are α_1 -adrenergic receptors and contractile elements present in the capsule of the spleen, responding to catecholamines by autotransfusion of erythrocytes [145]. This is particularly seen in diving mammals, with a large spleen and storage of erythrocytes. This mechanism has been considered to be less important in man [15]. Diving simulation in healthy volunteers caused a decrease in spleen volume and increase in haematocrit by 0,3 to 4,9% [146-148], the higher number in trained apnoea divers. In splenectomised subjects there were no change in haematocrit [148]. Maximal exercise causes a decrease in spleen volume by 56% [149] and the splenic erythrocyte count to 34% (44-26%) of the initial count together with an increase haematocrit by up to 7% [150]. It has been suggested that the spleen contributes for 30% of the increase in haematocrit during exercise.[151]

Infusion of low-dose epinephrine in healthy volunteers to increase plasma epinephrine levels to those seen during mental stress, causes an increase in haematocrit [152]. Other stressful situations like earthquake [152] and head-up tilt [153] also increases haematocrit. One could speculate that vasopressor therapy with catecholamines induces haemoconcentration, which may be the result of increased peripheral capillary filtration, due to α_1 -mediated venoconstriction [154] and partly by autotransfusion from the spleen.

CONCLUSIONS

Vasopressor therapy with norepinephrine or phenylephrine in clinically relevant doses after cardiac surgery does not jeopardize jejunal mucosal or gastric mucosal perfusion in spite of an impairment of the global splanchnic oxygen demand/supply relationship. Phenylephrine induces a more pronounced global splanchnic vasoconstriction compared to norepinephrine.

The lack of norepinephrine-induced impairment of gastrointestinal mucosal perfusion in post-cardiac surgery patients cannot be explained by a simultaneous α_1 -mediated vasoconstrictive and β_2 -mediated mucosal vasodilatory action.

The addition of a low-dose dopamine to norepinephrine increases global splanchnic blood flow as well as jejunal mucosal perfusion.

Increasing mean arterial pressure from 60 to 90 mmHg with norepinephrine in patients with vasodilatory shock does not affect jejunal or gastric mucosal perfusion or the splanchnic oxygen demand/supply relationship. Haematocrit and haemoglobin concentrations increase with increasing infusion rates of norepinephrine.

The autoregulatory capacity of the jejunal mucosa is well maintained during cardiopulmonary bypass. The amplitude and frequency of the cyclic oscillation of the mucosal perfusion (vasomotion) increase with increasing perfusion pressure. Prostacyclin increases jejunal mucosal perfusion and abolishes the autoregulatory capacity of the mucosa.



Christian Andreas Doppler

Christian Doppler

Born Nov. 29, 1803, Salzburg, Austria, died March 17, 1853, Venice

Christian Doppler studied mathematics and astronomy in Czechoslovakia and Austria, and ended up as the first director of the new Institute of Physics at Vienna University. In May 1842 he presented his paper "On the Coloured Light of Double Stars and Certain Other Stars of the Heavens," illustrating what has since been called the Doppler effect. He explained that the perceived change of frequency in light and sound waves was due to the relative motion of the source and the observer

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SAMMANFATTNING PÅ SVENSKA

Vid kirurgiska ingrepp, stort trauma eller svår intensivvårdskrävande sjukdom kan nedsatt blodflöde och syrebrist i bukorganen hota tarmslemhinnans barriärfunktion. Detta kan leda till genomträngning av bakterier, immunaktivering och utveckling av systemiskt inflammatoriskt syndrom. Upptäckande, förebyggande och behandling av regional syrebrist är därför viktigt för att hindra komplikationer hos kritiskt sjuka patienter.

I denna avhandling, bestående av fyra delstudier, utvärderas vanligen använda kärlsammandragande mediciners effekt på tarmens slemhinneblodflöde hos patienter under och efter hjärtkirurgi samt hos patienter med svår intensivvårdskrävande cirkulatorisk chock.

Tarmens slemhinneblodflöde utvärderades hos arton hjärtkirurgiska patienter under höjning av blodtrycket med noradrenalininfusion. Tarmslemhinneblodflödet förändrades inte av noradrenalin trots en kärlsammandragning totalt i mag-tarmpaketet. Tillägg av dopamin till noradrenalininfusionen ökade blodflödet både i tunntarmslemhinnan och i hela mag-tarmpaketet.

I en studie på tio postoperativa hjärtkirurgiska patienter jämfördes fenylefrin, en ren adrenerg α_1 -receptorstimulerare, med noradrenalin som har både α_1 -kärlsammandragande och β_1 - och β_2 - kärlvidgande effekt. Tarmslemhinneblodflödet ändrades inte av noradrenalin eller fenylefrin. Det totala syrgasutnyttjandet i bukorganen ökade med båda drogerna, talande för en kärlsammandragning totalt sett i mag-tarmpaketet. Syrgasutnyttjandet ökade mest av fenylefrin.

Hos tio kritiskt sjuka patienter med multipel organsvikt och noradrenalinbehandlad cirkulatorisk chock undersöktes effekten av variation av blodtrycket genom att ändra infusionshastigheten av noradrenalin. Varken tarmslemhinnans eller hela mag-tarmpaketets blodflöde ändrades trots en variation i medelblodtrycket mellan 60 och 90 mmHg.

Autoregleringen av blodflödet i tarmslemhinnan under hjärtlungmaskinscirkulation utvärderades hos tio patienter under hjärtkirurgi. Variation av artärblodtrycket genom förändring i hjärtlungmaskinens blodflöde, visade att tarmslemhinnans blodflöde är väl autoreglerat. Amplituden och frekvensen på den cykliska variationen av blodflödet (vasomotionen) ökade med ökande artärblodtryck. Kärilvidgning med prostacyclin ökade slemhinneblodflödet trots minskat artärtryck och slog ut autoregleringen vid artärtrycks variation.

Slutsats: Tarmslemhinnans blodflöde påverkas inte av kliniskt relevanta doser av de kärlsammandragande medicinerna noradrenalin eller fenylefrin hos postoperativa patienter eller hos patienter med intensivvårdskrävande cirkulatorisk chock. Dopamin ökar blodflödet till tunntarmens slemhinna under pågående noradrenalininfusion. Autoregleringen av tarmslemhinnans blodflöde är intakt under hjärtlungmaskinscirkulation.

ORIGINAL PAPERS

I

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Effects of norepinephrine alone and norepinephrine plus dopamine on human intestinal mucosal perfusion

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Abstract *Objectives:* To evaluate the effect of norepinephrine alone and norepinephrine combined with dopamine on jejunal mucosal perfusion, gastric-arterial pCO₂ gradient, and global splanchnic oxygen demand-supply relationship after cardiac surgery. *Design:* A prospective interventional study. *Setting:* A university cardiothoracic intensive care unit. *Patients:* Eighteen patients were studied during propofol sedation and mechanical ventilation after uncomplicated coronary artery bypass surgery. *Interventions:* After control measurements, each patient received norepinephrine (50±26 ng·kg·min) to increase mean arterial blood pressure by 30% followed by addition of low-dose dopamine (2.6±0.3 µg·kg·min). Postdrug control measurements were performed 120 min after discontinuation of the catecholamines. *Measurements and results:* Norepinephrine induced a 32% increase in systemic vascular resistance with no change in cardiac index. Neither jejunal mucosal perfusion, assessed by laser Doppler flowmetry, nor gastric-arterial pCO₂

gradient (tonometry) was affected by norepinephrine. Splanchnic O₂-extraction increased ($P<0.05$) and this increase was positively correlated to the individual dose of norepinephrine ($r = 0.78$, $P<0.0001$). Splanchnic lactate extraction was increased by norepinephrine ($P<0.05$). None of the patients had splanchnic lactate production during norepinephrine infusion. The addition of dopamine increased cardiac index by 27% ($P<0.001$) and decreased splanchnic O₂ extraction. Dopamine increased jejunal mucosal perfusion by 32% ($P<0.001$) while the gastric-arterial pCO₂ gradient remained unchanged. *Conclusions:* Vasopressor therapy with norepinephrine after cardiac surgery did not jeopardize intestinal mucosal perfusion in spite of a dose-dependent increase of the global splanchnic oxygen demand-supply relationship. The addition of dopamine increased intestinal mucosal perfusion.

Keywords Intestinal mucosa · Microcirculation · Norepinephrine · Dopamine

Introduction

Norepinephrine is a commonly used and recommended agent for treatment of hypotension in volume-resuscitated hyperdynamic septic shock [1]. Norepinephrine is also used to correct hypotension in the vasodilatory shock syndrome after cardiac surgery with cardiopulmo-

nary bypass [2, 3]. Norepinephrine has α_1 -agonistic as well as β_1 - and β_2 -agonistic properties and elevates systemic perfusion pressure mainly by an increase in systemic vascular resistance but also to some extent by an increase in cardiac output in patients with septic shock [4]. Splanchnic blood flow seems to be well-maintained during vasopressor therapy with norepinephrine in these

patients [4, 5, 6] and splanchnic blood flow is higher with norepinephrine when combined with low-dose dobutamine [7] compared to treatment with epinephrine alone [7]. Furthermore, at a certain cardiac index, splanchnic blood flow is higher with norepinephrine when compared to the pure α_1 -agonist phenylephrine [8].

It has recently been shown in man that there is no consistent association between global splanchnic blood flow and local intestinal mucosal perfusion evaluated by laser Doppler flowmetry or gastric mucosal perfusion assessed by gastric tonometry [9]. The lack of correlation between intestinal mucosal perfusion and splanchnic blood flow may thus indicate that global measurements of oxygen delivery across the whole splanchnic region do not necessarily reflect the degree of oxygenation or perfusion of the mucosal layer [9], probably the most vulnerable portion of the intestinal wall [10]. The fact that norepinephrine does not seem to jeopardize global splanchnic perfusion in patients with sepsis does not necessarily mean that vasopressor therapy with norepinephrine is harmless in terms of intestinal mucosal perfusion as norepinephrine might redistribute blood flow away from the mucosa. This is of particular importance since gut mucosal ischemia might damage the intestinal mucosal barrier with translocation of a bacterias and endotoxins perpetuating the systemic inflammatory response syndrome in patients with sepsis [11].

Data on the impact of catecholamine therapy on intestinal mucosal perfusion in man are sparse. Thorén et al, using laser Doppler flowmetry, have previously shown that at a certain increase in cardiac output, dopamine and dopexamine increased jejunal mucosal perfusion to a greater extent than dobutamine in postcardiac surgical patients [12]. To the best of our knowledge, there are no data on the effects of norepinephrine on intestinal mucosal perfusion in man.

The aim of the present investigation was therefore to study the effects of norepinephrine alone and norepinephrine plus low-dose dopamine infusion on jejunal mucosal perfusion by laser Doppler flowmetry and the gastric-arterial mucosal $p\text{CO}_2$ gradient by tonometry as well as the global splanchnic oxygen demand-supply relationship after uncomplicated cardiac surgery. Our hypothesis was that norepinephrine decreases intestinal mucosal perfusion and that low-dose dopamine increases intestinal mucosal perfusion when combined with a pressor dose of norepinephrine.

Materials and methods

The study protocol was approved by the Human Ethics Committee of the University of Göteborg, and informed consent was obtained from each patient. Eighteen patients (17 male, 1 female) with coronary artery disease and with a left ventricular ejection fraction $>50\%$, undergoing uncomplicated coronary artery bypass grafting

were included. Their mean age was 68 (range, 52–77) years. All patients were treated with long-acting beta $_1$ -selective adrenergic blockers (atenolol or metoprolol), including the morning of surgery.

The patients were premedicated with intramuscular morphine (5 mg) and scopolamine (0.2 mg) and oral flunitrazepam (1 mg). Anaesthesia was induced with thiopentone, 3–5 mg/kg, fentanyl, 5–7 $\mu\text{g}/\text{kg}$ followed by pancuronium 0.1 mg/kg and maintained by fentanyl 2–4 $\mu\text{g}/\text{kg}$ and enflurane. During cardiopulmonary bypass, anesthesia was maintained by propofol. All patients received 20 mg of oral cisapride at the end of the operation to facilitate the positioning of the jejunal catheter. In the intensive care unit (ICU) the patients were sedated with propofol and mechanically ventilated to normocapnea. Postoperative hypovolemia was treated according to routine clinical practice with hydroxethylstarch (HAES-steril, Fresenius Kabi, Uppsala Sweden) and crystalloid fluids. The hepatic vein and the pulmonary artery were catheterized with 7 F pulmonary artery catheters (Baxter Healthcare, USA) during fluoroscopic guidance. Cardiac index was measured in triplicate by the thermodilution technique (mean of three 10-ml ice-cold saline injections). Blood lactate concentrations were determined using an enzymatic method (YSI 2300 Stat Plus, YSI, Yellow Springs, Ohio, USA). Splanchnic oxygen extraction and lactate extraction were calculated using standard formulae. Blood gas analyses were performed with automated blood gas analyzer (Synthesis 25, Instrumental Laboratories, Italy). The arterial blood pressure, pulmonary arterial pressure, and central venous pressure as well as jejunal mucosal perfusion were continuously measured and stored in the Perisoft software (Perimed, Järfälla, Sweden). Temperature was measured in the pulmonary artery.

The technique of laser Doppler flowmetry of the intestinal mucosa in man has previously been described in detail [13]. A custom-made two-probe laser Doppler catheter (Perimed) was placed through the nasogastric route during fluoroscopic guidance endoluminally in the proximal jejunum 20–40 cm distal to the ligament of Treitz. The light source and the receiver of each probe are situated 23 mm and 123 mm from the tip of the catheter. Each probe consists of three triangular-placed optical fibers with a diameter of 150 μm and a fiber center separation of 200 μm . One fiber emits light with a wavelength of 780 nm and the other two receive the Doppler shifted and backscattered light. The jejunal mucosal perfusion was measured with a sampling frequency of 32 Hz with a laser Doppler flowmeter (Periflux PF 4001 Perimed). For measurements of jejunal mucosal perfusion, a time constant of 0.2 s and a bandwidth of 20–25 kHz was used and calibration of the probe was performed as recommended by the manufacturer. The jejunal mucosal perfusion was calculated as the mean value from the two channels during periods of intestinal quiescence. Gastric mucosal $p\text{CO}_2$ was measured every 10 min by using a standard tonometry nasogastric tube (TRIP, NGS tonometry catheter, Tonometrics, Helsinki, Finland) connected to an automated gas analyzer (Tonocap TC-200, Datex, Helsinki, Finland). The correct position of the tube was confirmed by fluoroscopy and continuous suction was applied to drain the stomach of air and juice. The gastric-arterial $p\text{CO}_2$ gradient was calculated.

Experimental procedures

The patients were sedated with propofol at a dose (4.8 ± 2.3 mg·kg $^{-1}$ ·h) to provide adequate sedation and a mean arterial pressure (MAP) of 65–75 mmHg according to our standard protocol. This dose was not changed during the experimental protocol. Measurements started approximately 6 h after the end of cardiopulmonary bypass after successful positioning of catheters and when the patients were considered normovolemic and having a body temperature >36.5 °C. The protocol consisted of four periods: 1) a predrug control period at a stable MAP level of approximately 70 mmHg; 2) norepinephrine infusion was commenced to

reach a target MAP of approximately 90 mmHg; 3) during steady-state norepinephrine infusion, a low-dose dopamine was started with a target dose of 3 $\mu\text{g}\cdot\text{kg}\cdot\text{min}$. The highest acceptable systolic blood pressure level during period 2) and 3) was 150 mmHg; and 4) postdrug control measurements were performed after a washout period of 120 min. Each of the four periods consisted of a 30-min measurement period preceded by a 20–30-min period for dose titration (period 2 and 3). Jejunal mucosal perfusion was continuously recorded during the four periods and mean jejunal mucosal perfusion was calculated during intestinal quiescence (average 16.4 ± 5.6 ml/period). Gastric mucosal pCO_2 was measured every 10 min and the mean value for each 30-min period was calculated. Systemic haemodynamics were measured and samples for blood gas analysis, lactate, and hemoglobin concentrations were taken at the end of each measurement period.

