ANTERO HEINO

Experimental Intestinal Ischemia

Doctoral dissertation

To be presented by permission of the Faculty of Medicine of the University
of Kuopio for public examination in Auditorium, Kuopio University Hospital,
on Friday 13th December 2002, at 12 noon

Department of Surgery
Kuopio University Hospital
Faculty of Medicine
University of Kuopio

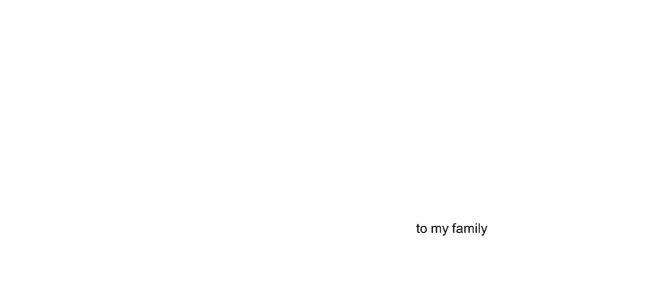KUOPION YLIOPISTO
KUOPIO 2002

ABSTRACT

Systemic and regional effects of progressive intestinal ischemia and
reperfusion were evaluated by graded occlusion of superior mesenteric artery
(SMA) by 40 %, 70 % and 100 % for 60-minute periods and the release
thereafter in 12 pigs. The influences of dobutamine and fluid treatment on
intestinal hemodynamics, tissue oxygenation and renal function during 70 %
SMA occlusion for 120 minutes and the release thereafter were evaluated in 24
pigs. In addition, 24 pigs served as non-ischemic controls. The animals were
assigned into four treatment arms (control, fluid therapy, dobutamine therapy
and combination of dobutamine and fluid therapy).

Intestinal ischemia occurred at 33 minutes after 70 % SMA occlusion, and was
related to decreased intramucosal pH (p<0.01) as well as increased portal
venous-arterial lactate gradient (p<0.01) and splanchnic oxygen extraction
(p<0.05). Systemic changes observed during the SMA occlusion were non-
specific and mostly related to hypovolemia. Ischemia decreased intramucosal
pH (p<0.05 vs sham control), but did not modify the effects of dobutamine or
fluid treatment on systemic hemodynamics and oxygen transport. In the
ischemic animals, dobutamine on its own reduced intramucosal pH further
(p<0.05 vs ischemic control) and increased portal venous-arterial lactate
gradient (p<0.05). Renal function and diuresis during the SMA occlusion and
reperfusion did not differ between ischemic and sham groups.

Severe regional splanchnic hypoperfusion may develop without any systemic
signs of oxygen supply/demand mismatch. Dobutamine on its own worsened
intestinal tissue perfusion during partial superior mesenteric artery occlusion.
Compared to sham treatment, intestinal ischemia and reperfusion did not
influence renal function.

to my family

ACKNOWLEDGEMENTS

ABBREVIATIONS

ATP	adenosine triphosphate
BE	base excess
CI	cardiac index
CO	cardiac output
C_{cr}	creatinine clearance
DO_2	oxygen delivery
HR	heart rate
MAP	mean arterial pressure.
MCVP	mean central venous pressure
MPAP	mean pulmonary artery pressure
PAOP	pulmonary artery occlusion pressure
PCO_2	carbon dioxide tension
PCWP	pulmonary capillary wedge pressure
PO_2	oxygen tension
PvO_2	mixed vein oxygen tension
Q_{SMA}	superior mesenteric artery blood flow
SD	standard deviation
SEM	standard error of mean
SIRS	systemic inflammatory response syndrome
SMA	superior mesenteric artery
SV	stroke volume
SvO_2	mixed venous oxygen saturation
SVRI	systemic vascular resistance index
VO_2	oxygen consumption

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals:

I.   Heino A, Hartikainen J, Merasto ME, Koski EMJ, Alhava E, Takala J. Systemic and regional effects of experimental gradual splanchnic ischemia. J Crit Care 1997; 12;92-98.

II. Heino A, Hartikainen J, Merasto ME, Alhava E, Takala J. Systemic and regional pCO_2 gradients as markers of intestinal ischaemia. Intensive Care Med 1998; 24;599-604.

III. Heino A, Hartikainen J, Merasto ME, Koski EMJ, Tenhunen J, Alhava E,Takala J. Effects of dobutamine on splanchnic tissue perfusion during partial superior mesenteric artery occlusion. Crit Care Med 2000; 28;3484-3490.

IV. Heino A, Merasto ME, Koski EMJ, Juvonen P, Alhava E, Hartikainen J. Effects of fluid and dobutamine   treatment on renal function during partial superior mesenteric artery occlusion and reperfusion. Scand J Urol Nephrol 2002; 36;5-13.

CONTENTS

1. INTRODUCTION

The splanchnic region receives 25 - 30 % of the cardiac output and accounts for a slightly greater proportion of the total body metabolic activity. It has been suggested that impaired splanchnic perfusion contributes to the pathogenesis of multiple organ dysfunction in critically ill patients (Carrico et al 1986, Deitch et al 1987). Early detection of splanchnic hypoperfusion is important in preventing the development of this morbid cascade. Mixed venous hypercarbia and an increased mixed venous-arterial carbon dioxide gradient in low flow states, such as hemorrhagic shock (Benjamin et al 1987, Van der Linden et al 1995), cardiogenic shock (Groeneveld et al 1991, Zhang and Vincent 1993) and septic shock (Bakker et al 1992, Mecher et al 1990) as well as abnormalities in oxygen delivery, consumption, extraction, base deficit, blood lactate concentration, arterial-venous oxygen content difference, mixed venous oxygen saturation and intramucosal pH have all been suggested to be good indicators of tissue hypoperfusion (Dhainaut et al 1990, Schlichting and Lyberg 1995). However, there is also evidence that regional splanchnic hypoperfusion may occur without there being any systemic signs of inadequate regional hemodynamics and the assessment of gastrointestinal intramucosal pH or carbon dioxide by tonometer have been proposed as promising methods for the detection of inadequate splanchnic perfusion (Antonsson et al 1995, Schlichting and Lyberg 1995).

The treatment methods, which prevent the development of splanchnic hypoperfusion are as important as its early detection. It has been suggested that the risk for multiple organ failure can be reduced by increasing the systemic oxygen delivery to supranormal levels using fluid therapy and vasoactive agents (Heyland et al 1996, Shoemaker et al 1988). One such vasoactive agent, dobutamine, increases cardiac output and oxygen delivery, but its effect on regional intestinal circulation has been controversial. In most studies, intestinal blood flow has increased as a result of dobutamine therapy (Biro et al 1988, Parviainen et al 1995, Ruokonen et al 1993). However, some studies have

reported unchanged (Karzai et al 1996, Priebe et al 1995) or even decreased
(Bersten et al 1992, Ferrara et al 1995) intestinal blood flow during dobutamine
treatment. The effects of dobutamine on intestinal blood flow distribution and
on the balance between oxygen delivery and consumption during existing
intestinal hypoperfusion are even less clear and the results have been
contradictory. In postoperative patients and in patients with septic shock,
intramucosal pH, a marker of intestinal hypoperfusion, has been found to
increase, remain unchanged or decrease in response to dobutamine therapy
(Gutierrez et al 1994, Parviainen et al 1995, Silverman and Tuma 1992, Uusaro
et al 1997)

Multiple organ dysfunction is often associated with renal failure. The
development of renal failure can be prevented by fluid treatment and vasoactive
therapy. The renal effects of dobutamine have been studied in normal (Fiser et
al 1988, Olsen et al 1993, Westman and Järnberg 1986) and in those
pathological conditions known to increase the risk of intestinal hypoperfusion
such as septic shock (Haywood et al 1991, Levy et al 1999, Palsson et al 1997),
heart failure (Baumann et al 1990, Good et al 1992), coronary artery bypass
grafting and cardiopulmonary bypass (Wenstone et al 1991), as well as after
major vascular surgery (Westman and Järnberg 1987). Dobutamine has
increased (Duke et al 1994, Fiser et al 1988), decreased (Bersten et al 1992,
Haywood et al 1991) or had no influence (Olsen et al 1993) on renal blood flow
and creatinine clearance. Thus, the influence of dobutamine on renal function
has been variable and may result in different effects on the renal vascular bed
which are not revealed by the measurement of systemic indices alone
(Haywood et al 1991).

This study evaluates the development of intestinal hypoperfusion caused by
the graded occlusion of the superior mesenteric artery, and the changes in
systemic and regional hemodynamics and oxygen transport occurring during
progressive intestinal ischemia, as well as the effects of dobutamine and fluid
treatment on experimental intestinal ischemia and renal function.

2. REVIEW OF THE LITERATURE

2.1. Anatomy , physiology and regulation of intestinal perfusion

The splanchnic organs receive 20 - 30 % of the cardiac output corresponding to a resting blood flow of 29 - 70 ml/min per 100 g intestine in normal conditions from the coeliac trunk and the superior and inferior mesenteric arteries (Granger et al 1980). The portal vein collects all the blood from the splanchnic region and together with the hepatic arterial blood flow represents the total hepato-splanchnic blood flow in the hepatic veins (portal venous 80 % / hepatic arterial 20 %). Portal venous and hepatic arterial blood flows interact in to maintain constant total liver blood flow since a change in one of the vascular systems leads to an opposite change in the other system (Richardson and Withrington 1981). The splanchnic oxygen consumption at rest is 20 - 35 % of the whole body oxygen consumption, resulting in a slightly increased splanchnic oxygen extraction fraction at rest compared to the systemic oxygen extraction (Takala 1996).

The artery to the intestinal villus runs in the core of each villus and at the tip of the villus branches to form a dense subepithelial capillary network surrounding the inflow vessel (Granger et al 1980). As blood through these two vascular systems flows in opposite directions, a countercurrent mechanism allows the oxygen to escape from the arterial side to the venous side resulting in decreased oxygen tension at the tip of the villus (Kampp et al 1968, Lundgren and Haglund 1978a). This countercurrent mechanism, together with the higher metabolic activity in the cells of the villus tip, means that the tip of the villus is susceptible to tissue hypoxia (Bohlen 1980, Lundgren and Haglund 1978a).

The blood flow to the intestine is distributed unevenly between the different layers of the intestinal wall. At rest, mucosa and submucosa receive the majority - up to 90 % - of blood flow, but this distribution can be disrupted by changes in total blood flow (Granger et al 1980). The intestinal blood flow is

regulated by intrinsic and extrinsic mechanisms.

The intrinsic factors include local metabolic and myogenic controls, local reflexes and vasoactive substances. The metabolic mechanism produces vasodilation and maintains a constant intestinal blood flow and oxygen delivery in response to changes in tissue PO_2 and products of cell metabolism. The myogenic mechanism responds to an increase in vascular transmural pressure by arterial vasoconstriction and maintains a constant intestinal capillary pressure and transcapillary fluid exchange. Intestinal blood flow autoregulation, defined as the ability to maintain a constant blood flow in respect to a fluctuating arterial pressure, is weak, but is enhanced by feeding. Both metabolic and myogenic mechanisms explain the tendency for the intestine to maintain blood flow and oxygen delivery when the arterial pressure falls. The myogenic mechanism predicts vasoconstriction if perfusion is sufficient, whereas the metabolic mechanism favors vasodilation during poor perfusion. The vascular tone favoring vasodilation is maintained by the interactions between endothelium-derived vasodilators (e.g. nitric oxide, prostacyclin, adenosine) and vasoconstrictors (e.g. endothelins) (Reilly and Bulkley 1993, Rodeberg et al 1995). Gastrointestinal hormones (e.g. cholecystokinin, gastrin, glucagon, secretin and neurotensin) do not influence intestinal blood flow at physiological concentrations, but are possibly involved in flow regulation during postprandial hyperemia (Lundgren 1989).

The extrinsic neural regulation of intestinal perfusion is limited to the sympathetic nervous system, since no parasympathetic vascular control has been demonstrated in the small intestine (Lundgren 1989). The sympathetic nervous system increases the vascular tone of arteries and arterioles, less so the veins, producing vasoconstriction and a reduction in intestinal blood flow (Takala 1996). Catecholamines are the most important vasoactive substances influencing the intestinal blood flow. The net effects of circulating catecholamines on intestinal blood flow depend on the concomitant effects of the catecholamines on cardiac output (Granger et al 1980), and whether they

produce alpha-adrenoceptor stimulation resulting in vasoconstriction or beta-adrenoceptor stimulation resulting in vasodilatation. With respect to the other circulating mediators, vasopressin and angiotensin II have been reported to be intestinal vasoconstrictors, and to be involved in the intestinal vasoconstriction during hypovolemia (Reilly and Bulkley 1993).

Oxygen delivery and oxygen extraction regulate splanchnic tissue oxygenation. Oxyden delivery is dependent on the hemoglobin concentration, hemoglobin oxygen saturation, blood flow and the amount of dissolved oxygen. Under normal conditions, oxygen consumption is not dependent on oxygen delivery. However, when metabolic demand increases, splanchnic perfusion increases in proportion to the increased oxygen consumption (Takala 1996), this being achieved by increased cardiac output, blood flow redistribution or by the combination of these two mechanisms (Brundin and Wahren 1991, Granger et al 1980). If the oxygen extraction is very low, increased extraction may precede the increase in blood flow. On the contrary, it the splanchnic perfusion is reduced, oxygen extraction increases, since the splanchnic region has a large capacity to adapt to reduced oxygen delivery by increasing its oxygen extraction even up to 86 % in extreme conditions (Rowell et al 1984). However, in experimental reports the intestine has become hypoxic much earlier, when the oxygen extraction has reached 70 % (Nelson et al 1988, Winsö et al 1986). As soon as oxygen delivery decreases beyond a critical point, where the oxygen extraction is no longer able to compensate for the decreased oxygen delivery, oxygen consumption becomes oxygen delivery dependent, leading to anaerobic metabolism and intestinal ischemia (Bulkley et al 1985, Cain 1977, Grum et al 1984, Schwartz et al 1981).

2.2. Intestinal ischemia

2.2.1. Definition of intestinal ischemia

Intestinal ischemia defines the state of intestinal hypoperfusion, which results in an inadequate energy supply to maintain cell metabolism and which may lead to injury, even death of the cell.

2.2.2. Incidence of intestinal ischemia

The annual incidence of acute intestinal ischemia has been reported to be one per 1000 hospital admissions corresponding to an incidence of 1:100 000 in the general population (Kairaluoma et al 1977, Ottinger and Austen 1967). Acute intestinal ischemia is equally distributed between the genders, and it can take place at any age but most often it is seen in senior patients (Järvinen et al 1994, Kairaluoma et al 1977), many of whom have other cardiovascular diseases (Andersson et al 1984, Wilson et al 1987).

2.2.3. Etiology of intestinal ischemia

2.2.3.1. Atherosclerosis

Superior mesenteric artery thrombosis is considered to account for 25 % to 70 % of all cases of acute intestinal ischemia (Järvinen et al 1994, McKinsey and Gewertz 1997). A gradual progression of atherosclerotic lesions in the arteries allows a protective collateral network to develop, whereas a sudden thrombotic occlusion may cause intestinal infarction. In autopsy and angiographic studies, the stenosis has been in two or all three mesenteric arteries in 20 % of cases (Koikkalainen and Kohler 1971) and multiple stenosis has been found in 3 % to 20 % of cases (Bron and Redman 1969, Koikkalainen and Kohler 1971).