Statistics

A Kolmogorov-Smirnov test for goodness-of-fit to normal distribution was performed and normality was obtained for all main measurements. Analysis of variance for repeated measurements followed by a contrast analysis were used to evaluate the effects of norepinephrine alone vs control and the effects of norepinephrine + dopamine vs norepinephrine and for comparing control and postdrug control periods. A linear regression analysis was performed to evaluate the relationship between the individual norepinephrine dose and absolute changes in splanchnic oxygen extraction, jejunal mucosal perfusion, and the gastric-arterial pCO_2 gradient. The group was arbitrarily divided into two subgroups depending on cardiac index at baseline (<2.4 l·min $^{-1}\cdot\text{m}^2$ or ≥ 2.4 l·min $^{-1}\cdot\text{m}^2$). A Mann Whitney test was performed to test difference between the groups with regard to dose of norepinephrine. A P -value <0.05 was considered statistically significant. Values are mean \pm standard deviation.

Table 1 Systemic effects of norepinephrine and norepinephrine plus low-dose dopamine. Values are expressed as mean \pm standard deviation. (NE norepinephrine, NE+DA norepinephrine plus low-dose dopamine, SVRI systemic vascular resistance index, PAOP pulmonary artery occlusion pressure, ANOVA analysis of variance)

	Control	NE	NE+DA	Postcontrol	ANOVA
Mean arterial pressure (mmHg)	70 \pm 3	90 \pm 4***	89 \pm 9	69 \pm 5	$P<0.0001$
Cardiac index (l·min $^{-1}\cdot\text{m}^2$)	2.5 \pm 0.5	2.5 \pm 0.5	3.1 \pm 0.5* ³	2.7 \pm 0.4*	$P<0.0001$
Heart rate (beats/min)	71 \pm 10	69 \pm 9	80 \pm 12* ³	75 \pm 12	$P<0.0001$
Stroke volume index (ml/m 2)	36 \pm 8	36 \pm 8	40 \pm 7* ²	37 \pm 7	$P<0.01$
SVRI (dyne·s·cm 5 ·m 2)	2034 \pm 402	2696 \pm 489***	2079 \pm 336* ³	1767 \pm 278*	$P<0.0001$
PAOP (mmHg)	11 \pm 2	12 \pm 3*	11 \pm 2	11 \pm 2	$P<0.05$
Temperature (°C)	37.1 \pm 0.5	37.2 \pm 0.4	37.4 \pm 0.5	37.7 \pm 0.5***	$P<0.0001$

* $P<0.05$ vs control; ** $P<0.01$ vs control; *** $P<0.001$ vs control, * $P<0.05$ vs NE; * $P<0.01$ vs NE; * $P<0.001$ vs NE

Table 2 Splanchnic effects of norepinephrine and norepinephrine plus low-dose dopamine. Values are expressed as mean \pm standard deviation. (NE norepinephrine, NE+DA norepinephrine plus low-dose dopamine, PU perfusion units, ANOVA analysis of variance)

	Control	NE	NE+DA	Postcontrol	ANOVA
Jejunal mucosal perfusion (PU)	190 \pm 42	188 \pm 53	249 \pm 95* ²	194 \pm 38	$P<0.01$
Gastric-arterial pCO_2 -gap (kPa)	0.9 \pm 0.5	0.8 \pm 0.5	0.8 \pm 0.5	1.0 \pm 0.4	n.s.
Splanchnic O $_2$ extraction(%)	39 \pm 7	42 \pm 10*	32 \pm 8* ²	37 \pm 10	$P<0.001$
Hepatic vein oxygen saturation(%)	60 \pm 7	57 \pm 10	65 \pm 8* ²	61 \pm 10	$P<0.001$
Mixed venous-hepatic vein oxygen saturation gradient (%)	11 \pm 7	14 \pm 9*	8 \pm 6* ¹	7 \pm 7*	$P<0.001$
Splanchnic lactate extraction (%)	42 \pm 12	47 \pm 13*	43 \pm 13***	34 \pm 13**	$P<0.001$

* $P<0.05$; ** $P<0.01$ vs control; *** $P<0.05$ vs NE; * $P<0.01$ vs NE; * $P<0.001$ vs NE

Results

Central haemodynamics

A norepinephrine infusion rate of 50 ± 26 ng·kg·min was needed to reach the target MAP level of 90 mmHg (Table 1). This norepinephrine-induced elevation in MAP was caused by a 33% increase in indexed systemic vascular resistance ($P<0.001$) while cardiac index (CI) did not change. Pulmonary artery occlusion pressure increased ($P<0.01$) while heart rate and stroke volume index were unchanged during norepinephrine infusion. Addition of low-dose dopamine (2.6 ± 0.3 $\mu\text{g}\cdot\text{kg}\cdot\text{min}$) caused an increase in cardiac index (27%, $P<0.0001$), heart rate (16%, $P<0.001$) and stroke volume index (10%, $P<0.001$), a decrease in indexed systemic vascular resistance (–23%, $P<0.0001$), while MAP and pulmonary artery occlusion pressure were unchanged. In the post-drug control period, cardiac index was higher and indexed systemic vascular resistance was lower compared to the predrug control period. Body temperature increased slightly but significantly during the experimental procedure.

Splanchnic circulation

Splanchnic oxygen extraction increased during norepinephrine infusion ($P<0.05$) (Table 2). In the subgroup of patients ($n=9$) with the lowest cardiac index (CI <2.4 , mean CI = 2.1 ± 0.2 l·min $^{-1}\cdot\text{m}^2$), norepinephrine induced a significant increase in splanchnic oxygen extraction from

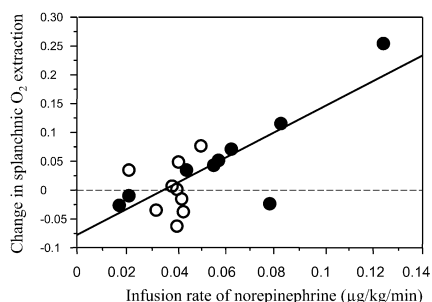


Fig. 1 A linear regression analysis relating the individual dose of norepinephrine to the norepinephrine-induced change in splanchnic oxygen extraction. There was a significant positive correlation between norepinephrine dose and the change in splanchnic oxygen extraction ($r = 0.78$, $P < 0.0001$). Filled circles represent patients ($n=9$) with a cardiac index <2.4 l·min $^{-2}$ at baseline and open circles patients ($n=9$) with a cardiac index >2.4 l·min $^{-2}$ at baseline

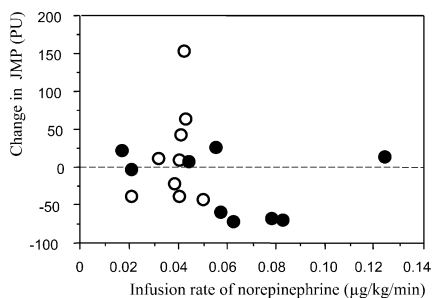


Fig. 2 A linear regression analysis relating the individual dose of norepinephrine to the norepinephrine-induced change in jejunal mucosal perfusion. There was no significant correlation between the individual dose of norepinephrine and the change in jejunal mucosal perfusion. ($r = 0.22$, n.s.). Filled circles represent patients with a cardiac index <2.4 l·min $^{-2}$ at baseline and open circles patients with a cardiac index >2.4 l·min $^{-2}$ at baseline

$36 \pm 4\%$ to $43 \pm 11\%$ ($P < 0.05$) which was not seen in the subgroup of patients ($n=9$) with high baseline cardiac index (CI >2.4 , mean CI $= 2.8 \pm 0.4$ l·min $^{-2}$) ($42 \pm 9\%$ to $42 \pm 10\%$, n.s.). A linear regression analysis revealed a positive correlation between the individual dose of norepinephrine and the absolute increase in splanchnic oxygen extraction ($r=0.78$, $P < 0.0001$), (Fig. 1). In the subgroup of patients with the lowest cardiac index, there was a dose-dependent increase in splanchnic oxygen extraction ($r=0.84$, $P < 0.01$) (Fig. 1), which could not be seen in the group of patients with high cardiac index ($r=0.11$, n.s.). Those patients with high cardiac index tended to need less norepinephrine (39 ± 8 ng·kg $^{-1}$ ·min $^{-1}$), than those with low cardiac index (60 ± 33 ng·kg $^{-1}$ ·min $^{-1}$) ($P=0.064$) to reach the target MAP. Neither jejunal mucosal perfusion

nor gastric-arterial pCO $_2$ -gradient were affected by norepinephrine and there were no significant correlation between individual dose of norepinephrine and change in jejunal mucosal perfusion or gastric-arterial pCO $_2$ gradient in the whole group or in the subgroups with low or high cardiac index (Fig. 2). Splanchnic lactate extraction increased significantly by norepinephrine. None of the patients produced lactate during norepinephrine infusion.

The addition of dopamine increased jejunal mucosal perfusion by 32% ($P < 0.001$) with no change in the gastric-arterial pCO $_2$ gradient. Dopamine infusion decreased splanchnic oxygen extraction ($P < 0.001$) and lactate extraction ($P < 0.05$). In the postdrug control period splanchnic lactate extraction was significantly lower than the predrug control value ($P < 0.01$).

Discussion

In the present study the effects of norepinephrine on local gastrointestinal mucosal perfusion assessed by jejunal mucosal laser Doppler flowmetry or gastric tonometry, as well as global splanchnic oxygen extraction were evaluated in patients after cardiac surgery. The major findings of the present study were that neither intestinal mucosal perfusion nor gastric-arterial pCO $_2$ gradient were changed by norepinephrine when used to increase mean arterial blood pressure by 30%. Norepinephrine caused, however, an increase in global splanchnic oxygen extraction, a direct measure of splanchnic oxygen demand-supply relationship. Furthermore, a highly significant positive correlation between the individual dose of norepinephrine and absolute increase in global splanchnic oxygen extraction was demonstrated, particularly in patients with low baseline cardiac index. Such an increase in splanchnic oxygen extraction by norepinephrine is likely to be caused by a decrease in splanchnic blood flow, as splanchnic blood flow is closely and inversely correlated to splanchnic oxygen extraction in man after cardiac surgery [9]. We cannot, however, completely rule out the possibility that the increase in splanchnic oxygen extraction, to some extent, is caused by a norepinephrine-induced increase in splanchnic oxygen consumption after cardiac surgery. On the other hand, previous studies on patients with septic shock have demonstrated that norepinephrine does not increase splanchnic oxygen consumption significantly [4, 5, 8]. Those patients with the lowest baseline cardiac index needed higher infusion rates of norepinephrine and were thus more likely to respond with a more pronounced increase in splanchnic oxygen extraction (decrease in splanchnic blood flow). One could therefore speculate that the lack of effect of norepinephrine on jejunal mucosal perfusion might be explained by a redistribution of intestinal blood flow to the mucosa during vasopressor therapy in postoperative patients.

Our data are in line with a recent experimental study on normal anesthetized pigs demonstrating that incremental infusion rates of norepinephrine or phenylephrine to increase MAP by 15–70% caused no changes in jejunal microvascular blood flow, mucosal tissue oxygen tension or microvascular hemoglobin oxygen saturation [14]. In endotoxin shock models, norepinephrine induced no adverse effects on intestinal mucosal perfusion [15, 16], or even attenuated mucosal acidosis [16] when used to maintain MAP at preshock levels. Revelly and coworkers demonstrated in a normodynamic pig model of endotoxin shock that norepinephrine maintained intestinal mucosal blood flow at the expense of the muscularis blood flow and that mucosal tissue ATP levels were higher than in the endotoxin treated animals not receiving norepinephrine [17].

The absence of norepinephrine-induced gastrointestinal mucosal vasoconstriction when used as a vasopressor agent could at least partly be explained by the so-called "autoregulatory escape" phenomenon. It is well-known that stimulation of sympathetic vasoconstrictor fibers or infusion of norepinephrine leads to an initial decrease in intestinal blood flow, which is followed by a return of flow to the base-line value [18]. It has been suggested that this "escape" from norepinephrine-induced vasoconstriction in the intestine is due to relaxation of constricted arterioles by local vasodilator metabolites, e.g., adenosine, and not by opening of arteriovenous anastomoses [18, 19]. Another possibility could be that the norepinephrine-induced α_1 -agonistic effect is counteracted by a β_2 -mediated vasodilatory action. Reinelt et al. recently demonstrated in patients with hyperdynamic septic shock that splanchnic blood flow decreased by 40% when norepinephrine was substituted for the pure α_1 -agonist phenylephrine at identical levels of MAP and cardiac index [8]. A third possibility could be that laser Doppler flowmetry technique is not sensitive enough to detect a norepinephrine-induced intestinal mucosal vasoconstriction in man. However, we have previously demonstrated in healthy volunteers that simulated mild hypovolemia by lower body negative pressure, reducing cardiac index by 15–20%, decreased jejunal mucosal perfusion by 17% [20].

When a low dose of dopamine was added to the continuous norepinephrine infusion, cardiac index increased (33%) and splanchnic oxygen extraction decreased indicating a concomitant increase in splanchnic blood flow. This was accompanied by a 32% increase in jejunal mucosal perfusion. These results confirm our previous findings in postoperative patients of a 20–27% increase in jejunal mucosal perfusion with low doses of the dopaminergic agents dexopamine (0.7 $\mu\text{g}\cdot\text{kg}\cdot\text{min}$) and dopamine (2.7 $\mu\text{g}\cdot\text{kg}\cdot\text{min}$) which is in striking contrast to the 7% increase with dobutamine when cardiac index was increased by 25% by each agent in a randomized blinded cross-over study [12]. Thus, the results of the present study and our previous one [12] suggest that dopaminergic agents should preferably be used in cardiac surgical

patients who may suffer from intestinal mucosal hypoperfusion. It has been demonstrated in animal studies that dopamine may redistribute jejunal blood flow to the mucosa and submucosa from the serosal and muscular layers and that this mucosal vasodilatation is mediated by DA_1 receptors [21, 22]. Furthermore, dopamine improves jejunal mucosal tissue oxygenation and microvascular hemoglobin oxygen saturation in anesthetized normal as well as endotoxemic pigs [23, 24]. In humans the effects of dopamine on gastric mucosal perfusion have been evaluated by using the endoluminal laser Doppler flowmetry technique [25, 26, 27] and the results of these studies are controversial. Karzai et al. found that dopamine at a dose of 6 $\mu\text{g}\cdot\text{kg}\cdot\text{min}$ increased gastric mucosal perfusion by 66% during cardiopulmonary bypass, whereas dobutamine at the same dose did not affect gastric mucosal perfusion [25, 26]. In striking contrast, Nevière et al. showed that in patients with sepsis 5 $\mu\text{g}\cdot\text{kg}\cdot\text{min}$ of dopamine caused a 28% decrease in gastric mucosal perfusion whereas the same dose of dobutamine increased gastric mucosal perfusion by 32% [27]. The gastric-arterial pCO_2 -gradient is considered to reflect the relationship between gastric mucosal metabolism (CO_2 production) and blood flow [28, 29, 30]. It has recently been shown that dopamine increases both splanchnic blood flow and oxygen consumption after uncomplicated cardiac surgery [31]. In the present study, dopamine did not affect the gastric-arterial pCO_2 -gradient, which could be explained by a proportional increase in both gastric mucosal blood flow and metabolism. However, it has also been demonstrated that the physiology of the gastric-arterial pCO_2 -gradient during therapeutic interventions after cardiac surgery is complex and that changes in splanchnic blood flow or oxygen delivery induced by catecholamine therapy, may not be associated by changes in the gastric-arterial pCO_2 -gradient [32].

There are only a few previous human studies that use the endoluminal approach in the small intestine [9, 12, 13, 20, 33]. The laser Doppler flowmetry signal is proportional to the number and velocity of red blood cells in the tissue volume of interest and thus can provide useful information on tissue oxygen delivery. A limitation of the laser Doppler flowmetry technique is that the exact measuring depth of the intestinal wall is unknown. The measuring depth depends partly on instrumental design factors such as fiber diameter and the distance between the transmitting and receiving fibers and the wavelength of the light used. It has previously been shown from measurements of the intestinal wall that the measuring depth of a probe of our design is less than 2.4 mm [34]. Given a thickness of human intestinal mucosa and submucosa of approximately 1.5–2.5 mm [35], our recorded flux values thus largely reflect mucosal/submucosal perfusion. Although laser Doppler flowmetry yields no absolute blood flow values, the laser Doppler flowmetry values correlate strongly with simultaneously obtained

absolute blood flow values using the total venous outflow technique both in man and animals [36, 37]. Furthermore, the laser Doppler flowmetry values from the mucosal side of the jejunum correlate strongly with simultaneously obtained absolute mucosal/submucosal blood flow measurements by hydrogen gas clearance and microsphere techniques [38]. One advantage of the laser Doppler flowmetry technique is that it is possible to measure mucosal perfusion continuously, whereas the drawback is that measurements can be performed only at a local site and during intestinal quiescence, because peristalsis causes motion artifacts. However, peristalsis is a smaller problem in patients during anesthesia/sedation compared with awake volunteers [20].