However, hemodynamically significant stenoses of 50 % have been reported
less frequently, ranging from 2 % to16 % (Croft et al 1981). Risk factors for the
development of mesenteric atherosclerosis are increasing age, diabetes and
hypertension (Kwaan and Connolly 1983). In addition to atherosclerosis, other
reasons for mesenteric artery thrombosis and ischemia have been reported,
such as trauma, drugs, hematologic, and endocrine disturbances as well as
vasculopathies (Krupski et al 1997).

2.2.3.2. Mesenteric artery embolus

Mesenteric artery embolus is the cause of about 50 % of the cases of acute
intestinal ischemia (McKinsey and Gewertz 1997). Predisposing factors for an
embolus are left atrial or ventricular mural thrombus, arrhythmias, endocarditis,
as well as a prior history of arterial peripheral embolism. About 15% of emboli
impact at the origin of the SMA, whereas the majority lodge distally 3 to 10 cm
in the tapered segment of the SMA (McKinsey and Gewertz 1997).

2.2.3.3. Mesenteric venous thrombosis

Mesenteric venous thrombosis, which are responsible for about 15 % of acute
intestinal ischemia, can be classified into acute and chronic forms, with the
borderline of the presenting symptoms being 4 weeks (McKinsey and Gewertz
1997). Chronic mesenteric venous thrombosis is frequently an incidental
finding as the patient is often asymptomatic with only vague abdominal pain or
distention. The diagnosis is based on computed tomography and
ultrasonography examinations. Since the collateral venous circulation has
usually matured to drain the affected intestine, the prognosis is better than in
cases of acute mesenteric venous thrombosis (Rhee and Gloviczki 1997).

In addition, mesenteric venous thrombosis can be divided according to its
etiology into primary and secondary forms. Primary mesenteric venous

thrombosis is spontaneous, idiopathic without any etiologic factors. Secondary mesenteric venous thrombosis accounts for 81 % of cases and is associated with a known predisposing condition: previous abdominal surgery, hypercoagulable state, previous mesenteric venous thrombosis, smoking, previous deep venous thrombisis, alcohol abuse, malignant tumor, cirrhosis or use of oral contraceptives. Delay in diagnosis is frequent and causes a high mortality rate of 13 % to 50 % (Rhee and Gloviczki 1997).

2.2.3.4. Nonocclusive intestinal ischemia

Nonocclusive intestinal ischemia is estimated to be the cause of acute intestinal ischemia in approximately 25 % of cases (McKinsey and Gewertz 1997). The cause is often multifactorial and it is usually associated with low cardiac output, hypovolemia, dehydration and vasoconstricting drugs (Hunter and Guernsey 1988).

In low flow states (e.g. cardiogenic shock and hypovolemia), intestinal blood flow decreases in order to maintain perfusion to the vital organs, such as the heart and the central nervous system (Takala 1996). However, once intestinal vasoconstriction and reduced intestinal blood flow have developed, they may persist even after the systemic hemodynamics have normalized (Edouard et al 1994). When intestinal blood flow decreases, oxygen extraction increases to preserve intestinal tissue oxygenation. The degree of the compensation mechanism and the tolerance of intestinal hypoperfusion are not well defined. Perioperative hepatic vein oxygen saturation below 30 % during liver resection has been associated with postoperative liver dysfunction (Kainuma et al 1992).

Severe systemic infection related to a systemic inflammatory response syndrome increases the metabolic demands of the splanchnic region (Dahn et al 1987, Gump et al 1970, Ruokonen et al 1993). Even though intestinal blood flow increases during normal or hyperdynamic hemodynamics, the highly increased oxygen consumption necessitates high oxygen extraction.

Endothelial injury resulting in abnormal vascular tone, blood flow maldistribution, hypovolemia, impaired oxygen delivery caused by acute respiratory failure associated with sepsis, decreased myocardial pump function, and increased oxygen consumption in spite of high oxygen delivery, may all complicate the situation (Antonsson and Haglund 1995, Parker et al 1984). Thus, during a systemic infection, intestinal hypermetabolism can increase the risk for an oxygen delivery/consumption mismatch, and even small changes in blood volume, cardiac output, arterial oxygenation or oxygen consumption in other tissues may lead to an imbalance between intestinal oxygen delivery and oxygen consumption and result in intestinal ischemia (Takala 1996).

2.2.4. Pathophysiology of intestinal ischemia

Intestinal ischemia leads to arterial vasoconstriction. The motility of the intestine decreases in response to sympathetic activity or local vasoregulatory factors (Patel et al 1992). Shock, intestinal ischemia and related insults rapidly produce an injury in the intestinal mucosa. The degree of the injury can be graded from 0 (normal mucosa) to 5 (destruction of the mucosa) (Chiu et al 1970). Experimental data has demonstrated that the grade of the injury correlates inversely with the intestinal blood flow and directly with the duration of the ischemia. The tissue injury following reduced oxygen delivery is characterized by lifting of the epithelial cells at the tips of the villi, and in more severe grades, the villus core structure becomes injured. During mechanical occlusion, it takes about 20 min for the light microscopic mucosal changes to appear (Park et al 1990), though the changes are detectable much earlier with an electron microscope (Brown et al 1970). Microscopic signs of injury up to transmural infarction are observed in the deeper layers of the intestinal wall after 8 - 16 h (Haglund et al 1987). Circulatory shock states never induce tissue injury to deeper mucosal structures than the villus layer (Haglund et al 1975),

and it takes 1 - 2 h for the injury to become detectable with light microscopic examination.

Experimental evidence shows that mucosal injury caused by ischemia is paradoxically exacerbated after reperfusion of the ischemic intestinal segment (Haglund et al 1975, Parks and Granger 1986, Parks et al 1982). Although the degree of the preceding ischemic insult influences the severity of the reperfusion injury, a serious ischemic attack will mask the exacerbation of the reperfusion injury and make it undetectable (Park et al 1990).

As a consequence of intestinal ischemia, the mucosal barrier becomes impaired resulting in extravasation of fluid and electrolytes into the intestine leading to hypovolemia. Gastrointestinal bleeding may occur resulting in a risk of bacteremia, local infection and sepsis. Later, cardiac failure, pulmonary insufficiency, septic shock and renal failure can all develop and result in the multiple organ failure syndrome (Carrico et al 1986). If the hemodynamic situation is normalized, the superficial mucosal injury confined to the villi can heal rapidly within 4 h, but the deeper injury takes 18 h to heal (Park and Haglund 1992).

2.2.5. Intestinal ischemia and renal failure

Acute renal failure is the most common renal complication encountered in the intensive care unit (Bock 1998) with a poor prognosis since only 25 - 54 % of patients with acute renal failure will leave the hospital alive (Neveu et al 1996). The causative mechanisms of acute renal failure can be divided into six groups: hypotension/ischemia, endotoxin, cytokines, oxidant injury, vasoconstriction and nephrotoxic antibiotics (Bock 1998). With respect to intestinal ischemia, LaNoue et al. (LaNoue et al 1996) reported that intestinal ischemia and reperfusion injury in rats was associated with a profound reduction in renal blood flow which was temporally related to reduced renal tissue ATP levels and renal tubular dysfunction. Rothenbach et al. (Rothenbach et al 1997) observed

that the decrease in renal function after SMA ischemia and reperfusion was due to the presence of toxic oxygen metabolites, such as a decrease in the levels of vasodilator but an increase in the vasoconstrictor eicosanoids. The contribution of intestinal ischemia to renal function was further supported by the finding that both increased intrahepatic portal systemic shunting and hepatocyte impairment contributed to alterations in renal hemodynamics and function (Javle et al 1998).

2.2.6. Diagnosis of intestinal ischemia

2.2.6.1. Clinical symptoms

Acute intestinal ischemia can present with abdominal pain and hemodynamic decompensation over a few hours or insidiously with symptom progression over days, leading to considerable variation in the symptoms. Typical symptoms consist of abdominal pain, nausea, vomiting, changes in bowel habits, abdominal distention, occult blood in stools and shock (McKinsey and Gewertz 1997). Tenderness, rebound tenderness and muscle guarding suggest the progressive loss of intestinal viability and transmural gangrene (Kaleya and Boley 1995). Abdominal pain out of proportion to the physical findings is a cardinal symptom in patients with acute intestinal ischemia and is commonly manifested after embolic or thrombotic SMA occlusion. There are some variations in the progress of symptoms in the different forms of acute intestinal ischemia. In the case of a mesenteric embolus, the pain starts abruptly, whereas mesenteric artery thrombosis is often associated with a more insidious onset of the pain. In nonocclusive intestinal ischemia, the symptoms start slowly but progress in severity, whereas in mesenteric venous thrombosis the pain is usually not as severe as in arterial disease.

2.2.6.2. Laboratory findings

Leukocytosis, an increase in hemoglobin/hematocrit consistent with hemoconcentration and blood in the peritoneal fluid with an elevated amylase content suggest advanced intestinal necrosis and sepsis (Andersson et al 1984, Järvinen et al 1994, Kairaluoma et al 1977, Kaleya and Boley 1995, McKinsey and Gewertz 1997). In some patients, amylase, lactic dehydrogenase, creatine phosphokinase, phosphate or alkaline phosphatase may be elevated and metabolic acidosis is common (McKinsey and Gewertz 1997). However, the sensitivity and specificity of these variables in the diagnosis of intestinal ischemia remains low.

2.2.6.3. Blood lactate

The blood lactate level depends on the balance between lactate production and lactate uptake by different organs. Generalized tissue hypoperfusion such as cardiogenic, hypovolemic and septic shock as well as regional hypoperfusion may cause lactic acidosis. As the intestine is capable of producing large quantities of lactic acid, severe lactic acidosis may be the predominant indicator of intestinal ischemia. In experimental studies, the blood lactate level has been a good marker of intestinal ischemia, although a normal blood lactate concentration does not exclude intestinal ischemia (Jonas et al 1996, Nutz et al 1987). The sensitivity and specificity of blood lactate as a marker of intestinal ischemia have been reported to be 100 % and 42 %, respectively (Lange and Jackel 1994), and increased plasma lactate concentration together with a suspicion of intestinal ischemia can be interpreted as an indicator for an emergency operation. In the assessments of the postoperative course, increased lactate concentration during the first two postoperative hours has been found to be a significant predictor of postoperative complications (Marnitz

et al 1994). In another study, severe lactatemia proved to be a predictor of death in critically ill patients (Bakker et al 1991).

The difference between peritoneal and plasma lactic acid values has been used in those patients in whom the diagnosis of acute abdomen is not otherwise obvious (DeLaurier et al 1994). Blood D-lactate concentration, a product of bacterial metabolism, was reported to be elevated in a rat model of intestinal ischemia, and has also been observed in clinical studies in cases of acute intestinal ischemia (Murray et al 1994). A new method with the potential for having clinical applications in the detection of intestinal hyperlactatemia is gut luminal microdialysis (Tenhunen et al 1999).

There are conflicting opinions, e.g. neither determination of the plasma lactate concentration nor the results of the separate standard laboratory tests in patients with acute abdominal insult resulted in a better sensitivity for the determination of an indication for acute surgery than clinical examination combined with standard laboratory tests and radiology (Vahl et al 1998).

2.2.6.4. Systemic and regional pCO_2 and O_2

Mixed venous hypercarbia and increased systemic venous-arterial PCO_2 gradient have been reported to be markers of systemic hypoperfusion during hemorrhagic shock, cardiogenic shock, septic shock as well as after cardiopulmonary resuscitation (Bakker et al 1992, Benjamin et al 1987, Groeneveld et al 1991, Mathias et al 1988, Van der Linden et al 1995, Weil et al 1986, Zhang and Vincent 1993). Changes in the cardiac output have been found to reflect changes in PCO_2 (Bowles et al 1992, Mathias et al 1988), and based on these results, it has been suggested that systemic mixed venous-arterial PCO_2 gradient might be useful for detecting oxygen supply/demand mismatch during systemic hypoperfusion (Bowles et al 1992).

2.2.6.5. Oxygen delivery/oxygen consumption

SvO$_2$ or PvO$_2$ have been used to monitor the balance between oxygen delivery and oxygen consumption. Although PvO$_2$ is more sensitive than SvO$_2$ in the detection of changes in cardiac output and mixed venous oxygen content, the possibility to use the fiberoptic pulmonary artery oximeter catheter to measure SvO$_2$ has increased the use of SvO$_2$ (Waller et al 1982). SvO$_2$ is widely used to evaluate systemic perfusion even though it is subject to a wide range of limitations: poor correlation with changes in cardiac output (Magilligan et al 1987, Vaughn and Puri 1988), poor predictive value of SvO$_2$ in low flow states (Schlichtig et al 1986), and poor correlation with the development of lactic acidosis (Astiz et al 1988).

2.2.6.6. Radiological, radionuclide and endoscopic methods

Clinically available radiological examinations can be used in the macroscopic diagnosis of the splanchnic vasculature, but they are not able to reveal intestinal mucosal hypoperfusion. Plain abdominal radiographs are useful in excluding other possible causes of abdominal pain such as perforation and obstruction (Andersson et al 1984, McKinsey and Gewertz 1997). Even though duplex doppler ultrasound can be used to measure blood flow in the inital portions of the mesenteric arteries as a screening study before angiography, the wide range of normal blood flow limits as well as the associated ileus make ultrasound scanning unreliable (Dalton et al 1995, McKinsey and Gewertz 1997, Nicoloff et al 1997). Computed tomography has been used in the diagnosis of mesenteric venous thrombosis with good results (Smerud et al 1990, Vogelzang et al 1988). Esophagogastroscopy is not helpful, whereas sigmoidoscopy and colonoscopy can detect ischemic colitis. However, insufflation during the procedure may worsen intestinal ischemia, and the ischemic intestinal wall is susceptible to perforation (Laustsen et al

1990). Radionuclides have been used in experimental studies though these have still not led to any clinical applications (Oster et al 1989). Magnetic resonance angiography imaging has been claimed to hold potential in detecting intestinal ischemia (Ernst et al 2000, Ha et al 2000). Angiography has remained the most reliable radiological method in the diagnosis of intestinal ischemia and in the attempts to achieve a good revascularization.

2.2.6.7. Laparotomy and laparoscopy

The diagnosis of intestinal ischemia during laparotomy is usually apparent by clinical findings; the colour and peristaltis of the intestine and mesenteric artery pulsation. In addition, doppler flowmetry, fluorescence with ultraviolet light, visceral surface oximetry and measurement of intramucosal pH have been used to evaluate the viability of the intestine (Bastien et al 1999, Bulkley et al 1981, Kuttila et al 1994, Locke et al 1984). Laparoscopy can be used in the diagnosis of intestinal ischemia in patients not suitable for laparotomy. Even though only the serosal surface of the intestinal wall can be seen, and the increase in intra-abdominal pressure during the procedure may further decrease intestinal blood flow (Knolmayer et al 1998), laparoscopy does provide the possibility to perform perioperative ultrasound (Roayaie et al 2000). Spectrophotometry provides an index of mucosal hemoglobin concentration and an index of oxygen saturation of hemoglobin based on spectral analysis of light reflected from the mucosal surface (Leung et al 1987), and oxygen electrodes have also been used to measure visceral PO_2 (Antonsson et al 1990). Hepatic vein catheterization allows the measurement of hepatic venous oxygen saturation, lactate concentrations and splanchnic blood flow (Uusaro et al 1995). However, many of these methods are experimental and invasive as well as susceptible to artefacts caused by breathing movements, intestinal peristaltis and poor contact.