In the present study, norepinephrine and dopamine were administered in uncomplicated, normotensive postcardiac surgical patients. Obviously, the results of the present study cannot immediately be transposed to, for example, patients with septic shock, requiring norepinephrine. One major limitation of this study is that we did not include a time-control group. We chose a difficult, but clinically relevant, time period to evaluate the effects of norepinephrine alone and norepinephrine plus dopamine on systemic and splanchnic perfusion. One could, therefore, argue that changes in the measured variables were not entirely caused by the catecholamines themselves, but also, to some extent, by spontaneous fluctuations or time-dependent effects on these variables. This is illustrated by the fact that the postcontrol values of body temperature and cardiac index, obtained 2 h after discontinuation of the catecholamines, were higher than predrug control values. However, the primary variables of interest in the present study, jejunal mucosal perfusion, gastric-arterial pCO_2 gradient as well as splanchnic oxygen extraction did not change significantly over time.

Furthermore, we have previously shown that neither splanchnic blood flow nor jejunal mucosal perfusion change significantly over time in a similar group of postcardiac surgical patients studied during similar conditions [9, 12]. We therefore believe that the effects of the catecholamines on the measured variables in the present study are caused by the catecholamines themselves and not by spontaneous fluctuations or time-dependent changes of these variables. Changes in the flow-dependent variable splanchnic lactate extraction during the experimental procedure are most likely explained by reciprocal changes in splanchnic blood flow. The inotropic and chronotropic cardiac response to norepinephrine and dopamine were probably attenuated in the present study, as all patients received their prescribed long-acting β_1 -selective adrenergic blocker (atenolol or metoprolol) on the morning of surgery. However, the potential effects of these agents on splanchnic vascular α_1 -, β_2 - or dopaminergic receptors were probably not affected by the treatment with β_1 -selective adrenergic blockers.

In conclusion, we have shown that vasopressor therapy with norepinephrine in postcardiac surgical patients to increase mean arterial pressure by 30% does not affect jejunal mucosal perfusion or gastric mucosal pCO_2 -gradient in spite of a dose-dependent decrease in global splanchnic oxygenation suggesting an intramural redistribution of flow to the gastrointestinal mucosa. The addition of low-dose dopamine induced a decrease in splanchnic oxygen extraction, which was accompanied by a 32% increase in jejunal mucosal perfusion.

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III

Vasopressors and intestinal mucosal perfusion after cardiac surgery: Norepinephrine vs. phenylephrine

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Objectives: To evaluate the potential differential effects of norepinephrine, an α_1 -, β_1 -, and β_2 -receptor agonist, to the α_1 -agonist phenylephrine on jejunal mucosal perfusion, gastric-arterial P_{CO_2} gradient, and the global splanchnic oxygen demand-supply relationship after cardiac surgery.

Design: A randomized, prospective, interventional crossover study.

Setting: A university cardiothoracic intensive care unit.

Patients: Ten patients were studied during propofol sedation and mechanical ventilation after uncomplicated coronary artery bypass surgery.

Interventions: Each patient received randomly and sequentially norepinephrine ($0.052 \pm 0.009 \mu\text{g/kg/min}$) and phenylephrine ($0.50 \pm 0.22 \mu\text{g/kg/min}$) to increase mean arterial blood pressure by 30%.

Measurements and Main Results: Data on jejunal mucosal perfusion, jejunal mucosal hematocrit, and red blood cell velocity (laser Doppler flowmetry) as well as gastric-arterial P_{CO_2} gradient (tonometry) and splanchnic oxygen extraction were obtained before (control) and during a 30-min drug infusion period after the target mean arterial blood pressure was reached. The procedure was sequentially repeated for the second vasopressor. Both drugs induced a 40–46%

increase in systemic vascular resistance with no change in cardiac index. Neither jejunal mucosal perfusion, jejunal mucosal hematocrit, red blood cell velocity, nor gastric-arterial P_{CO_2} gradient was affected by any of the vasopressors. Splanchnic oxygen extraction increased from 38.2% to 43.1% ($p < .001$) with norepinephrine and from 39.3% to 47.5% ($p < .001$) with phenylephrine. This increase was significantly more pronounced with phenylephrine compared with norepinephrine ($p < .05$). Mixed venous-hepatic vein oxygen saturation gradient increased with both drugs ($p < .01$), and the increase was more pronounced with phenylephrine ($p < .05$). Splanchnic lactate extraction was not significantly affected by any of the vasopressors.

Conclusions: Phenylephrine induced a more pronounced global α_1 -mediated splanchnic vasoconstriction compared with norepinephrine. Neither of the vasoconstrictors impaired perfusion of the gastrointestinal mucosa in postcardiac surgery patients. The lack of norepinephrine-induced, α_1 -mediated impairment of gastrointestinal perfusion is not explained by a β_2 -mediated counteractive vasodilation but instead by possible mucosal autoregulatory escape. (Crit Care Med 2006; 34:722–729)

Key Words: intestinal mucosa; microcirculation; norepinephrine; phenylephrine; laser Doppler

Clinical septic shock and the vasodilatory shock syndrome after cardiac surgery are characterized by a profound arteriolar vasodilation resulting in a low systemic vascular resistance and hypotension. Norepinephrine is com-

monly used and recommended for the treatment of hypotension in volume-resuscitated hyperdynamic septic shock and in postcardiotomy vasodilatory shock (1–3). Norepinephrine has α_1 -agonistic as well as β_1 - and β_2 -agonistic properties and elevates systemic perfusion pressure mainly by an increase in systemic vascular resistance. Splanchnic blood flow seems to be well maintained during vasopressor therapy with norepinephrine in these patients (4–6), but data on the effects of vasopressors on intestinal mucosal perfusion in patients with or without vasodilatory shock are scarce.

There is no consistent association between global splanchnic blood flow and local intestinal mucosal perfusion evaluated by laser Doppler flowmetry or gastric mucosal perfusion assessed by gastric tonometry in humans (7). The lack of correlation between intestinal mucosal perfusion and splanchnic blood flow may thus indicate that global measurements of oxygen delivery across the whole

splanchnic region do not necessarily reflect the degree of oxygenation or perfusion of the mucosal layer (7), which probably is the most vulnerable portion of the intestinal wall (8).

It has recently been shown that vasopressor therapy with norepinephrine after cardiac surgery does not jeopardize intestinal or gastric mucosal perfusion in spite of a dose-dependent increase of the global splanchnic oxygen demand-supply relationship (9). This could, at least partly, be explained by a counteraction of the norepinephrine-induced α_1 -agonistic vasoconstriction by a β_2 -mediated vasodilation of the gastrointestinal mucosa. To evaluate the presence and the magnitude of this potential β_2 -mediated vasodilatory action on the gastrointestinal mucosa, we compared the effects of norepinephrine to those of the pure α_1 -agonist phenylephrine on human intestinal mucosal perfusion, assessed by laser Doppler flowmetry, as well as gastric mucosal perfusion, reflected by the gastric-

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arterial mucosal Pco_2 gradient. In the present study we thus tested the null hypothesis that neither the pure α_1 -adrenoceptor agonist phenylephrine nor norepinephrine with its combined α_1 -mediated vasoconstrictive and β_2 -mediated vasodilatory action impairs splanchnic mucosal perfusion.

MATERIALS AND METHODS

The Human Ethics Committee of the University of Göteborg approved the study protocol, and informed consent was obtained from each patient. Ten patients (nine male, one female) with a mean age of 66 (range, 52–77) yrs with coronary artery disease and with a left ventricular ejection fraction $>50\%$, undergoing uncomplicated coronary artery bypass grafting, were included. All patients were treated with long-acting β_1 -selective adrenergic blockers (atenolol or metoprolol), including the morning of surgery.

The patients were premedicated with oral flunitrazepam (1 mg), intramuscular morphine (5 mg), and scopolamine (0.2 mg). Anesthesia was induced with thiopentone (3–5 mg/kg) and fentanyl (5–7 $\mu\text{g/kg}$), followed by pancuronium (0.1 mg/kg) and maintained by fentanyl (2–4 $\mu\text{g/kg}$) and enflurane. Anesthesia was maintained by propofol during cardiopulmonary bypass. An oral dose of 20 mg of cisapride was given at the end of the operation to facilitate the positioning of the jejunal catheter. In the intensive care unit, the patients were sedated with propofol and mechanically ventilated to normocapnea. Postoperative hypovolemia was treated according to routine clinical practice with hydroxethylstarch (HAES-steril, Fresenius Kabi, Uppsala Sweden) and crystalloid fluids. The hepatic vein and the pulmonary artery were catheterized with 7-Fr. pulmonary artery catheters (Baxter Healthcare Corporation) during fluoroscopic guidance. Cardiac index was measured in triplicate by the thermodilution technique (mean of three 10-mL ice-cold saline injections). Blood lactate concentrations were determined using an enzymatic method (YSI 2300 Stat Plus, YSI, Yellow Springs, OH). Splanchnic oxygen extraction and lactate extraction were calculated using standard formulas. Blood gas analyses were performed with automated blood gas analyzer (Synthesis 25, Instrumental Laboratories, Italy). The arterial blood pressure, pulmonary arterial pressure, and central venous pressure as well as jejunal mucosal perfusion were continuously measured and stored with Perisoft software (Perimed AB, Järfälla, Sweden) at a sampling frequency of 32 Hz. Temperature was continuously measured in the pulmonary artery.

The technique of laser Doppler flowmetry of the intestinal mucosa in humans has pre-

viously been described in detail (10, 11). A custom-made laser Doppler catheter (Perimed AB, Järfälla, Sweden) was placed through the nasogastric route during fluoroscopic guidance endoluminally in the proximal jejunum, 20–40 cm distal to the ligament of Treitz. The probe consists of three triangular-placed optical fibers with a diameter of 150 μm and a fiber center separation of 200 μm placed 23 mm from the tip of the catheter. One fiber emits light with a wavelength of 780 nm and the other two receive the Doppler shifted and backscattered light. The jejunal mucosal perfusion was measured with a laser Doppler flowmeter (Periflux PF 4001 Perimed AB, Järfälla, Sweden). For measurements of jejunal mucosal perfusion, a time constant of 0.2 secs and a bandwidth of 20–25 kHz were used, and calibration of the probe was performed as recommended by the manufacturer. Jejunal mucosal perfusion (JMP) is defined as number of red blood cells (RBC)-area $^{-1}$ -time $^{-1}$. The laser Doppler equipment used in the present study has the ability to separately analyze the two components of the JMP: jejunal mucosal hematocrit (JMht), defined as the number of RBC-volume $^{-1}$, and RBC velocity, defined as length-time $^{-1}$. The JMP is thus the product of the JMht and RBC velocity (12, 13). All the JMP, JMht, and RBC velocity values presented in this study were calculated from periods of intestinal quiescence. Gastric mucosal Pco_2 was measured every 10 mins by a standard air-filled tonometry nasogastric tube (TRIP®, NGS tonometry catheter, Tonometrics, Helsinki, Finland) connected to an automated gas analyzer (Tonocap TC-200, Datex, Helsinki, Finland). The correct position of the tube was confirmed by fluoroscopy, and continuous suction was applied to drain the stomach of air and juice. The gastric-arterial Pco_2 gradient was calculated.

Experimental Procedures. The patients were sedated with propofol at a dose (3.4 ± 0.6 mg/kg/hr) to provide adequate sedation and a mean arterial pressure (MAP) of 65–75 mm Hg according to our standard protocol. This dose was not changed during the experimental protocol. Measurements started 345 \pm 40 mins after the end of cardiopulmonary bypass after successful positioning of catheters and when the patients were considered not to have a bleeding problem, with a mixed venous oxygen saturation of $>60\%$ and a body temperature $>36.5^\circ\text{C}$. Each patient received sequentially and randomly both norepinephrine and phenylephrine in a crossover study design. The infusion rate of each vasopressor was titrated to the target MAP of 90 mm Hg. The protocol thus consisted of four periods: period 1, a predrug control period at a stable MAP of 65–75 mm Hg; period 2, infusion of the first vasopressor; period 3, a second predrug control period after a washout period of 60 mins; and period 4, infusion of the second vasopressor. The highest acceptable systolic blood

pressure level during periods 2 and 4 was 150 mm Hg. Each of the four periods consisted of a 30-min measurement period preceded by a 10- to 20-min period for dose titration (periods 2 and 4). JMP was continuously recorded during the four periods, and mean JMP was calculated during intestinal quiescence (average 17 ± 6 min/period). Gastric mucosal Pco_2 was measured every 10 mins, and the mean value for each sampling period was calculated. Systemic hemodynamics were measured, and samples for blood gas analysis and lactate and hemoglobin concentrations were taken at the end of each period.

Statistics. A Kolmogorov-Smirnov test for goodness of fit to normal distribution was performed, and normality was obtained for all main measurements. Each patient received randomly and sequentially norepinephrine and phenylephrine. A two-way analysis of variance for repeated measurements followed by *post hoc* single degree of freedom comparisons (contrast analyses) was used a) to evaluate the effects of each vasopressor vs. its respective control (within-group comparison); b) to evaluate the effects of phenylephrine vs. those of norepinephrine (between-group comparison); and c) to compare the control periods preceding norepinephrine to the control period preceding phenylephrine. To evaluate the effect of time on various variables, a paired Student's *t*-test was performed on the first and the second predrug control period. We considered $p < .05$ to be statistically significant. Values are mean \pm sd.

RESULTS

Central Hemodynamics. A norepinephrine infusion rate of 0.052 ± 0.009 $\mu\text{g/kg/min}$ (range, 0.021–0.124 $\mu\text{g/kg/min}$) was needed to reach the target MAP of 90 mm Hg. This norepinephrine-induced elevation in MAP was caused by a 40% increase in systemic vascular resistance index ($p < .001$), whereas cardiac index did not change. Pulmonary artery occlusion pressure and central venous pressures increased slightly ($p < .01$), whereas heart rate and stroke volume index were unchanged during norepinephrine infusion. Infusion of phenylephrine at a rate of 0.50 ± 0.22 $\mu\text{g/kg/min}$ (range, 0.21–0.94 $\mu\text{g/kg/min}$) caused an increase in systemic vascular resistance index by 46% ($p < .001$). Central venous pressure ($p < .001$) and pulmonary artery occlusion pressures ($p < .01$) increased slightly, whereas cardiac index was not significantly changed. Hemodynamic changes during vasopressor infusions did not differ between norepinephrine and phenylephrine (Table 1).

Splanchnic Circulation. An individual recording of JMP, JMht, and RBC mea-

Table 1. Systemic effects of norepinephrine (NE) and phenylephrine (PHE)

	Predrug	NE	Predrug	PHE	ANOVA
Mean arterial pressure, mm Hg	69 ± 3	92 ± 3 ^a	68 ± 5	92 ± 4 ^a	<i>p</i> < .0001
Cardiac index, L/min/m ²	2.48 ± 0.32	2.43 ± 0.44	2.55 ± 0.32	2.41 ± 0.35	NS
Heart rate, beats/min	68 ± 11	67 ± 9	73 ± 14	69 ± 10	NS
Stroke volume index, mL/m ²	37 ± 8	37 ± 9	36 ± 9	35 ± 7	NS
SVRI, dynes · sec/cm ⁵ /m ²	2007 ± 216	2811 ± 433 ^a	1917 ± 336	2808 ± 348 ^a	<i>p</i> < .0001
PAOP, mm Hg	11.3 ± 2.9	12.6 ± 3.6 ^b	10.7 ± 2.6	12.2 ± 3.2 ^b	<i>p</i> < .01
CVP, mm Hg	7.9 ± 2.1	8.7 ± 2.2 ^b	7.8 ± 2.2	9.0 ± 2.7 ^b	<i>p</i> < .001

ANOVA, analysis of variance; NS, not significant; SVRI, systemic vascular resistance index; PAOP, pulmonary artery occlusion pressure; CVP, central venous pressure.

^a*p* < .001 vs. predrug; ^b*p* < .01 vs. predrug. Values are expressed as mean ± SD. The following comparisons were made: a) the effects of each vasopressor vs. their respective control; b) the effects of phenylephrine vs. those of norepinephrine; and c) the control period preceding norepinephrine versus the control period preceding phenylephrine.

sured by laser Doppler flowmetry and the arterial pressure before and during a steady-state infusion of phenylephrine is seen in Figure 1. JMP, JMHT, RBC velocity, and the gastric-arterial PCO₂ gradient were not affected by any of the vasopressors. Splanchnic oxygen extraction increased during both norepinephrine and phenylephrine infusion (*p* < .001). The increase in splanchnic oxygen extraction was significantly more pronounced with phenylephrine than with norepinephrine (*p* < .05). Both agents increased the mixed venous-hepatic venous oxygen saturation gradient (*p* < .05). Phenylephrine increased the mixed venous-hepatic venous oxygen saturation gradient to a greater extent than norepinephrine (*p* < .05). Arterial lactate levels increased significantly with phenylephrine (*p* < .01) but not with norepinephrine. There was a tendency for an increase in splanchnic lactate extraction with both vasopressors (analysis of variance, *p* = .059). None of the vasopressors induced individual lactate production. No apparent difference in response to vasopressors between patients with or without hypertension was observed in JMP, gastric mucosal-arterial PCO₂ difference, or splanchnic oxygen extraction (Figs. 2–4, Table 2).

The second predrug control mean values of cardiac index were slightly higher and the systemic vascular resistance index was slightly lower compared with the first predrug control values (2.64 ± 0.24 L/min/m² vs. 2.39 ± 0.23, *p* < .01, and 1871 ± 243 vs. 2053 ± 173 dyne-sec/cm⁵/m², *p* < .01). The second predrug control mean value of body temperature was significantly higher compared with the first predrug control mean value (37.4 ± 0.6 vs. 37.2 ± 0.6°C, *p* < .05). Otherwise, there were no significant changes in predrug baseline values over time of any of the recorded variables.

DISCUSSION

In the present study, the potential differential effects of norepinephrine and phenylephrine infusion on local gastrointestinal mucosal perfusion were assessed by jejunal mucosal laser Doppler flowmetry and gastric tonometry in postcardiac surgery patients. The major finding of the present study were that neither intestinal mucosal perfusion nor gastric-arterial PCO₂ gradient was changed by any of the drugs when used to increase mean arterial blood pressure by 30–35%; that is, we accepted the null hypothesis.

Both vasopressors increased global splanchnic oxygen extraction, a direct measure of the splanchnic oxygen demand-supply relationship, as well as the mixed venous-hepatic vein oxygen saturation gradient. An increase of these variables by a pure α₁-agonist, such as phenylephrine, indicates that a splanchnic vasoconstriction occurred with a redistribution of global splanchnic blood flow away from the gastrointestinal territory. An increase in splanchnic oxygen extraction and mixed venous-hepatic vein oxygen saturation gradient might, however, also be explained by an increase in splanchnic oxygen consumption, mainly mediated by β₂-adrenoceptors (14, 15). Norepinephrine with its β₂-agonistic properties has been found to increase splanchnic oxygen consumption (6), whereas others found unchanged splanchnic oxygen consumption with norepinephrine (4, 5). Data on the effects of phenylephrine on splanchnic oxygen consumption are scarce. Reinelt et al. (16) compared the effects of phenylephrine with those of norepinephrine and at an identical cardiac index and mean arterial pressure in six patients with hyperdynamic septic shock and found no significant difference in splanchnic oxygen

consumption between the vasopressors. These authors concluded that norepinephrine-induced β₂-adrenoceptor stimulation does not determine splanchnic oxygen utilization in septic shock. The finding of the present study that phenylephrine caused a more pronounced increase in splanchnic oxygen extraction and mixed venous-hepatic vein oxygen saturation gradient, compared with norepinephrine, suggests that phenylephrine induces a more pronounced global splanchnic vasoconstriction compared with norepinephrine. From a global splanchnic point of view, one should therefore be cautious in the use of phenylephrine or even should avoid phenylephrine for treatment of normovolemic hypotension after cardiac surgery. Our data support the results from Reinelt et al. (16), who demonstrated in septic patients that splanchnic blood flow decreased by 40% when norepinephrine was substituted for the pure α₁-agonist phenylephrine at identical levels of MAP and cardiac index.

One could speculate that the lack of effect of norepinephrine and phenylephrine on gastrointestinal mucosal perfusion, in spite of their global splanchnic vasoconstrictive effect, might be explained by a transmural redistribution of gastrointestinal blood flow toward the mucosa during vasopressor therapy. Our data are in line with experimental studies on dogs demonstrating that norepinephrine (200 ng/kg/min) did not change ileal mucosal perfusion (17) and studies on normal anesthetized pigs showing that incremental infusion rates of norepinephrine or phenylephrine, to increase MAP by 15–70%, caused no changes in jejunal microvascular blood flow, mucosal tissue oxygen tension, or microvascular hemoglobin oxygen saturation (18). In endotoxin shock models, norepineph-

rine induced no adverse effects on intestinal mucosal perfusion (19, 20) or even attenuated mucosal acidosis (20) when used to maintain MAP at preshock levels. In a normodynamic pig model of endotoxin shock, it was demonstrated that norepinephrine maintained intestinal mucosal blood flow at the expense of the

muscularis blood flow and that mucosal tissue adenosine triphosphate levels were higher than in the endotoxin-treated animals not receiving norepinephrine (21). The absence of vasopressor-induced reduction in gastrointestinal mucosal perfusion could at least partly be explained by the so-called autoregulatory

escape phenomenon. It is well known that stimulation of sympathetic vasoconstrictor fibers or infusion of norepinephrine leads to an initial decrease in hepato mesenteric blood flow, which is followed by a return of flow toward the baseline value (22–29). Thus, vascular escape is seen as a partial or full recovery

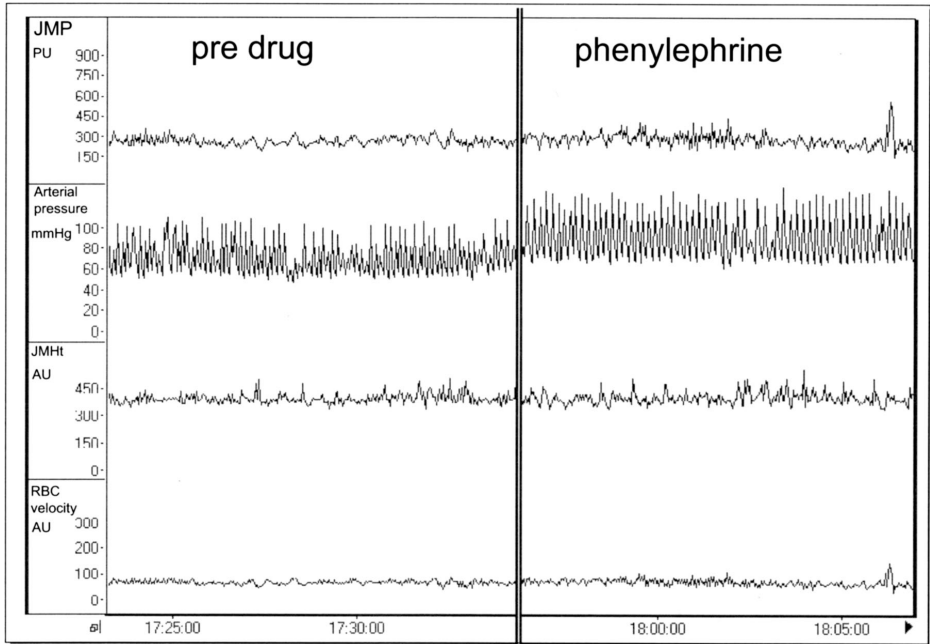


Figure 1. An individual recording of jejunal mucosal perfusion (*JMP*), jejunal mucosal hematocrit (*JMHt*), and red blood cell (*RBC*) velocity measured by laser Doppler flowmetry and the arterial pressure before and during a steady-state infusion of phenylephrine. *AU*, arbitrary units; *PU*, perfusion units.

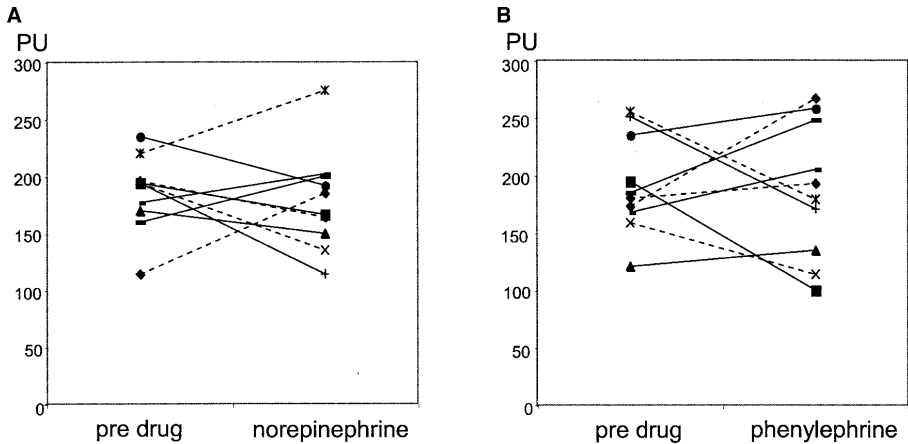


Figure 2. Individual data on jejunal mucosal perfusion measured by laser Doppler flowmetry before and during infusion of norepinephrine (*a*) and phenylephrine (*b*). *PU*, perfusion units. Patients with a history of hypertension (*n* = 4) are depicted with dashed lines.

from initial vasoconstriction despite continued constrictor stimuli. It has been suggested that this "escape" from norepinephrine-induced vasoconstriction in the intestine is due to relaxation of initially constricted arterioles by local vasodilator metabolites (e.g., adenosine) and not by opening of arteriovenous anastomoses (29, 30). Others have suggested that norepinephrine-induced autoregulatory escape involves simultaneous β -adrenoceptor, purinergic, and nitric oxide mediation (27, 28, 31). It has been shown that both the muscularis and the mucosal circulation exhibit the ability to escape an

α_1 -mediated vasoconstrictor influence but that the propensity to escape is greater in the mucosa than in the muscularis (24, 25), particularly in humans (24).

Gastric-arterial PCO_2 gradients reflect the relationship between local gastric mucosal metabolism and perfusion. In the present study, the drugs did not affect the gastric-arterial PCO_2 gradient, suggesting that the vasopressors did not alter the regional gastric mucosal relationship between blood flow and metabolism. However, changes in gastric-arterial PCO_2 gradient must be interpreted with cau-

tion after cardiac surgery. It has been demonstrated that the physiology of the gastric-arterial PCO_2 gradient during therapeutic interventions after cardiac surgery is complex and that changes in splanchnic blood flow or oxygen delivery induced by catecholamine therapy may not be associated with changes in the gastric-arterial PCO_2 gradient (32). It has previously been shown that there is a lack of association between gastric-arterial PCO_2 gradients and jejunal mucosal perfusion, assessed by laser Doppler flowmetry, after cardiac surgery (7). In other words, changes in gastric and intestinal

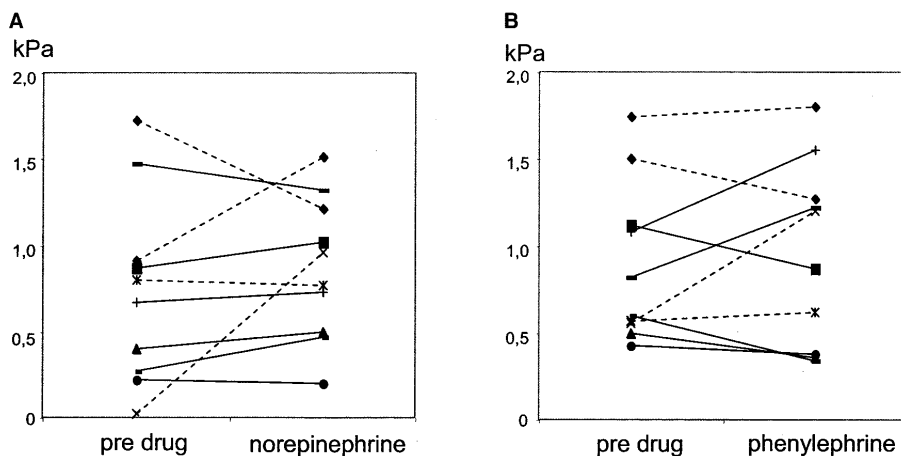


Figure 3. Individual data on gastric-arterial PCO_2 gradient before and during infusion of norepinephrine (a) and phenylephrine (b). Patients with a history of hypertension ($n = 4$) are depicted with *dashed lines*.

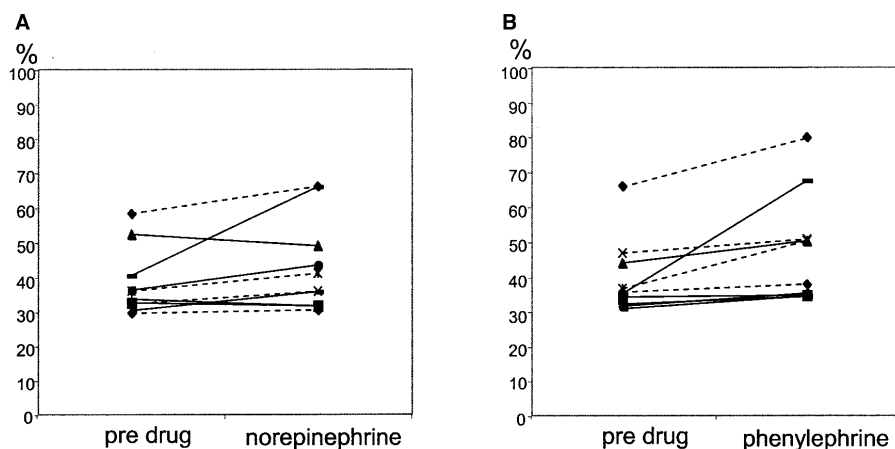


Figure 4. Individual data on splanchnic oxygen extraction before and during infusion of norepinephrine (a) and phenylephrine (b). Patients with a history of hypertension ($n = 4$) are depicted with *dashed lines*.

Table 2. Splanchnic effects of norepinephrine (NE) and phenylephrine (PHE)

	Predrug	NE	Predrug	PHE	ANOVA
Jejunal mucosal perfusion, PU	185 ± 33	178 ± 44	192 ± 43	187 ± 59	NS
RBC velocity, AU	73 ± 17	76 ± 20	86 ± 28	82 ± 24	NS
JMHT, AU	260 ± 68	236 ± 44	228 ± 41	229 ± 54	NS
Gastric-arterial Pco ₂ gap, kPa	0.7 ± 0.5	0.9 ± 0.4	0.9 ± 0.4	1.0 ± 0.4	NS
Splanchnic oxygen extraction, %	38 ± 10	43 ± 13 ^b	39 ± 11	48 ± 16 ^{b,c}	<i>p</i> < .05
Hepatic vein oxygen saturation, %	61 ± 9	56 ± 13	59 ± 11	52 ± 16	NS (<i>p</i> = .06)
Mixed venous-hepatic vein oxygen saturation gradient, % units	9 ± 8	14 ± 11 ^a	9 ± 8	20 ± 12 ^{b,c}	<i>p</i> < .05
Arterial lactate, mmol/L	0.93 ± 0.44	0.96 ± 0.39	0.91 ± 0.40	1.09 ± 0.52 ^a	<i>p</i> < .01
Hepatic vein lactate, mmol/L	0.56 ± 0.38	0.49 ± 0.29	0.57 ± 0.43	0.68 ± 0.61	NS
Splanchnic lactate extraction, %	43 ± 14	50 ± 14	40 ± 19	44 ± 20	NS (<i>p</i> = .059)

ANOVA, analysis of variance; PU, perfusion units; NS, not significant; RBC, red blood cell; AU, arbitrary units; JMHT, jejunal mucosal hematocrit.