2.2.6.8. Gastrointestinal tonometry

Gastrointestinal tonometry was originally founded on the principal that tissue PCO_2 and PO_2 can be estimated by sampling the saline instilled in the urinary bladder after it has reached equilibrium with the surrounding tissue (Bergofsky 1964). This principle was applied to the intestinal lumen (Dawson et al 1965) and a tonometric technique was adopted for assessing intestinal luminal PCO_2 and for the calculation of pH (Fiddian-Green et al 1982). Gastrointestinal tonometry is a gas-impermeable tube connected distally with a gas-permeable silicone balloon which can be placed in the stomach and/or in the sigmoid colon. The tonometer balloon is filled with saline, and the CO_2 equilibrates between the intestinal wall, intestinal lumen and the saline in the balloon. Full equilibrium takes about 90 minutes, but by using a time dependent correction factor, PCO_2 can be estimated after a shorter time period. Mucosal bicarbonate is assumed to be equal to arterial bicarbonate, which is measured. The pH is calculated from a modified Henderson-Hasselbach equation: $pH = 6.1 + \log$ ($[HCO_3^-]/(pCO_2 \times k)$, where k is the time-dependent correction factor (Fiddian-Green et al 1983).

The gastrointestinal tonometry has been validated by measuring directly gastric pH by microelectrodes during endotoxemia and intestinal hypoperfusion (Antonsson et al 1990). In this latter condition it underestimated the decrease in pH in low flow states but in cases of endotoxemia it was more reliable. In addition, the tonometric method has been suggested to be a good marker of the adequacy of tissue oxygenation because it correlates well with oxygen consumption when oxygen delivery has decreased below the critical point and oxygen consumption becomes dependent on oxygen delivery (Grum et al 1984). The tonometric measurements in the different parts of the gastrointestinal tract have correlated with reduced intestinal blood flow (Montgomery et al 1989), although small bowel tonometry was reported to be

more accurate than gastric tonometry in detecting intestinal hypoperfusion during hemorrhagic shock (Walley et al 1998).

The clinical use of tonometry has revealed several technical and physiological problems. The reflux of bicarbonate back from the duodenum into the stomach produces CO_2 resulting in erroneously low pH values. To avoid this error, antihistamine H_2 – blockers have been recommended to prevent CO_2 formation (Bams et al 1998). However, in some reports ranitidine has not influenced pH measurements or the reproducibility of the measurements in critically ill patients and in healthy volunteers (Calvet et al 1998, Parviainen et al 1996).

Enteral feeding decreases gastric pH by stimulating the secretion of hydrogen ions, which are buffered then generating CO_2. It has been suggested that the feeding should be temporarily discontinued for at least one hour before the measurement of gastric pH (Marik and Lorenzana 1996). In addition, sampling technique, delay in the analysis of the sample and the problem of the analysis of the samples being performed with different blood gas analyzers all contribute to the errors in pH measurements (Takala et al 1994, Wood and Lawler 1996). Phosphate bicarbonate buffer and succinylated gelatin have been found to be more accurate than saline as the tonometric fluid but their equilibration is too slow for clinical application (Kolkman et al 1997). A new air filled tonometry seems to avoid these errors and because it is easy to automate, it offers advantages over the traditional saline tonometry (Heinonen et al 1997)

Systemic alkalosis and acidosis may also influence the intramucosal pH calculations. Thus, it is recommended that one should measure the difference between arterial and intramucosal pH and PCO_2 values. During metabolic acidosis, only a high pH difference is evidence of hypoperfusion. With mathematical simulations, it has been shown that the PCO_2 difference offers the same information as the pH difference (Schlichtig et al 1996). Since intramucosal PCO_2 and arterial PCO_2 are measurable variables, the source of the error is less than that inherent in the calculation of pH values. In addition, when the PCO_2 difference is used, there is no need for the assumption that the

arterial bicarbonate equals the intramucosal bicarbonate. However, the PCO_2 difference as an indicator of intestinal hypoperfusion during systemic hypocapnia may not be totally reliable, because low systemic PCO_2 leads only to a small PCO_2 difference even in cases of severe ischemic insults (Guzman and Kruse 1999).

The reports from the relationship between gastric pH and other variables assessing tissue hypoperfusion are controversial. In cardiac surgical patients, pH has correlated with the hepatic venous lactate concentration, oxygen tension and pH (Landow et al 1991). In one study, gastric pH correlated with base deficits in intensive care patients (Boyd et al 1993), but in another set of critically ill patients, no relationship between gastric pH and systemic lactate or oxygen delivery values was found (Friedman et al 1995). Low pH values have been related to morbidity and mortality in critically ill patients, and in patients after cardiac surgery and major trauma (Doglio et al 1991, Fiddian-Green and Baker 1987, Gutierrez et al 1992a, Marik 1993, Roumen et al 1994).

2.2.7. Assessment of renal function

Inulin is a unique example of a substance that is cleared solely by glomerular filtration. Inulin clearance is determined by measuring the concentration of inulin in urine and plasma samples obtained during intravenous inulin infusion. Although inulin clearance is the most precise measurement of glomerular filtration rate, it is cumbersome and necessitates specific laboratory expertise and is not used in the routine assessment of the glomerular filtration rate (Levey et al 1991). More often the glomerular filtration rate is measured by levels of endogenous compounds (e.g. creatinine) which is generated by a nonenzymatic conversion from creatine and phosphocreatine present in the muscle. Creatinine is a small molecule, which is freely filtered by the glomerulus and is not metabolized by the kidney even though it is secreted by the proximal tubule. Creatinine clearance therefore reflects glomerular filtration as well as tubular

secretion, and therefore it exceeds the glomerular filtration rate. There is a great variability in the levels of serum creatinine due to methodological problems and individual variation (Blumenfeld and Vaughan 1998).

2.3. Intestinal ischemia and multiple organ failure

Multiple organ failure remains the leading cause of delayed mortality in surgical intensive care units; as up to 61 % of late deaths in a trauma center have been reported to be attributable to multiple organ failure. The mortality of multiple organ failure ranges from 40 % to 100 % and is related to the number and duration of organ failures (Biffl and Moore 1996). In the early reports, infection was considered to be the etiological factor of multiple organ failure (Polk and Shields 1977). However, later it was found that infection was related to multiple organ failure in only 50 % of cases, and the term "systemic inflammatory response syndrome" (SIRS) was introduced referring to an inflammatory response to infectious or non-infectious processes (Biffl and Moore 1996). The observation that the infection was not the only cause of multiple organ failure, was followed by research to find other etiological factors. In the "two-hit" model, the initial insult was thought to prime the inflammatory system in such a way that the response of the system to a second insult became exaggerated (Biffl and Moore 1996). One of these "two-hit" theories is the "gut theory" with bacterial translocation according to which the hypoperfusion of gut is the initial insult and "motor of multiple organ failure", after which a number of other clinical conditions (e.g. infection, inadequate tissue perfusion, inflammation, dead or injured tissue) may act as the second insult and lead to multiple organ failure (Meakins and Marshall 1986). This is supported by the findings that in low-flow states such as hemorrhagic shock, intestinal blood flow can decrease out of proportion to the decrease in cardiac output and is the last parameter to recover after resuscitation (Bailey et al 1987a, Edouard et al 1994). Low gastric intramucosal pH value has been found

to predict morbidity and mortality in critically ill patients, and in patients after cardiac surgery and major trauma (Doglio et al 1991, Fiddian-Green and Baker 1987, Gutierrez et al 1992a, Marik 1993, Roumen et al 1994). The basic mechanism may be that the intestinal mucosal injury and increased permeability promote the translocation of luminal bacteria and endotoxin into the systemic circulation, where they can activate macrophages, circulating neutrophils and humoral plasma mediators (Deitch et al 1988, Deitch 1992, Sullivan et al 1991). However, there are also reports, where no translocation of bacteria has been verified thus leaving the clinical relevance of intestinal hypoperfusion unresolved (Lemaire et al 1997, Morales et al 1992, Peitzman et al 1991). The pathophysiology of multiple organ failure remains very complicated. After the inflammatory process is initiated, large numbers of endogenously produced mediators of inflammation (arachidonic acid metabolites, cytokines, complement, nitric oxide, vasoactive peptides), activated blood cells (macrophages, neutrophils), free radicals, and exogenous bacterial toxins all interact. The products of these activated cascades may impair the intestinal microcirculation and oxygenation, further impairing the intestinal hypoperfusion and intestinal permeability.

2.4. Treatment of intestinal and renal hypoperfusion

2.4.1. Fluid therapy

Ischemia-reperfusion, endotoxic shock, hemorrhagic shock, pancreatitis and cardiopulmonary resuscitation decrease intestinal blood flow and impair tissue oxygenation (Juvonen et al 1999, Miller et al 1998, O'Neill et al 1994, Oi et al 2000, Scannell et al 1992). Aggressive fluid therapy after ischemia-reperfusion as well as fluid resuscitation and moderate hemodilution in trauma patients with hydroxyethylstarch have improved survival and increased intestinal perfusion (Kleen et al 1997, Miller et al 1998, O'Neill et al 1993, O'Neill et al 1994). The

greater hemodilution may be detrimental to tissue oxygenation as Noldge et al. (Noldge et al 1991) reported that although intestinal flow did increase secondary to the severe hemodilution, portal and hepatic venous pH as well as surface PO_2 of liver and intestine decreased. They concluded that increased flow and oxygen extraction could not compensate for the decrease in oxygen delivery resulting from the hemodilution. In septic patients, hypertonic saline with dextran, Ringer's lactate and hetastarch have increased tissue oxygenation (Baum et al 1990, Boldt et al 1996a, Horton and Walker 1991, Oi et al 2000) whereas human albumin did not have this effect (Boldt et al 1996b). The decrease in portal blood flow during pancreatitis could be prevented by a combination of Ringer's lactate and hetastarch (Juvonen et al Takala 1999). After hemorrhagic shock, hypertonic saline, hetastarch and dextran were found to be better than Ringer's lactate in increasing intestinal and renal blood flow (Diebel et al. 1993;Mäkisalo et al. 1989;Maningas 1987;Prough et al. 1991). However, there are some reports indicating that Ringer's lactate was not able to maintain intestinal blood flow at all (Diebel et al 1993, Maningas 1987, Scannell et al 1992, Smail et al 1998). These result show that adequate volume restoration is important in guaranteeing correct intestinal perfusion.

2.4.2. Vasoactive drugs

The effects of vasoactive drugs on the different receptors and regional blood flows are summarized in Tables I and II (Meier-Hellmann and Reinhart 1995).

Table 1. Effects of the different catecholamines on the adrenergic and dopaminergic (DA) receptors

Catecholamine	alpha1	alpha2	beta1	beta2	DA1	DA2
Dobutamine	++	0	+++	++	0	0
Epinephrine	+++	+++	++	+++	0	0
Norepinephrine	+++	+++	++	+	0	0
Dopamine						
0 - 3 µg/kg/min	0	+	0	0	+++	++
2 - 10 µg/kg/min	+	+	++	+	++	++
> 10 µg/kg/min	++	++	++	+	+	+
Dopexamine	0	0	+	+++	++	+

(Meier-Hellmann and Reinhart 1995)

Table 2. Effects of different catecholamines on regional blood flow

Catecholamine	Kidney	Brain	Heart	Splanchnic	Muscle	Skin
Dobutamine	+	+	+	+	++	+
Epinephrine	- / +	+	+	- / +	+ / 0	-
Norepinephrine	- / +	+	+	- / +	- / 0	0
Dopamine						
0 - 3 µg/kg/min	+++	+	0	+++	0	0
2 - 10 µg/kg/min	++ / +	+	+	++ / +	0	0
> 10 µg/kg/min	- / +	+	+	- / +	-	-
Dopexamine	+++	+	+	+++	+	+

(Meier-Hellmann and Reinhart 1995)

Vasoactive drugs are known to increase cardiac contractility and cardiac output, and to improve tissue perfusion, if optimization of preload with adequate volume resuscitation is not sufficient to restore hemodynamic stability, sufficient oxygen delivery and tissue perfusion. The hyperdynamic circulation and increased oxygen delivery achieved by the use of the vasoactive drugs have been claimed to reduce mortality in critically ill patients (Boyd et al 1993, Heyland et al 1996, Shoemaker et al 1988).

2.4.2.1. Dopamine

Dopamine is a catecholamine which can activate alpha, beta and dopaminergic receptors, which can be divided into presynaptic and postsynaptic receptors (Goldberg 1972, Meier-Hellmann and Reinhart 1995). The effect of dopamine is dose dependent. At low doses (< $3\,\mu g/kg/min$), stimulation of dopaminergic and beta-adrenergic receptors may increase blood flow in the splanchnic and renal regions. However, as the dose is increased, these effects are masked by alpha$_1$-adrenergic receptor stimulation resulting in vasoconstriction (Silva et al 1998) and the use of higher dosages of dopamine to increase arterial pressure may have a deleterious influence on the clearly disturbed microcirculation.

In an experimental ischemic model, dopamine did not influence tonometric PCO_2 after supracoeliac aortic cross-clamping and declamping (Studer and Wu 2000). Sakio et al. (Sakio et al 1994) showed that during partial SMA occlusion (70 %) intravenous dopamine increased SMA flow but further decreased intramucosal pH suggesting that dopamine could evoke constriction of the intestinal mucosal arterioles. Similar results were obtained by Segal et al. (Segal et al 1992) during hemorrhagic shock as in their study dopamine hastened the onset of intestinal ischemia relative to onset of the whole body ischemia. In contrast, Nordin et al. (Nordin et al 1994) reported that dopamine together with volume resuscitation did improve tissue oxygenation. During endotoxin shock and sepsis, dopamine did not induce a redistribution of systemic blood flow to the splanchnic region, which was observed in the non-septic part of the study (Bersten et al 1992, Breslow et al 1987). Dopamine has increased renal blood flow and produced renal vasodilatation in healthy animals as well as during hemorrhagic shock (Bersten and Rutten 1995, Gordon et al 1995, Hamed et al 1983, Robie and Goldberg 1975). During sepsis, dopamine has improved renal hemodynamics (Fink et al 1985), but there are also studies where this effect has not been detected (Bersten and Rutten 1995, Breslow et

al 1987). The ability of dopamine to produce renal vasodilatation becomes attenuated with time due to tachyphylaxis (Gordon et al 1995, MacCannell et al 1983).