^a*p* < .01 vs. predrug; ^b*p* < .001 vs. predrug; ^c*p* < .05 vs. NE. The following comparisons were made: a) the effects of each vasopressor vs. their respective control; b) the effects of phenylephrine vs. those of norepinephrine; and c) the control period preceding norepinephrine vs. the control period preceding phenylephrine.

mucosal perfusion might not occur in parallel. This inconsistent relationship could be explained by the fact that laser Doppler flowmetry measures perfusion whereas gastric tonometry reveals the relationship between gastric mucosal CO₂ production and perfusion or by the presence of uneven flow distribution within jejunal and/or gastric mucosal tissues. Neither norepinephrine nor phenylephrine affected the relationship between the local gastric mucosal metabolism and perfusion or the jejunal mucosal perfusion in striking contrast to the impairment of the global splanchnic oxygen demand-supply relationship seen with these agents. To our knowledge, there are no data on the effects of norepinephrine or phenylephrine on gastric-arterial Pco₂ gradients or jejunal mucosal perfusion in postoperative patients.

The phenylephrine-induced increase in arterial lactate could be caused by increased global or regional (e.g., splanchnic) lactate production with or without combined decreased (splanchnic, renal, or muscular) lactate clearance. As splanchnic lactate extraction if anything tended to increase with phenylephrine, it is not likely that the increased arterial lactate level with phenylephrine was caused by increased splanchnic lactate production and/or decreased splanchnic clearance of lactate. However, our data on splanchnic lactate extraction should be interpreted with caution as they are based on single measurements and therefore might be subjected to errors.

There are only a few previous human studies that used the endoluminal approach in the small intestines (7, 9–11, 33, 34). The laser Doppler flowmetry signal is proportional to the number and

velocity of red blood cells in the tissue volume of interest and thus can provide useful information on tissue oxygen delivery. Although laser Doppler flowmetry yields no absolute blood flow values, the laser Doppler flowmetry values correlate strongly with simultaneously obtained absolute blood flow values using the total venous outflow technique both in humans and animals (35, 36). Furthermore, the laser Doppler flowmetry values from the mucosal side of the jejunum correlate strongly with simultaneously obtained absolute mucosal/submucosal blood flow measurements by hydrogen gas clearance and microsphere techniques (37). One advantage of the laser Doppler flowmetry technique is that it is possible to measure mucosal perfusion continuously, whereas the drawback is that measurements can be performed only at a local site and during intestinal quiescence, because peristalsis causes motion artifacts. Peristalsis is, however, a smaller problem in patients during anesthesia/sedation compared with awake volunteers (11).

In the present study, on uncomplicated, normotensive postcardiac surgery patients, low doses of norepinephrine (0.052 ± 0.009 µg/kg/min) and phenylephrine (0.50 ± 0.22 µg/kg/min) induced a substantial increase in MAP (30%). Obviously, the results of the present study cannot immediately be transposed to patients with septic shock or to patients with severe postcardiotomy vasodilatory shock, requiring considerably higher doses of vasopressors. However, these relatively low infusion rates of vasopressors have been shown in other clinical trials on postcardiac surgery patients to induce an increase in MAP of similar magnitude, as observed in the present study. Thus,

DiNardo et al. (38) studied the effects of vasopressors on saphenous vein graft and internal mammary flows after myocardial revascularization. In their study, norepinephrine and phenylephrine increased MAP by 25–30% at infusion rates of 0.049 ± 0.036 and 0.87 ± 0.37 µg/kg/min, respectively. Morimatsu et al. (39) studied the effect of norepinephrine for hypotensive (<70 mm Hg) vasodilation after cardiac surgery and found that a mean peak dose of 0.088 ± 0.064 µg/kg/min was needed to maintain MAP between 70 and 90 mm Hg.

One limitation of this study is that we chose a crossover design and did not include a time-control group. In crossover studies, carryover effects cannot be ruled out despite washout periods preceding the infusion of the study drugs. Although the direct postoperative period is a clinically relevant time period to evaluate the effects of vasopressors on systemic and splanchnic perfusion, spontaneous fluctuations and time-dependent effects on variables do occur during recovery. Changes in the measured variables could therefore, to some extent, be explained by other factors than the catecholamines themselves. However, the baseline values of the recorded variables of primary interest in the present study, the splanchnic variables, did not change significantly over time. Furthermore, we have previously shown that neither splanchnic blood flow nor jejunal mucosal perfusion change significantly over time in a similar group of postcardiac surgical patients studied during similar conditions (7, 9, 33). We therefore believe that the effects of the catecholamines on the measured variables in the present study are caused by the catecholamines themselves and

Phenylephrine induced a more pronounced global α_1 -mediated splanchnic vasoconstriction compared with norepinephrine.

not by spontaneous fluctuations or time-dependent changes of these variables.

Four of our patients had a history of hypertension. No obvious vascular hyperactivity was seen in these patients, as demonstrated by the same global, regional, and local vascular responses to vasopressors, compared with normotensives (Fig. 2–4). This could be explained by the fact that these patients had been under treatment for years with various combinations of antihypertensives and their blood pressures were well controlled.

CONCLUSIONS

We have shown that vasopressor therapy with norepinephrine or phenylephrine in postcardiac surgery patients to increase MAP by 30–35% does not affect jejunal mucosal perfusion or gastric mucosal PCO_2 gradient despite a decrease in global splanchnic oxygenation, suggesting an intramural redistribution of flow to the gastrointestinal mucosa. The lack of norepinephrine-induced impairment of gastrointestinal mucosal perfusion in postoperative patients could not be explained by a simultaneous α_1 -mediated vasoconstrictory and β_2 -mediated mucosal vasodilatory action.

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III

Effects of norepinehrine-induced variations in perfusion pressure on intestinal mucosal perfusion in vasodilatory shock after cardiac surgery

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Abstract

Objectives: To evaluate the effects of norepinehrine-induced variations in mean arterial pressure (MAP) on jejunal mucosal perfusion, gastric-arterial pCO₂ gradient and the global splanchnic oxygen demand- supply relationship in patients with vasodilatory shock.

Design: Prospective interventional study.

Setting: A university cardiothoracic intensive care unit.

Patients: Ten mechanically ventilated patients who required norepinehrine to maintain MAP \geq 70 mmHg because of septic/postcardiotomy vasodilatory shock and multiple organ failure after cardiac surgery were included.

Interventions: Norepinehrine infusion rate was randomly and sequentially titrated to target MAPs of 60, 75 and 90 mmHg.

Measurements and Main results: At each target MAP, data on central hemodynamics (pulmonary artery catheter), jejunal mucosal perfusion, jejunal mucosal hematocrit and red blood cell velocity (laser Doppler flowmetry) as well as gastric-arterial pCO₂ gradient (gastric tonometry) and splanchnic oxygen and lactate extraction (hepatic vein catheter) were obtained during a 30 min period. Doses of norepinehrine to obtain target MAPs of 60, 75, 90 mmHg were 0.25 ± 0.24 , 0.37 ± 0.21 and 0.55 ± 0.39 ng/kg/min, respectively. Cardiac index, stroke volume index, systemic vascular resistance, systemic oxygen delivery and cardiac filling pressures increased significantly, while heart rate or global oxygen consumption did not change with increasing norepinehrine dose. Jejunal mucosal perfusion, jejunal mucosal hematocrit and red blood cell velocity, arterial-gastric-mucosal pCO₂ gradient, splanchnic oxygen or lactate extraction or mixed venous – hepatic venous oxygen saturation gradient were not affected by increasing infusion rates of norepinehrine. Hemoglobin and hematocrit increased significantly with norepinehrine (7%)

Conclusions: Increasing MAP from 60 to 90 mmHg with norepinehrine in patients with vasodilatory shock after cardiac surgery, increases cardiac index and does not affect intestinal mucosal perfusion, gastric or global splanchnic oxygen demand/supply relationships.

Introduction

Clinical septic shock and the vasodilatory shock syndrome after cardiac surgery are characterized by a profound arteriolar vasodilation resulting in a low systemic vascular resistance and hypotension. Norepinephrine is the recommended agent and commonly used for treatment of hypotension in volume-resuscitated hyperdynamic septic shock [1]. Norepinephrine is also used to correct hypotension in the vasodilatory shock syndrome after cardiac surgery with cardiopulmonary bypass [2-5]. Norepinephrine elevates systemic perfusion pressure mainly by an increase in systemic vascular resistance but also to some extent by an increase in cardiac output in patients with septic shock [6].

Splanchnic blood flow seems to be well maintained during vasopressor therapy with norepinephrine in these patients [7-9], but data on the effects vasopressors on intestinal mucosal perfusion in patients with vasodilatory shock are lacking. It has been shown in man that there is no consistent association between global splanchnic blood flow and local intestinal mucosal perfusion evaluated by laser Doppler flowmetry or gastric mucosal perfusion assessed by gastric tonometry [10]. The lack of correlation between intestinal mucosal perfusion and splanchnic blood flow may thus indicate that global measurements of oxygen delivery across the whole splanchnic region do not necessarily reflect the degree of oxygenation or perfusion of the mucosal layer [10], the probably most vulnerable portion of the intestinal wall [11]. The fact that norepinephrine does not seem to jeopardize global splanchnic perfusion in patients with septic shock does not necessarily mean that vasopressor therapy with norepinephrine is harmless in terms of intestinal mucosal perfusion as norepinephrine might redistribute blood flow away from the mucosa. This is of particular importance since gut mucosal ischemia might damage

the intestinal mucosal barrier with translocation of microorganisms and endotoxins perpetuating the systemic inflammatory response syndrome in septic patients [12].

In patients with volume-resuscitated vasodilatory shock the restoration of adequate perfusion pressure to a level that allows appropriate organ perfusion is the end-point of vasopressor therapy. The optimal perfusion pressure with respect to systemic, regional or local perfusion is, however, not yet established. In the present study on patients with vasodilatory shock after cardiac surgery, we evaluated the effects of norepinephrine-induced changes in perfusion pressure over a range of 60 to 90 mmHg, on jejunal mucosal perfusion, gastric mucosal perfusion (gastric-arterial $p\text{CO}_2$ gradient) and the splanchnic oxygen demand/supply relationship. Our hypothesis was that increasing infusion rates of norepinephrine impair intestinal mucosal and gastric mucosal perfusion.

Patients and methods

The study was approved by the ethics committee of University of Göteborg and informed consent was obtained from next of kin. Ten post-cardiac surgery patients, who suffered from vasodilatory shock, with or without sepsis [13] and who met the following inclusion criteria: a) $\text{MAP} < 70$ mmHg despite optimal preload as assessed by right- and left-sided cardiac filling pressures and transesophageal echocardiography, b) the need for norepinephrine to obtain a mean arterial pressure of ≥ 70 mmHg, c) cardiac index > 2.5 l/min/m² and d) the need for mechanical ventilation, were included to the study. All patients were sedated with fentanyl (43 ± 6 ng/kg/min) and midazolam (1.7 ± 0.2 μ g/kg/min). The hemodynamic management of these patients was at the discretion of the attending intensive care physicians. The clinical treatment protocol included inotropic support with dopamine

(2.5-10 $\mu\text{g/kg/min}$) and/or milrinone (0.37-0.75 $\mu\text{g/kg/min}$) with norepinephrine to maintain a mean arterial pressure ≥ 70 mmHg and a whole-body oxygen extraction $< 35\%$. Sequential organ failure assessment score (SOFA score) was calculated in each patient [14]. Since all patients were sedated, neurological status was not scored. Heart rate was monitored continuously. Arterial pressure was monitored via a radial or femoral arterial catheter. All patients were catheterized with a 7.5 F pulmonary artery catheter (Baxter Healthcare, USA). Transducers were referenced to the midaxillary line. Cardiac index was measured in triplicate by the thermodilution technique (mean of three 10-ml ice-cold saline injections). The hepatic vein was catheterized with a 7.0 F pulmonary artery catheter (Baxter Healthcare, USA) via the right internal jugular vein during fluoroscopic guidance. Blood gas analyzes were performed with automated blood gas analyzer (Synthesis 25, Instrumental Laboratories, Italy). Blood samples for lactate concentrations were determined using an enzymatic method (YSI 2300 Stat Plus, YSI, Yellow Springs, Ohio, USA). Systemic oxygen delivery and consumption as well as splanchnic oxygen and lactate extraction were calculated using standard formulae. Body temperature was continuously monitored measured via the pulmonary artery catheter. The arterial blood pressure, pulmonary arterial pressure, and central venous pressure (CVP) as well as jejunal mucosal perfusion were continuously measured and stored in the Perisoft software (Perimed, Järfälla, Sweden).

The technique of laser Doppler flowmetry of the intestinal mucosa in man has previously been described in detail [15]. A custom made two-probe laser Doppler catheter (Perimed) was placed through the nasogastric route during fluoroscopic guidance endoluminally in the proximal jejunum 20-40 cm distal to the ligament of Treitz. To facilitate positioning of the probe, erythromycin 0.1-0.5g was administered intravenously to improve gastric propagation

motility. The probe consists of three triangular placed optical fibers with a diameter of 150 μm and a fiber center separation of 200 μm . One fiber emits light with a wavelength of 780 nm and the other two receive the Doppler shifted and backscattered light. The jejunal mucosal perfusion was measured with a sampling frequency of 32 Hz with a laser Doppler flowmeter (Periflux PF 4001 Perimed). For measurements of jejunal mucosal perfusion, a time constant of 0.2 s and a bandwidth of 20-25 kHz was used and calibration of the probe was performed as recommended by the manufacturer. Jejunal mucosal perfusion (JMP) is defined as number of red blood cells (RBC) $\cdot \text{area}^{-1} \cdot \text{time}^{-1}$. The laser Doppler equipment used in the present study has the ability to separately analyze the two components of the JMP: jejunal mucosal hematocrit (JMHT), defined as the number of RBC $\cdot \text{volume}^{-1}$, and red blood cell (RBC) velocity, defined as length $\cdot \text{time}^{-1}$. The JMP is thus the product of the JMHT and RBC velocity [16, 17]. All the JMP, JMHT and RBC velocity values presented in this study were calculated from periods of intestinal quiescence.

Gastric mucosal pCO_2 was measured every 10 min by using a standard tonometry nasogastric tube (TRIP, NGS tonometry catheter, Tonometrics, Helsinki, Finland) connected to an automated gas analyzer (Tonocap TC-200, Datex, Helsinki, Finland). The correct position of the tube was confirmed by fluoroscopy and continuous suction was applied to drain the stomach of air and gastric juice. The gastric-arterial pCO_2 gradient was calculated in each patients. In one patient tonometry was not performed due to technical problems.

Study protocol. After entering into the study, the patient's norepinephrine dose was adjusted to attain a mean arterial pressure (MAP) of 75 mmHg. Vascular pressures as well as jejunal mucosal perfusion were continuously measured for 30 minutes. The infusion rate of norepinephrine was then randomly increased or decreased to obtain a

30 min sampling period at a MAP of 60 mmHg and a 30 min period at a MAP of 90 mmHg. A titration period of 15–30 min was needed for each new MAP level to obtain the target pressure. Thereafter, a post-intervention period of 30 min at a MAP 75 mmHg was obtained. The inotropic medication was not changed during the experimental procedure. JMP, RBC velocity and JMht were continuously recorded during the four periods and mean values were calculated during intestinal quiescence. Gastric mucosal pCO₂ was measured every 10 min and the mean value for each 30-min period was calculated. Systemic hemodynamics were measured and samples for blood gas analysis, lactate, and hemoglobin concentrations were performed at the end of each measurement period.

Statistics. Analysis of variance for repeated measurements (ANOVA) as well as linear trend tests were used to evaluate the effects of norepinephrine-induced variations in perfusion pressure on measured variables. Pre- and post-intervention values were compared using a paired Student's t-test. Differences were considered significant at $p < 0.05$. Data are presented as mean \pm standard deviation (SD)

Results

The study population included ten patients, nine male and one female with a mean age of 70 ± 7 years (range 60–77) (Table 1). The patients were studied 2–19 days after the surgical procedure. SOFA scores were ≥ 9 in all patients and all patients suffered from multiple organ failure and fulfilled the criteria for severe septic shock [13]. Four patients had an identified source of infection (pneumonia or urosepsis) and were entered into the study within 5–19 days after the surgical procedure. The remaining six patients were entered into the study 2–4 days after surgery and had no identified source of infection. Four patients received dopamine and five received intravenous milrinone. Four patients were treated with an intraaortic balloon pump and two had continuous renal

replacement therapy. All but one patient were discharged from the cardiothoracic intensive care unit alive. The non-surviving patient died of multiple organ failure ten days after study.