In septic patients, while dopamine did increase intestinal blood flow and improved oxygen delivery, it simultaneously also increased oxygen consumption causing a deleterious effect on intestinal oxygenation (Meier-Hellmann et al 1997a, Ruokonen et al 1993) and studies where it even decreased gastric mucosal blood flow without influencing intramucosal pH (Neviere et al 1996, Olson et al 1996). In patients with heart failure or gastrointestinal acidosis, dopamine did not influence intestinal blood flow (Leier 1988, Maynard et al 1995). Thoren et al. (Thoren et al 2000) reported that in cardiac surgical patients, dopamine increased jejunal mucosal perfusion and decreased splanchnic oxygen extraction, whereas in patients with coronary artery bypass grafting and abdominal aortic aneurysm, intramucosal pH remained unchanged or even decreased (Gärdebäck and Settergren 1995, Maynard et al 1995). In healthy humans, dopamine has increased renal blood flow, decreased renal vascular resistance, increased effective renal plasma flow and sodium excretion, decreased the absolute proximal reabsorption rate and did not influence the glomerular filtration rate (Christiansen et al 1988, Mousdale et al 1988, Olsen et al Leyssac 1993, Olsen 1998, Stephan et al 1990). In septic patients, dopamine has increased fractional renal blood flow, decreased renal oxygen extraction, increased diuresis and sodium excretion but not influenced creatinine clearance (Day et al 2000, Juste et al 1998, Lherm et al 1996, Olson et al 1996). As Lherm et al. (Lherm et al 1996) reported increased diuresis and creatinine clearance with dopamine, they also found that the renal response to dopamine decreased significantly after a 48 h dopamine infusion, suggesting that the stimulation of dopaminergic receptors causes evoked renal sodium excretion (Kulka and Tryba 1993) and that the diuretic effect of low-dose dopamine was mediated by the proximal tubular inhibition of sodium reabsorption not by increased renal blood flow. Since this is not

associated with any increased creatinine clearance, it may be injurious to the malfunctioning kidney by augmenting the medullary workload, thereby aggravating medullary ischemia (Bellomo et al 1998).

2.4.2.2. Dopexamine

Dopexamine hydrochloride is a synthetic catecholamine with dopaminergic and beta$_2$-adrenergic receptor agonist activity but which does not activate alpha-adrenergic receptors (Silva et al 1998). It can cause an improvement in tissue perfusion in the renal, splanchnic, coronary, pulmonary and skeletal muscle vascular beds (Kulka and Tryba 1993).

In experimental studies, dopexamine has been reported to increase intestinal blood flow and to decrease vascular resistance (Bastien et al 1999, Madorin et al 1999, van Kesteren et al 1993), to improve tissue oxygenation (Schmidt et al 1996), to protect hepatic ultrastructure and mitochondrial integrity (Tighe et al 1993, Webb et al 1991), and to decrease leucocyte adherence and vascular permeability (Schmidt et al 1998) as well as preventing hypoxia and the positive end-expiratory pressure induced changes in intestinal blood flow (Aliabadi-Wahle et al 1999, Steinberg et al 1996, Thomas et al 1997). The influence is equally distributed to the various organs during sepsis (Cain and Curtis 1991, van Lambalgen et al 1993). In conflicting reports, it was claimed that dopexamine did not influence intestinal blood flow or tissue oxygenation (Sautner et al 1998, Stamler et al 1998, Studer and Wu 2000). Dopexamine has increased renal blood flow, glomerular filtration rate, urine volume and sodium excretion (Chintala et al 1990, Kirchhoff et al 1999, van Kesteren et al 1993) due to tubular dopaminergic-receptor stimulation and strong beta-adrenergic mediated vasodilatatory effects both being receptors which increase sodium excretion, creatinine clearance, glomerular filtration rate and urine output (Baumann et al 1990, Gray et al 1991, Stephan et al 1990). There are also studies, in which it has not had any influence on renal hemodynamics,

renal blood flow, glomerular filtration rate or urine volume (Kirchhoff et al 1999, van Kesteren et al 1993)

In clinical studies, dopexamine has been shown to increase intestinal blood flow (Maynard et al 1995, Meier-Hellmann et al 1999, Uusaro et al 2000) and mucosal perfusion (Booker and Pozzi 2000, Kaisers et al 1996, Maynard et al 1995, Sinclair et al 1997, Thoren et al 2000) based on selective vasodilatation and increases in cardiac output (Maynard et al 1995, Sharpe et al 1999). In septic patients, although the splanchnic blood flow increased, the fractional splanchnic flow decreased (Kiefer et al 2000) or increased proportionally to cardiac output (Meier-Hellmann et al 1999). Dopexamine had no influence on mucosal perfusion in septic, cardiac and abdominal surgery patients (Gärdebäck and Settergren 1995, Piper et al 2000, Temmesfeld-Wollbruck et al 1998) and in some studies dopexamine decreased mucosal perfusion in cardiac patients (Gärdebäck et al 1995, Uusaro et al 2000). Dopexamine has increased renal blood flow, the glomerular filtration rate, diuresis, the creatinine clearance rate and the fractional excretion of sodium (Atallah et al 1992, Baumann et al 1990, Blunt et al 1999, Stephan et al 1990). It has also protected kidney during aortic reconstruction and liver transplantation (Gray et al 1991, Welch et al 1995). On the other hand, dopexamine did not improve the fractional renal blood flow in patients undergoing coronary artery bypass grafting or in children (Habre et al 1996, Stephan et al 1990), and it did not increase renal blood flow and it has been reported to even increase renal vascular resistance and decrease diuresis in patients with chronic heart failure or undergoing coronary arterey bypass grafting (Jamison et al 1989, Sherry et al 1997).

2.4.2.3. Dobutamine

Dobutamine is a synthetic catecholamine with predominantly positive inotropic effects resulting from $beta_1$-adrenoceptor stimulation. It has weak $beta_2$-

agonistic and alpha-adrenergic activity but no dopaminergic receptor effects (Kulka and Tryba 1993, Meier-Hellmann and Reinhart 1995, Silva et al 1998). Dobutamine increases cardiac output and reduces total vascular resistance (Kulka and Tryba 1993), but it is not clear whether dobutamine influences selectively intestinal or renal perfusion (Meier-Hellmann and Reinhart 1995) or whether the effects of dobutamine on these vascular beds depend on its ability to increase cardiac output (Bellomo et al 1998).

In experimental studies dobutamine has increased intestinal blood flow and tissue oxygenation (Neviere et al 1996, Neviere et al 1997, Schneider et al 1991) without influencing the distribution of cardiac output into the various organs (Schneider et al 1991). Bersten et al (Bersten et al 1992) reported that even though in the non-septic part of their study, the infusion of dobutamine was accompanied by a redistribution of systemic blood flow favouring the heart and away from the brain, kidney, small intestine, liver, and pancreas, in the septic part of the study this was not observed. In conflicting reports, dobutamine has not influenced intestinal blood flow or tissue oxygenation (Azar et al 1996, Germann et al 1997, Nordin et al 1996, Priebe et al 1995) or has even decreased intestinal blood flow (Ferrara et al 1995) as well as caused marked hepatocellular destruction (Webb et al 1991). In most clinical studies, dobutamine does seem to increase intestinal blood flow and tissue perfusion (Levy et al 1997b, Levy et al 1997a, Levy et al 1999, Neviere et al 1996, Parviainen et al 1995) without favoring any organ in the blood flow distribution (Parviainen et al 1995, van Lambalgen et al 1993). There are some reports indicating that dobutamine does not influence blood flow (Karzai et al 1996, Leier et al 1978) or tissue oxygenation or it may even decrease these parameters (Parviainen et al 1995, Silverman and Tuma 1992, Uusaro et al 1997). In pancreatitis patients, dobutamine was reported to have inconsistent influence on intestinal blood flow (Ruokonen et al 1997).