Systemic variables (table 2): The doses of norepinephrine to obtain target MAP:s of 60, 75 and 90 mmHg were 0.25 ± 0.24 , 0.37 ± 0.21 and 0.55 ± 0.39 ng/kg/min, respectively. The infusion rate of norepinephrine at a target MAP of 75 mmHg in patients receiving milrinone ($n=5$), was 0.40 ± 0.26 μ g/kg/min, which was not significantly different from those who did not receive milrinone (0.38 ± 0.18 μ g/kg/min, $n=5$). The NE-induced elevation in MAP (from low to high) was accompanied by a significant increase in systemic vascular resistance index (39%), cardiac index (12%), stroke volume index (11%, $p=0.056$), global oxygen delivery index (21%) mixed venous oxygen saturation (6%), central venous pressure (16%) and pulmonary artery occlusion pressure (36%), while global oxygen extraction index decreased (12%). There were no significant changes in heart rate or global oxygen consumption. Hemoglobin and hematocrit increased significantly with norepinephrine (7%). Body temperature was unchanged during the experimental procedure (37.8 ± 1.0 to 37.9 ± 1.0 °C) Arterial lactate tended to increase (trend test $p=0.034$) with increasing norepinephrine infusion rates. Post-intervention values of hematocrit and mixed venous oxygen saturation were slightly but significantly lower than pre-intervention values, 32.1 ± 4.2 % ($p=0.032$) and 64.9 ± 7.1 % ($p=0.028$), respectively. Otherwise, pre- and post-intervention values of the various systemic variables did not differ significantly.

Splanchnic perfusion (table 3): Individual data on JMP, arterial-gastric mucosal pCO₂ gradient and splanchnic oxygen extraction are seen in Fig 1–3. Increasing doses of norepinephrine did not affect JMP. Neither arterial-gastric mucosal pCO₂ gradient nor gastric mucosal pH was affected by variations in norepinephrine

dose. Hepatic venous oxygen saturation, hepatic venous oxygen extraction and the mixed venous – hepatic venous oxygen saturation gradient were not affected by increasing doses of norepinephrine. Hepatic vein lactate or splanchnic lactate extraction were not affected by variations in norepinephrine dose. Pre-and post-intervention values of the various splanchnic variables did not differ significantly.

Discussion

In the present study the effects of norepinephrine-induced variations in MAP on local gastrointestinal mucosal perfusion assessed by jejunal mucosal laser Doppler flowmetry or gastric tonometry, as well as global splanchnic oxygen extraction, were evaluated in patients with vasodilatory shock after cardiac surgery. The main findings of the study were that neither intestinal mucosal perfusion nor gastric-arterial pCO₂ gradient was changed when target MAP was increased from 60 to 90 mmHg by a more than 100% increase in the norepinephrine dose and a 40% increase in systemic vascular resistance index. Furthermore, increasing doses of norepinephrine did not seem to redistribute blood flow away from the splanchnic territory, as indicated by the lack of significant change in the mixed venous – hepatic venous oxygen gradient.

These data are in line with previous studies demonstrating that norepinephrine does not impair intestinal or gastric mucosal perfusion after uncomplicated cardiac surgery [18, 19]. The lack of norepinephrine-induced, α_1 - mediated impairment of gastrointestinal perfusion at higher infusion rates in the present study could be explained by a β_2 -mediated counteractive vasodilation. Reinelt et al thus demonstrated in patients with hyperdynamic septic chock that splanchnic blood flow decreased by 40% when norepinephrine was substituted for the pure α_1 -agonist phenylephrine at identical levels of MAP and cardiac index [20]. However, it has recently been shown, in nonseptic postoperative patients, that neither

norepinephrine nor the pure α_1 - agonist phenylephrine impairs human intestinal mucosal perfusion [19], indicating that the lack of α_1 - mediated impairment of intestinal mucosal perfusion with norepinephrine is not explained by a β_2 -mediated counteractive vasodilation.

The absence of vasopressor-induced reduction in gastrointestinal mucosal perfusion, at higher infusion rates, could at least partly be explained by the so-called "autoregulatory escape" phenomenon. It is well known that stimulation of sympathetic vasoconstrictor fibers, or infusion of norepinephrine lead to an initial decrease in hepatomesenteric blood flow, which is followed by a return of flow towards the base-line value [21-28]. Thus, vascular escape is seen as a partial or full recovery from initial vasoconstriction despite continued constrictor stimuli. It has been suggested that this "escape" from norepinephrine-induced vasoconstriction in the intestine is due to relaxation of initially constricted arterioles by local vasodilator metabolites e.g. adenosine and not by opening of arteriovenous anastomoses [28, 29]. Others have suggested that norepinephrine-induced autoregulatory escape involves simultaneous beta-adrenoceptor, purinergic, and nitric oxide mediation [26, 27, 30]. It has been shown that both the muscularis and the mucosal circulation exhibit the ability to escape an α_1 -mediated vasoconstrictor influence, but that the propensity to escape is greater in the mucosa than in the muscularis [23, 24], particularly in humans [23]. A second possibility could be that laser Doppler flowmetry technique is not sensitive enough to detect a norepinephrine-induced intestinal mucosal vasoconstriction in man. However, we have previously demonstrated in healthy volunteers that simulated mild hypovolemia by lower body negative pressure, reducing cardiac index by 15-20%, decreased jejunal mucosal perfusion by 17% [31].

Gastric-arterial pCO₂ gradients reflect the relationship between local gastric mucosal metabolism and perfusion. In the

present study, norepinephrine-induced variations in perfusion pressure caused no changes in the gastric-arterial $p\text{CO}_2$ -gradient, suggesting that norepinephrine did not alter the regional gastric mucosal relationship between blood flow and metabolism in patients with vasodilatory shock. Our results are in line with those of the study by LeDoux et al, demonstrating, in patients with septic shock, that increasing MAP from 65 to 85 mmHg by a 100% increase in the dose of norepinephrine, did not affect the gastric-arterial $p\text{CO}_2$ -gradient. Furthermore, increasing MAP from 70 to 90 mmHg, with norepinephrine or phenylephrine, did not affect the gastric-arterial $p\text{CO}_2$ -gradient after uncomplicated cardiac surgery.

Increasing doses of norepinephrine did not cause any change in hepatic venous oxygen saturation or splanchnic oxygen extraction, indicating that in patients with vasodilatory shock, the global splanchnic demand/supply relationship is maintained during norepinephrine-induced alterations in perfusion pressure. This could be explained by the, for this group of patients with severe heart disease, relatively high levels of cardiac index. In a previous study on uncomplicated post-cardiac surgery patients [18], it was shown that norepinephrine caused a dose-dependent increase in splanchnic oxygen extraction in patients with a cardiac index $< 2.4 \text{ l/min/m}^2$, which could not be seen in patients with high cardiac index ($> 2.4 \text{ l/min/m}^2$). In other words, norepinephrine-induced variations in MAP within a range of 60-90 mmHg do not seem to jeopardize the global splanchnic oxygen demand/supply relationship in patients with vasodilatory shock. A further support of this finding is the lack of effect of norepinephrine on hepatic vein lactate levels or splanchnic lactate extraction in the present study.

In the treatment of vasodilatory shock it is important to improve tissue oxygenation with an appropriate perfusion pressure and a sufficient systemic oxygen delivery. In the present study, norepinephrine increased cardiac index and systemic oxygen delivery by 12% and 21%, respectively. These results

confirm the data from two previous studies showing that cardiac index increased by approximately 20% when increasing MAP by norepinephrine in patients with septic shock, due to the β_1 -stimulatory effect of norepinephrine [32, 33]. The relatively lower effect of norepinephrine on cardiac index increase in the present study could be explained by a lower myocardial contractile reserve in our patients and higher afterload sensitivity due to the nature of their primary disease. Thus, in the present study, pulmonary artery occlusion pressure increased by 36% when afterload was increased by norepinephrine, while in the above cited studies, pulmonary artery occlusion pressure was not affected by increased afterload [32, 33].

Interestingly, there was a highly significant 7% increase in hemoglobin and hematocrit with increasing infusion rates of norepinephrine in the present study. Infusion of low-dose epinephrine in healthy volunteers to increase plasma epinephrine levels to those seen during mental stress, causes an increase in hematocrit [34]. Other stressful situations like earthquake [34] and head-up tilt [35] also increases hematocrit. One could speculate that vasopressor therapy with catecholamines induces hemoconcentration, which may be the result of increased peripheral capillary filtration, due to α_1 -mediated venoconstriction [36]. Another possible explanation could be a norepinephrine-induced autotransfusion of erythrocytes from the spleen, which contains a blood reservoir with high hematocrit. In animals, especially diving mammals, the contractile capacity of the spleen causing autotransfusion of erythrocytes is substantial. A decrease in spleen size and increase in hematocrit have also been shown in humans during diving simulation [37-39] and during exercise [40, 41].

Although laser Doppler flowmetry yields no absolute blood flow values, the laser Doppler flowmetry values correlate strongly with simultaneously obtained absolute blood flow values using the total venous outflow technique both in man and

animals [42, 43]. Furthermore, the laser Doppler flowmetry values from the mucosal side of the jejunum correlate strongly with simultaneously obtained absolute mucosal/submucosal blood flow measurements by hydrogen gas clearance and microsphere techniques [44]. One advantage of the laser Doppler flowmetry technique is that it is possible to measure mucosal perfusion continuously, whereas the drawback is that measurements can be performed only at a local site and during intestinal quiescence, because peristalsis causes motion artifacts. Peristalsis is, however, a smaller problem in patients during anesthesia/sedation compared with awake volunteers [31].

One major limitation of the present study is that the number of patients studied is small, which limits the certainty with which conclusions can be drawn. On the other hand, the sample size was sufficient enough to demonstrate significant increases in several systemic variables, while concomitant changes in regional variables were not seen. Another major limitation of this study is that we did not include a time-control group. One could, therefore, argue that changes in the measured variables were not entirely caused by variations of the norepinephrine dose itself, but also, to some extent, by spontaneous fluctuations or time-dependent effects on these variables. On the other hand, neither the major systemic nor the splanchnic hemodynamic variables were significantly changed when compared at a MAP of 75 mmHg before and after intervention. We therefore believe that the effects of

norepinephrine dose on the measured variables in the present study are caused by norepinephrine itself and not by spontaneous fluctuations or time-dependent changes of these variables. Five patients in the present study received milrinone, which is a potent vasodilator. One could argue that the need for norepinephrine in these patients was a pharmacological consequence of milrinone treatment and not because of vasodilatory shock. The milrinone doses were low to moderate and the infusion rates of norepinephrine at a target MAP of 75 mmHg did not differ between those patients who received and those who did not receive milrinone. Four patients had an identified source of infection (pneumonia or urosepsis) and were considered to have a septic vasodilatory shock, while the remaining six patients were considered to have a postcardiotomy vasodilatory shock [2-5]. It is not immediately obvious that these two subgroups should have the same splanchnic response to variations in norepinephrine dose. However, as can be seen from Fig. 1-3, there were no obvious differences in global and regional splanchnic vascular responses to norepinephrine between the two subgroups.

In conclusion: increasing MAP from 60 to 90 mmHg by increasing infusion rates of norepinephrine, increases cardiac index and systemic oxygen delivery and does not jeopardize intestinal mucosal perfusion or the gastric or global splanchnic oxygen demand/supply relationship in post-cardiac surgery patients with multiple organ failure and vasodilatory shock.

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Figures

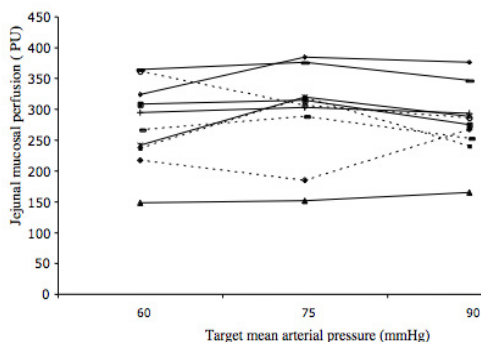


Fig.1 Individual data on jejunal mucosal perfusion measured by laser Doppler flowmetry during norepinephrine-induced variations in mean arterial pressure. Patients with septic vasodilatory shock (n=4) are depicted with dashed lines and patients with postcardiotomy vasodilatory shock (n=6) are depicted with solid lines. PU=perfusion units.

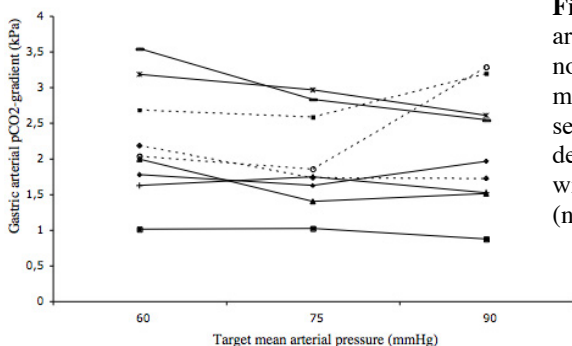


Fig. 2 Individual data (n=9) on gastric-arterial pCO₂-gradient during norepinephrine-induced variations in mean arterial pressure. Patients with septic vasodilatory shock (n=4) are depicted with dashed lines and patients with postcardiotomy vasodilatory shock (n=6) are depicted with solid lines.

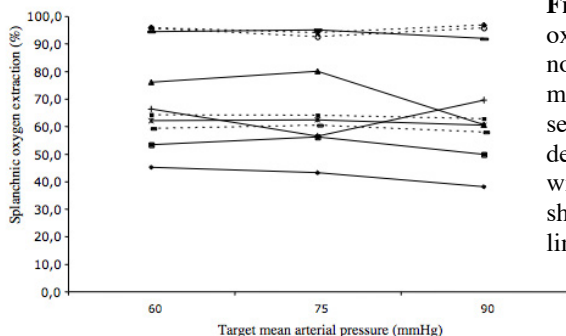


Fig. 3 Individual data on splanchnic oxygen extraction during norepinephrine-induced variations in mean arterial pressure. Patients with septic vasodilatory shock (n=4) are depicted with dashed lines and patients with postcardiotomy vasodilatory shock (n=6) are depicted with solid lines.

Table 1. Clinical characteristics at inclusion

Patient No.	Age / gender	Study entry postop day	Site of infection	SOFA score	Cardiac index	Norepinephrine Dosage $\mu\text{g/kg/min}$	IABP	CRRT	Dopamine Dosage $\mu\text{g/kg/min}$	Milrinone Dosage $\mu\text{g/kg/min}$
1	71/m	9	Pneumonia	10	2.5	0.13	-	-	-	0.52
2	76/m	3	-	9	3.2	0.63	-	-	-	-
3	60/m	4	-	10	2.5	0.18	+	-	-	0.57
4	67/m	19	Urogenital	15	3.4	0.28	-	+	-	-
5	76/m	2	-	11	3.2	0.32	-	-	5.0	-
6	72/m	5	Pneumonia	12	3.5	0.78	-	-	2.2	0.44
7	66/f	2	-	9	2.7	0.49	+	-	-	0.36
8	77/m	8	Pneumonia	9	3.0	0.26	-	-	-	-
9	77/m	2	-	12	2.7	0.41	+	+	4.3	0.43
10	60/m	2	-	9	2.5	0.22	+	-	5.5	-

SOFA = Sequential Organ Failure Assessment; IABP=intra-aortic balloon pump; CRRT=continuous renal replacement therapy

Table 2: Systemic effects of norepinephrine-induced variations in perfusion pressure

	Target mean arterial pressure				
	60 mmHg	75 mmHg	90 mmHg	ANOVA	Linear trend test
Infusion rate of norepinephrine (µg/kg/min)	0.25±0.24	0.37±0.21	0.55±0.39	-	-
Mean arterial pressure (mmHg)	62±3	76±2	91±2	-	-
SVRI (dynes•s/cm ⁵ /m ²)	1456±269	1764±306	2018±327	0.0001	0.0001
Cardiac index (l/min/m ²)	2.7±0.3	2.9±0.4	3.1±0.5	0.0076	0.0021
CVP (mmHg)	12.9±2.5	13.6±2.5	15.0±2.0	0.0002	0.0001
PAOP (mmHg)	16.8±4.8	19.0±4.2	22.9±4.1	0.0006	0.0002
Stroke volume index (ml/m ²)	29±7	31±7	32±8	0.056	0.021
Heart rate (bpm)	97±13	95±11	98±13	0.38	0.44
Systemic oxygen delivery index (ml/min/m ²)	374±49	422±54	452±74	0.0002	0.0001
Systemic oxygen consumption index (ml/min/m ²)	127±15	131±19	135±15	0.22	0.09
Systemic oxygen extraction (%)	34.7±7.2	31.5±5.9	30.6±7.7	0.0015	0.0006
Mixed venous oxygen saturation (%)	63.2±6.8	66.7±6.1	67.2±7.9	0.0007	0.0004
Hemoglobin (g/l)	102±13	108±13	110±13	0.0001	0.0001
Hematocrit (%)	31.5±3.9	33.1±4.0	33.8±4.0	0.0001	0.0001

Values are expressed as mean ± standard deviation. ANOVA = analysis of variance; SVRI = systemic vascular resistance index; PAOP = pulmonary artery occlusion pressure; CVP= central venous pressure.

Table 3: Splanchnic effects of norepinephrine-induced variations in perfusion pressure

	Target mean arterial pressure				
	60 mmHg	75 mmHg	90 mmHg	ANOVA	Linear trend test
JMP (PU)	276±68	294±74	278±57	0.36	0.85
JMHt (AU)	298±57	281±47	273±46	0.20	0.08
RBC velocity (AU)	96±17	105±19	107±14	0.21	0.11
Arterial – gastric mucosal pCO ₂ gradient (mmHg)	2.2±0.8	2.0±0.7	2.1±0.9	0.38	0.62
Splanchnic oxygen extraction (%)	71.2±18.4	70.4±18.5	68.3±20.1	0.32	0.15
Hepatic venous oxygen saturation (%)	28.0±17.9	28.9±18.2	29.3±19.5	0.61	0.34
Mixed venous –hepatic venous oxygen gradient (percent unit)	35.2±13.5	37.8±14.2	37.9±14.2	0.098	0.054
Arterial lactate (mmol/l)	1.43±0.53	1.54±0.56	1.57±0.52	0.084	0.034
Hepatic vein lactate (mmol/l)	1.02±0.58	1.01±0.66	1.08±0.61	0.79	0.59
Splanchnic lactate extraction (%)	32±18	38±21	34±25	0.56	0.68

Values are expressed as mean ± standard deviation. ANOVA = analysis of variance; PU = perfusion units; AU = arbitrary units; JMP=jejunal mucosal perfusion; RBC = red blood cell; JMHt = jejunal mucosal hematocrit.

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IV

Autoregulation of Human Jejunal Mucosal Perfusion During Cardiopulmonary Bypass

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Abstract

Previous animal studies have suggested that autoregulation of intestinal blood flow is severely impaired during cardiopulmonary bypass (CPB). We investigated the jejunal mucosal capacity to autoregulate perfusion during non-pulsatile CPB (34°C) in ten patients undergoing elective cardiac surgery. Changes in mean arterial pressure (MAP) were induced by altering the CPB flow rate randomly for periods of 3 minutes from 2.4 l/min/m² to either 1.8 or 3.0 l/min/m². Jejunal mucosal perfusion (JMP) was continuously recorded by laser Doppler flowmetry. A typical pattern of flow motion (vasomotion) was recorded in all patients during CPB. Variations in CPB flow rates caused no significant changes in mean JMP, jejunal mucosal hematocrit or red blood cell velocity within a range of MAP from 50±15 to 74±16 mmHg. The vasomotion frequency and amplitude was positively correlated with CPB flow rate. Intravenous injections of prostacyclin (10µg, Flolan®) blunted vasomotion and increased JMP from 192±53 to 277±70 (p<0.05) PU despite a reduction in MAP from 59±12 to 45±10 mmHg (p<0.05). Prostacyclin-induced vasodilation resulted in loss of mucosal autoregulation (pressure-dependent perfusion). We conclude that autoregulation of intestinal mucosal perfusion is maintained during cardiopulmonary bypass in man.

Key words: Laser Doppler, intestinal mucosal perfusion, autoregulation, cardiopulmonary bypass, prostacyclin, vasomotion

Implication statement

Hypoperfusion of the intestinal mucosa has been suggested to be an important pathogenic mechanism for development of postoperative complications after cardiac surgery. In this study, the autoregulatory response of the intestinal mucosal perfusion to variations in perfusion pressure was found to be well maintained in humans undergoing nonpulsatile cardiopulmonary bypass.

Introduction

Splanchnic oxygen delivery decreases during hypothermic cardiopulmonary bypass (CPB) due to hemodilution-induced decrease in arterial oxygen content and a decreased (1,2) or unchanged (3,4) splanchnic blood flow. Splanchnic ischemia during CPB has been suggested to be a causal factor for the development of the systemic inflammatory response syndrome and multiple organ failure after cardiac surgery. The latter is speculated to be due to disruption of intestinal mucosal barrier function and translocation of endotoxin and microorganisms leading to a release of proinflammatory cytokines that contribute to organ ischemia-reperfusion injury (5-7). This hypothesis has been supported by the results of studies on gastric mucosal perfusion during CPB in humans. Using the laser Doppler flowmetry (LDF) technique, it has repeatedly been shown that gastric mucosal perfusion decreases during CPB in humans (8,9) also when systemic oxygen delivery was deliberately maintained at prebypass levels. Furthermore, it has been shown in an animal model that intestinal tissue perfusion during CPB is primarily dependent on CPB flow rate (10). A linear relationship between CPB flow rate and intestinal tissue perfusion over a wide range of CPB flow rates was described, indicating a severely disturbed autoregulatory control of intestinal tissue perfusion (10). This impairment of the intestinal autoregulatory control of blood flow, could to some extent explain how systemic hypotension might induce intestinal ischemia during CPB. Using the LDF technique, we have recently shown that jejunal mucosal perfusion increases during mild hypothermic CPB in man (11). The aim of the present study was to further characterize the behavior of the vascular bed of the intestinal mucosa during mild hypothermic CPB in man. Our hypothesis was that the autoregulatory capacity of the intestinal mucosa was impaired during CPB.

Methods

The study procedures were approved by the Ethics Committee of the University of Göteborg and informed consent was obtained from each patient. Ten patients, five male and five female, with a mean age of 75 years (range 51-84) undergoing elective cardiac valve surgery with or without coronary artery bypass grafting were included in the study. Exclusion criteria were: diabetes mellitus, preoperative cerebral infarction or carotid artery disease, bowel disease or laboratory evidence of liver dysfunction. Seven of the patients were treated with long-acting beta-1-selective adrenergic blockers (metoprolol 25-100 mg), including the day of surgery and all patients had a left ventricular ejection fraction > 0.4.

The patients were premedicated with oral flunitrazepam (0.5-1 mg) and anesthesia was induced with 0.1– 0.2 mg fentanyl and 100– 200 mg propofol with 0.1 mg/kg pancuronium given for skeletal muscle relaxation. All patients were orally intubated and mechanically ventilated with oxygen/air to achieve an arterial oxygen tension (PaO_2) > 15 kPa and a PaCO_2 level of 4.5-5.5 kPa. Anesthesia was maintained prior to CPB with an intravenous infusion of propofol 200-600 mg/h until the LDF catheter was positioned, and was then maintained with a combination of fentanyl (total dose, including the induction dose, $7.9 \pm 1.5 \mu\text{g/kg}$) and isoflurane. After induction of anesthesia, a pulmonary artery catheter was inserted during fluoroscopic guidance (7.5 F pulmonary artery catheter, Baxter Healthcare, USA). Cardiac output was measured in triplicate with ice-cold boluses of 10-mL saline, not timed to the respiratory cycle, after induction of anesthesia. Before aortic cannulation, heparin $393 \pm 24 \text{ U/kg}$ (Heparin, Loewens, Ballerup, Denmark) was administered intravenously and supplemented as required to achieve an activated coagulation time of >480 seconds. During CPB, anesthesia was maintained by propofol (200-400 mg/h).

Cardiopulmonary bypass: The perfusion system consisted of a hollow fiber membrane oxygenator (Dideco Synthesis, Mirandola, Italy) a hard shell venous reservoir and roller pumps (Jostra HL20). The extracorporeal circuit was primed with 1600±260 ml of Ringer acetate® (Fresenius-Kabi, Uppsala, Sweden), 100 ml of Tribonate® (Fresenius-Kabi, Uppsala, Sweden) and 200 ml of mannitol 150 mg/l (Fresenius-Kabi, Uppsala, Sweden). Cardioprotection was achieved with intermittent cold blood cardioplegia (Plegisol®, Abbott, USA) plus potassium 60 mmol/l, and procainamide 2.5mmol/l). Target flow using non-pulsatile CPB was $2.4 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ at a target body temperature of 34°C, continuously measured by a thermistor in the urinary bladder. During CPB PaO₂ was maintained between 15 and 22 kPa and PaCO₂ between 4.1-5.6 kPa, using α -stat pH management. The trigger hematocrit for transfusion of erythrocytes was 20%.

Jejunal mucosal measurements: A custom-made two-probe laser Doppler catheter (Perimed, Järfälla, Sweden) was placed through the nasogastric route during fluoroscopic guidance endoluminally in the proximal jejunum 20-40 cm distal to the ligament of Treitz. The light source and the receiver of each probe are situated 23mm and 123mm from the tip of the catheter. Each probe consists of three triangular-placed optical fibers with a diameter of 150 μm and a fiber center separation of 200 μm . One fiber emits light with a wavelength of 780 nm and the other two receives the Doppler shifted and backscattered light. The jejunal mucosal perfusion was measured with a sampling frequency of 32 Hz with a laser Doppler flowmeter (Periflux PF 4001™; Perimed AB, Järfälla, Sweden). For measurements of jejunal mucosal perfusion (JMP), a time constant of 0.2 s and a bandwidth of 20-25 kHz were used and calibration of the probe was performed as recommended by the manufacturer. The laser Doppler equipment used in the present study has the ability to separately analyze the two components of the JMP, jejunal mucosal

hematocrit (JMHct), and red blood cell (RBC) flow velocity. The JMP (perfusion units, PU) is thus the product of the JMHct and RBC flow velocity or number of RBC $\times \text{area}^{-1} \times \text{time}^{-1}$, number of RBC $\times \text{volume}^{-1}$ and length $\times \text{time}^{-1}$. The JMP, JMHct, and RBC flow velocity values presented in this study were calculated from periods of intestinal quiescence using Perisoft software (Perimed Järfälla Sweden). The frequency, as well as the amplitude, of the cyclic changes in JMP was calculated for each period (mean of the two probes).

Protocol: At a body temperature of 34°C and a CPB flow rate index of 2.4 l/min/m², mean arterial pressure (MAP), JMP (JMHct and RBC flow velocity), as well as CPB flow rate were continuously recorded (baseline). Approximately 5 minutes after the first administration of cardioplegia, 15-20 minutes after start of CPB, the patients were subjected, in random sequence, to 3-min periods of low CPB flow rate (1.8 l/min/m²), standard CPB flow rate (2.4 l/min/m²) and high CPB flow rate (3.0 l/min/m²). In each patient, this CPB flow rate variation procedure was performed 1-3 times, depending on the duration of the operation. Thereafter, at a CPB flow rate of 2.4 l/min/m², systemic vasodilation was induced by an intravenous injection of prostacyclin 10 μg (Flolan®, GlaxoSmith Kline) (n=6) and then the maximal change in MAP and JMP were recorded. During the prostacyclin-induced vasodilation, the CPB flow rate was again randomly altered, as described above, but now only for periods of 30 seconds at each CPB flow rate. Intravenous injections of prostacyclin were repeated 1-2 times depending on the duration of the surgical procedure.

Data analysis: Students paired t-tests were performed for comparing PaO₂, PaCO₂, mixed venous oxygen tension (SvO₂), hematocrit, and body temperature before and after the experimental procedure and to evaluate the effects of prostacyclin on JMP and MAP. Analysis of variance for repeated measures, followed by contrast analysis were used to evaluate the effects of

variations in CPB flow rate on MAP, SVRI, SvO₂, JMP, JMHct, RBC flow velocity, and vasomotion frequency and amplitude. Mean values for each patient were obtained at each CPB flow rate if more than one CPB flow rate variation procedure was performed. A correlation within subjects analysis (12) was also performed to evaluate a potential correlation between MAP and JMP during CPB flow variations, without and with prostacyclin. Values are expressed as mean \pm standard deviation.

Results

Cardiac index, MAP, SvO₂, hemoglobin, and hematocrit prior to initiation of CPB were 2.1 ± 0.4 l/min/m², 81 ± 15 mmHg, $67 \pm 15\%$ (range 42-82%), 114 ± 13 g/l and $35 \pm 4\%$, respectively. The duration of CPB was 117 ± 39 (range 74-194) minutes. PaO₂, PaCO₂, SvO₂ and body temperature did not change significantly (data not shown), while there was a slight increase in hemoglobin (82 ± 13 to 87 ± 17 g/l, $p < 0.05$) and hematocrit (25.5 ± 4.0 to $27.2 \pm 3.4\%$, $p < 0.05$) during the experimental procedure. One of the patients received transfusion of erythrocytes before performing the experimental protocol.

A representative recording of the effects of CPB flow rate variations on arterial pressure and JMP is seen in Figure 1. In six patients we were able to repeat the CPB flow rate variation procedure at least once. The autoregulatory response to flow rate variations did not differ between the first and the subsequent CPB flow variation. Seventeen sequences of variation in CPB flow rate were thus performed in the ten patients. Individual data on the effects of changes in CPB flow rate index on MAP and JMP are shown in Figure 2. The effects of varying CPB flow rate index on mean MAP, SVRI, SvO₂ (venous line of the CPB circuit) and jejunal mucosal perfusion are shown in Table 1. MAP and SvO₂ increased while SVRI decreased with higher CPB flow rates. JMP, JMHct, and RBC flow velocity were unchanged during the variations in CPB flow rate index. In all patients, SvO₂ was $\geq 70\%$

at a CPB flow rate of 1.8 l/min/m². Individual data on the relation between MAP and JMP are seen in Figure 3a and the relation between absolute changes in MAP vs. absolute changes in JMP in Figure 3b. There was no significant within-subject correlation between MAP and JMP ($r = 0.06$, $p = 0.58$).

Cyclic variation in JMP (vasomotion) was seen in all patients during CPB (Figure 1). The vasomotion was present during $72 \pm 18\%$ of the recorded time. Both vasomotion frequency and amplitude increased with higher CPB flow rates (Table 1).

Six patients received 13 bolus doses of prostacyclin at a CPB flow rate index of 2.4 L/min/m². A representative recording of the effects of prostacyclin on JMP and perfusion pressure is shown in Figure 4. Prostacyclin abolished the vasomotion waves while JMP increased from 192 ± 53 to 277 ± 70 PU ($p < 0.05$) despite a reduction in MAP from 59 ± 12 to 45 ± 10 mmHg ($p < 0.05$). During prostacyclin-induced vasodilation, CPB flow rate variations caused changes in perfusion pressure within a range of 30-69 mmHg. Individual data on the relation between MAP and JMP during prostacyclin-induced vasodilation are seen in Figure 5a and individual data on the relation between absolute changes in MAP vs. absolute changes in JMP in Figure 5b. A within-subject positive correlation between MAP and JMP ($r = 0.66$, $p < 0.0001$) was demonstrated during prostacyclin-induced vasodilation, indicating that JMP was pressure-dependent.

Discussion

In this study we evaluated the autoregulation of the JMP during mild hypothermic CPB in patients undergoing elective cardiac surgery. The major findings were that neither JMP nor its composite variables, JMHct and RBC flow velocity, were significantly affected by flow-induced variations in MAP within the pressure range of 50-75 mmHg. These data indicate that intestinal mucosal autoregulation is

maintained during CPB in man.

Our results are in contrast to previous experimental studies evaluating regional splanchnic circulation during CPB. Mackay et al (13) and O'Dwyer et al (14) both evaluated the effects of variations in CPB flow rate on regional blood flow in pigs using microsphere technique. These investigators found that splanchnic blood flow was pressure-dependent indicating impaired auto-regulation. Bastien et al (10) evaluated the importance of systemic flow for intestinal perfusion, as measured by laser Doppler flowmetry (LDF), during mild hypothermic CPB in rabbits. They found a linear relationship between CPB flow rate and perfusion of gastric, ileal, jejunal, and hepatic regions, further indicating impairment of intestinal autoregulation during CPB. In the latter experiment, intestinal perfusion was measured via the serosal side of the intestinal wall rather than from the lumen as in our study. It is possible that LDF recordings from exterior of the intestine reflect blood flow to the serosa/muscularis layers rather than the actual mucosa thus explaining, at least in part, the discordant findings between this study and prior animal experiments.

Ohri et al (8) and Sicsic et al (9) have shown that significant *gastric* mucosal hypoperfusion, assessed by the laser Doppler flowmetry technique, occurs during CPB in man. In contrast, we have previously shown that *intestinal* mucosal perfusion increases during CPB in man (11,15). This increase in JMP was accompanied by an increase in red blood cell velocity and the lack of changes in JHctin spite of a decrease in systemic oxygen delivery and systemic hemodilution. That is, data obtained from measurements of gastric mucosal perfusion during CPB may not necessarily be extrapolated as representative of intestinal mucosal perfusion. In the present investigation we have extended our prior studies of the intestinal microcirculation during CPB and demonstrating that intestinal mucosal autoregulation is maintained during variations in MAP caused by changes in CPB

flow rate. Thus, these results from humans suggest that intestinal mucosal perfusion is not compromised during CPB. These results further suggest that, the previously described disruption of intestinal mucosal barrier function and translocation of endotoxins and microorganisms during CPB (7,16) might not necessarily be explained by intestinal mucosal hypoperfusion.

The arterioles supplying blood to the capillary network exhibit rhythmic oscillations in vascular tone, independent of external influences such as cardiac, intestinal peristaltic, or respiratory cycles. This phenomenon of periodic diameter variations is referred to as *vasomotion* and is a natural property observed in most microcirculatory vascular beds (17). The mechanism for vasomotion is believed to be due to intermittent calcium release from the sarcoplasmic reticulum leading to cyclic smooth muscle depolarization of the blood vessels via activation of chloride channels (17). Cyclic microcirculatory blood flow variations have previously been described in the human jejunal mucosa (18), but not the serosa further emphasizing potential differences between the characteristics of intestinal perfusion between measurements sites (19). The frequency of vasomotion in human jejunal mucosa is usually between 1.9 and 5 cycles \cdot min⁻¹ (10,18). Jejunal vasomotion has also been observed experimentally as variations in jejunal mucosal tissue oxygenation and microvascular hemoglobin oxygen saturation using a Clark-type surface oxygen electrode and with tissue reflectance spectrophotometry, respectively (19,20). The pattern of vasomotion varies considerably between both species and vascular beds and may be affected by vasoactive agents (21) or changes in blood pressure, hematocrit, or oxygen tension (22). In the present study, vasomotion amplitude increased in parallel to increased systemic perfusion and vice versa, which could be explained by the myogenic mechanism, by which vascular smooth muscle contracts as tension is increased. Changes in vasomotion

amplitude to variations in arterial blood pressure could thus be one mechanism by which the intestinal mucosa autoregulates perfusion.

Elevation of cAMP levels has been considered to be a key cellular event to trigger blood vessel relaxation by prostacyclin and its analogues (23). Plasma membrane K^+ channels located on the smooth muscle are believed to be the primary downstream effector of prostacyclin mediating smooth muscle cell hyperpolarization and relaxation (23). In our study, prostacyclin induced a 25% decrease in mean arterial pressure during CPB but JMP increased by 45%, indicating a pronounced prostacyclin-induced arteriolar vasodilation. This vasodilation could also to some extent be attributed to a myogenic, autoregulatory response to the fall in systemic pressure. During prostacyclin injection intestinal perfusion became pressure-dependent.

Furthermore, vasomotion was abolished in all patients with prostacyclin, suggesting that increased intracellular cAMP in vascular smooth muscle cells inhibits intestinal mucosal vasomotion. One mechanism behind the prostacyclin-induced inhibition of vasomotion could be hyperpolarization of the cell membrane, which would block spontaneous depolarization set up by the sarcoplasmic reticulum basic oscillator. It could also be a direct effect of cAMP on the sarcoplasmic reticulum by influencing intracellular calcium availability, uptake and/or release (17).

Although laser Doppler flowmetry yields no absolute blood flow values, the laser Doppler flowmetry values correlate strongly with simultaneously obtained absolute blood flow values using the total venous outflow technique both in man and animals (24,25). Furthermore, the laser Doppler flowmetry values from the mucosal side of the jejunum correlate strongly with

simultaneously obtained absolute mucosal/submucosal blood flow measurements by hydrogen gas clearance and microsphere techniques (26). One advantage of the laser Doppler flowmetry technique is that it is possible to measure mucosal perfusion continuously, whereas the drawback is that measurements can be performed only at a local site and during intestinal quiescence, because peristalsis causes motion artifacts. Peristalsis is, however, a smaller problem in patients during anesthesia/sedation compared with awake volunteers (27). Furthermore, during CPB, the occurrence of peristalsis is even more uncommon. Another limitation with the present study was that the effects of prostacyclin on intestinal mucosal perfusion was studied only during the influence of bolus doses of prostacyclin, and not during a continuous steady-state infusion, which we were not able to obtain due to time restraint. However, the vasodilatory response to bolus prostacyclin lasted at least 90 seconds in all patients, during which time we were able to decrease/increase CPB flow rate from baseline. (see Figure 4). It could be argued that lowering CPB flow rate to 1.8 l/min/m^2 for 3-minute periods could have jeopardized organ perfusion in the present study. We consider this less likely as mixed venous oxygen saturation was $\geq 70\%$ in all patients at a CPB flow rate of 1.8 l/min/m^2 . Bypass values of cardiac index and mixed venous oxygen saturation, at a body temperature of $35\text{--}36^\circ\text{C}$, were 2.1 ± 0.4 and $67 \pm 15\%$, respectively.

In conclusion our results suggest that autoregulation of human JMP is well maintained during mild hypothermic CPB. Intestinal mucosal vasomotion and the capacity of the mucosa to autoregulate perfusion are abolished by vasodilation with prostacyclin

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Tables

Table 1 Effects of variations in cardiopulmonary bypass (CPB) flow rate on jejunal mucosal perfusion (JMP).

	Low flow 1.8 l/min/m ²	Standard flow 2.4 l/min/m ²	High flow 3.0 l/min/m ²	ANOVA
CPB flow index (l/min/m ²)	1.8	2.4	3.0	
MAP (mmHg)	50±15 ***	63±16	74±16 *** ###	p<0.0001
SVRI (dynes*s/cm ⁵ /m ²)	2088±615	1996±524	1862±423 ##	p<0.05
SvO ₂	72.6±1.9 ***	79.1±3.6	82.9±3.5 *** ###	P<0.0001
JMP (PU)	204±55	214±53	213±70	p=0.59
JMHct (AU)	229±56	220±51	220±56	p=0.58
RBC flow velocity (AU)	94±31	92±15	93±33	p=0.94
Frequency (cpm)	2.62±0.66 **	2.91±0.47	3.00±0.44 ###	p<0.001
Amplitude (PU)	137±50 *	159±48	164±54 #	p<0.05

ANOVA=analysis of variance, MAP=mean arterial pressure, SVRI=systemic vascular resistance index, JMP=jejunal mucosal perfusion, JMHct=jejunal mucosal hematocrit, PU=perfusion unit, AU=arbitrary unit, CPM=counts per minute.

* = p<0,05, ** = p<0,01, *** = p<0,001 vs. standard flow, respectively

= p<0,05, ## = p<0,01, ### = p<0,001 vs. low flow, respectively.

Figures

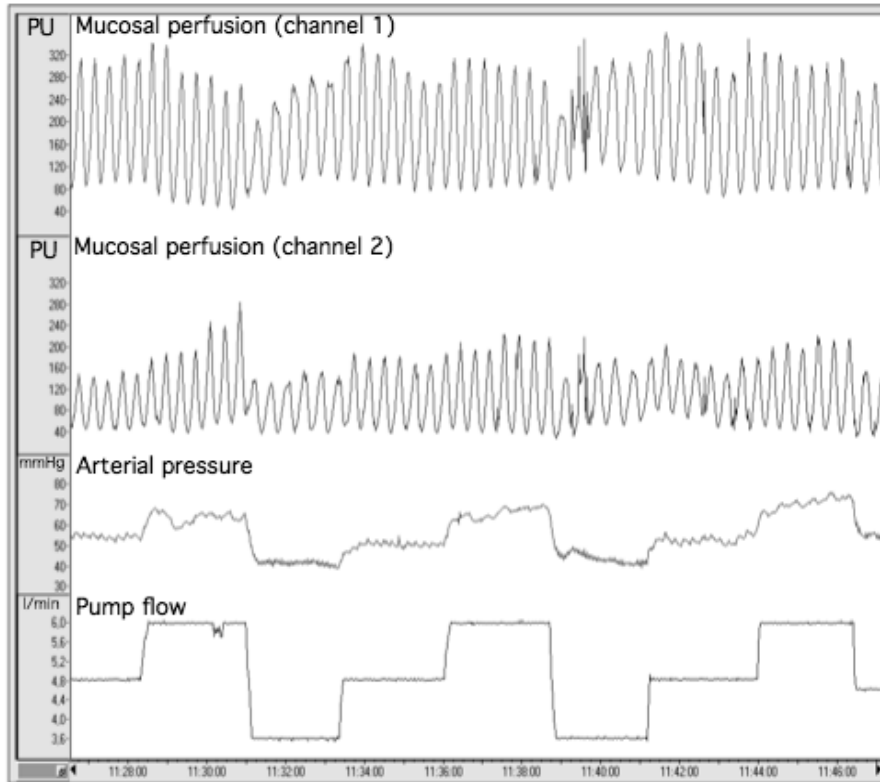


Figure 1. Individual recording of jejunal mucosal perfusion, arterial blood pressure, and flow rate during cardiopulmonary bypass (CPB). Cyclic oscillations in jejunal mucosal perfusion (vasomotion) are present during CPB at various flow rates. Random variations in CPB flow rate induced no change in the mean mucosal perfusion. Vasomotion frequency and amplitude increased with increasing arterial pressures and CPB flow rates. (PU=perfusion units).

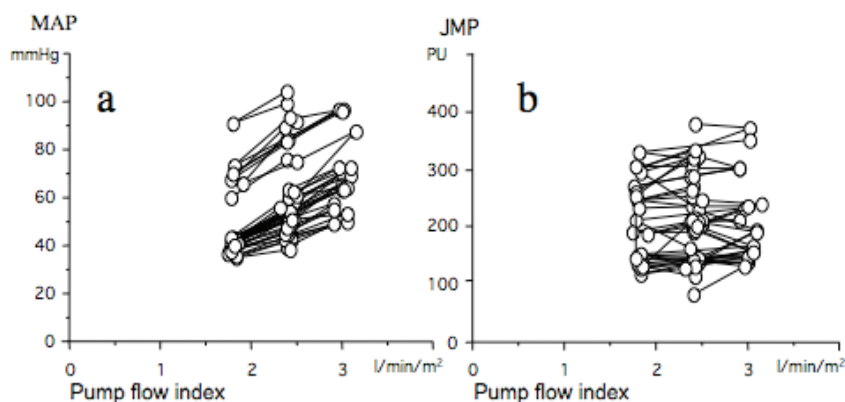


Figure 2. Individual data on the effects of variations in cardiopulmonary bypass (CPB) flow rate index on a) mean arterial pressure (MAP) and b) jejunal mucosal perfusion (JMP). Seventeen sequences of CPB flow rate variation were performed in 10 patients. Each dot represents the mean of a 3-minute recording period at each CPB flow rate. There was no consistent relation between CPB flow rate index and jejunal mucosal perfusion indicating intact autoregulation of perfusion. (PU=perfusion units).

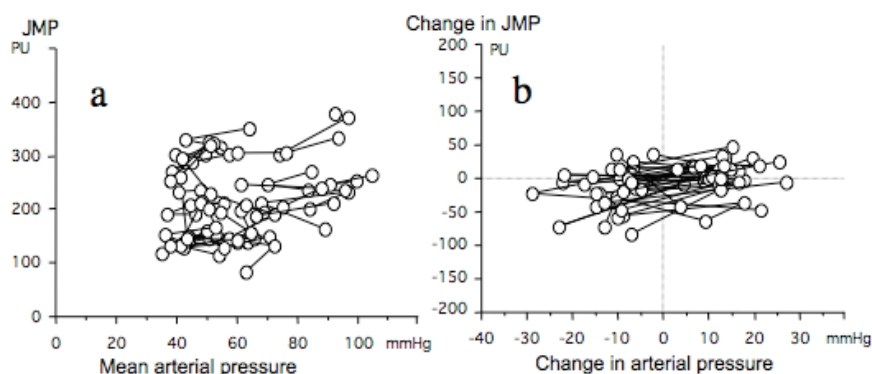


Figure 3. Individual data on a) the effects of variations in mean arterial pressure on jejunal mucosal perfusion (JMP) and b) on the effects absolute changes in mean arterial pressure and absolute changes in JMP. Each dot represents the mean of a 3-minute recording period at each cardiopulmonary bypass flow rate. There was no consistent relation between mean arterial pressure and JMP. (PU=perfusion units).

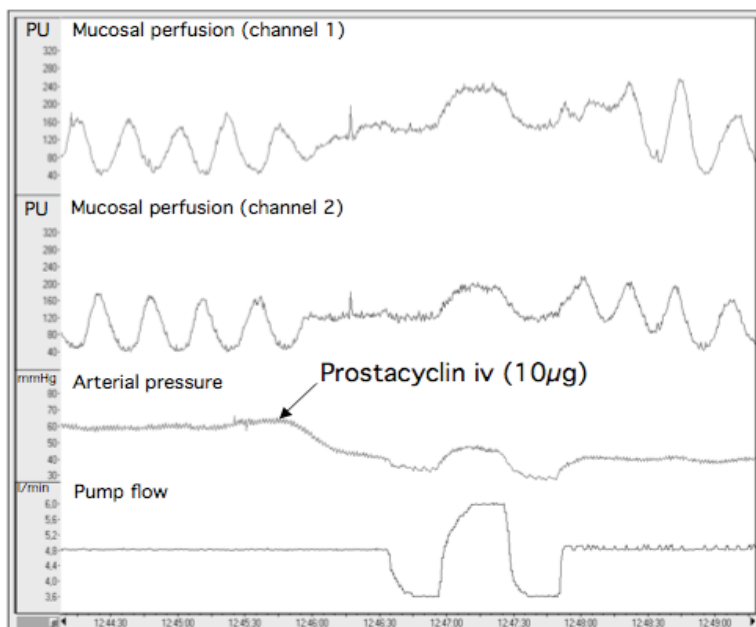


Figure 4. Individual recording on the effects of intravenous prostacyclin (10 µg), on jejunal mucosal perfusion (JMP), and arterial blood pressure during cardiopulmonary bypass (CPB). Typical cyclic oscillations of JMP are seen prior to prostacyclin injection. Prostacyclin induced a systemic vasodilation, blunted the cyclic oscillations of JMP and increased JMP. During the influence of prostacyclin, variation in CPB flow rate induced parallel changes in arterial pressure and JMP. (PU=perfusion units).

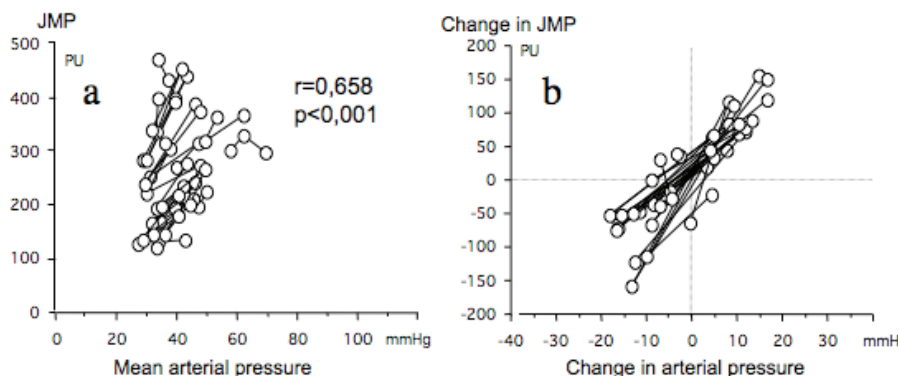


Figure 5. Individual data on a) the effects of variations in mean arterial pressure on jejunal mucosal perfusion (JMP), and b) on the effects absolute changes in mean arterial pressure and absolute changes in JMP during the influence of prostacyclin. Twelve sequences of variation in cardiopulmonary bypass flow rate were performed in five patients. Each dot represent the mean of a 30-second recording period. Prostacyclin induced pressure-dependent changes in JMP, indicative of absence of flow autoregulation. (PU=perfusion units).

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