The renal effects of dobutamine have been reported in experimental and clinical studies in healthy subjects (Fiser et al 1988, Olsen et al 1993,

Vainionpaa et al 1983, Westman and Järnberg 1986) as well as during pathological conditions known to increase the risk of intestinal hypoperfusion such as septic shock (Bersten et al 1992, Haywood et al 1991, Levy et al 1999, Palsson et al 1997), heart failure (Good et al 1992, Leier et al 1978, Leier 1988), coronary artery bypass grafting and cardiopulmonary bypass (MacGregor et al 1994, Wenstone et al 1991) and after major vascular surgery and in critically ill patients (Duke et al 1994, Westman and Järnberg 1987). So that there are studies in which dobutamine has increased (Duke et al 1994, Fiser et al 1988, Good et al 1992, Leier et al 1978, Leier 1988, MacGregor et al 1994, Vainionpaa et al 1983, Good et al 1992), decreased (Bersten et al 1992, Haywood et al 1991, Westman and Järnberg 1986) or had no influence (Leier 1988, Levy et al 1999, Olsen et al 1993, Westman and Järnberg 1986, Westman and Järnberg 1987) on renal blood flow or function. Based of these results, one must conclude that the influence of dobutamine on renal function is variable and may result in different effects on the renal vascular bed which are not revealed by the measurement of systemic indices alone (Haywood et al 1991).

2.4.2.4. Norepinephrine

Norepinephrine is the naturally occurring neurotransmitter in most postganglionic sympathetic neurons and it is also synthesized in the adrenal gland. When given exogenously, the pharmacodynamic effects of norepinephrine vary in a dose-dependent manner. At low doses < 2 µg/min, it is a $beta_1$-agonist, increasing myocardial inotropy and heart rate. If the dose exceeds 4 µg/min, the alpha-adrenergic action of norepinephrine becomes predominant, resulting in elevated peripheral resistance (Kulka and Tryba 1993). Due to this predominant alpha-adrenergic receptor influence, it is commonly used in the treatment of septic shock to restore arterial pressure (Silva et al 1998).

In most experimental and clinical studies norepinephrine alone or together with dobutamine has increased intestinal blood flow and tissue oxygenation (Duranteau et al 1999, Marik and Mohedin 1994, Ruokonen et al 1993). However, in some reports even though it has increased oxygen delivery it has not influenced (Creteur et al 1999, Meier-Hellmann et al 1996) or has even compromized tissue oxygenation (Hayes et al 1998, Sautner et al 1998). While norepinephrine may increase splanchnic blood flow, its influence does not tend to be uniform (Ruokonen et al 1993). In a non-septic study, it decreased the fractional splanchnic blood flow (Bersten et al 1992), whereas during sepsis it has not influenced the distribution of blood flow (Bersten et al 1992, Breslow et al 1987, Schneider et al 1991).

There is no consensus on the renal influences of norepinephrine. Bellomo et al. (Bellomo et al 1999) concluded that unlike the effects of norepinephrine during baseline conditions, norepinephrine infusion during endotoxic shock actually increased renal blood flow and that this effect was not the result of an increase in perfusion pressure alone. Marin et al. (Marin et al 1990) reported that normalization of systemic hemodynamics with norepinephrine was followed by re-establishment of urine flow, decrease in serum creatinine and an increase in creatinine clearance, suggesting that norepinephrine infusion does not worsen renal ischemia related to hemodynamic disturbances in septic shock patients, and may have beneficial effects on renal function even though the increase in renal function may be secondary to the improved hemodynamics. Buckley et al. (Buckley et al 1979) reported that norepinephrine restored renal flow only in older pigs who possessed an active alpha-adrenergic vasoconstrictor mechanism but did not have a beta-adrenergic vasodilator mechanism in their renal circulation at birth. In septic shock patients, norepinephrine increased diuresis, creatinine, and osmolar clearance and decreased free water clearance which led the authors to conclude that norpinephrine could be used in the treatment of human septic shock without evoking deleterious renal effects (Desjars et al 1989). Norepinephrine was

found to be effective and reliable at reversing the abnormalities of
hyperdynamic septic shock. In the great majority of the study patients,
norepinephrine was able to increase mean perfusion pressure without causing
any apparent adverse effects on peripheral blood flow or on renal blood flow
(Martin et al 1993). In healthy male volunteers and in sedated sheep,
norepinephrine infusion did decrease renal blood flow (Richer et al 1996,
Schiffer et al 1995).

2.4.2.5. Epinephrine

Epinephrine at low doses acts predominantly on peripheral $beta_1$-and $beta_2$-
adrenergic receptors whereas at higher doses it has $alpha_1$-adrenergic receptor
mediated vasoconstrictor effects (Silva et al 1998).

In experimental studies, low epinephrine dose did not influence SMA flow
whereas a dose exceeding 3.2 μg/kg/min of epinephrine during normo- and
hypovolemia decreased SMA blood flow and increased SMA vascular
resistance (Bigam et al 1998). Giraud et al. (Giraud and MacCannell 1984)
reported that epinephrine infused into the canine SMA increased SMA blood
flow but decreased mucosal flow. In concordance, epinephrine has been found
to decrease SMA flow and tissue oxygenation and damage the mucosa of the
ileum and colon (Hayes et al 1998, Pawlik et al 1975, Sautner et al 1998).
Voelckel et al. (Voelckel et al 2000) did reporte that epinephrine had a better
influence on SMA blood flow than vasopressin during cardiopulmonary
resuscitation. The clinical reports do not show a consensus. In a group of
septic patients epinephrine increased gastric mucosal perfusion as detected by
laser Doppler flowmetry (Duranteau et al 1999) whereas in other studies it
decreased splanchnic blood flow and intramucosal pH (Levy et al 1997a, Meier-
Hellmann et al 1997b).

Epinephrine did not influence (Bersten and Rutten 1995) or decrease renal
blood flow (Bersten and Rutten 1995, Bigam et al 1998) as well as decreasing

the renal blood flow cardiac output ratio (Day et al 2000). At the same time it has been claimed to increase the renal vascular resistance (Bigam et al 1998;Day, Phu et al 2000). Since it does not appear to influence creatinine clearance or urine output, it has been suggested that epinephrine does not produce either a beneficial or a deleterious effect on renal oxygen metabolism or function (Day et al 2000).

3. AIMS OF THE STUDY

The aim of this thesis was to evaluate systemic and regional effects of the progressive intestinal ischemia caused by graded occlusion of the superior mesenteric artery with special emphasis on:

1. determining the level of reduction of superior mesenteric artery flow that causes intestinal ischemia (I)

2. investigating whether assessment of systemic hemodynamics and oxygen transport can be used in detecting the development of intestinal ischemia (I-II)

3. evaluating the effects of dobutamine and fluid therapy on systemic and regional hemodynamics and oxygen transport during intestinal ischemia (III)

4. studying the effects of dobutamine and fluid therapy on renal function during intestinal ischemia (IV)

4. MATERIALS AND METHODS

4.1. Experimental animals and anesthesia

Sixty female pigs, 12 pigs (weight 28 ± 1 kg) (I, II) and 48 pigs (weight 27.9 ±
0.4 kg) (III, IV) were used as experimental animals. The pigs were
premedicated with intramuscular ketamine hydrochloride (30 mg/kg). The
anesthesia was induced with intravenous pentobarbital sodium (15 mg/kg),
maintained with a continuous infusion of pentobarbital sodium and small
boluses when needed. The pigs were ventilated through a tracheostomy with
30 % oxygen in room air to achieve normoventilation with an end tidal PCO_2 of
40 ± 5 mmHg at the end of the stabilization period with no changes in
ventilatory settings thereafter. Fluid therapy was maintained with 0.9 % saline
infused at a rate of 5 ml/kg/hr.

4.2. Surgical procedures

The right carotid artery and pulmonary artery were cannulated for
hemodynamic monitoring, cardiac output determination and intravenous access
(Figure 1).

Figure. 1 Experimental model

A midline laparotomy was performed, and the root of the SMA was exposed. In studies I and II, a 4 or 6 mm electromagnetic flow probe (IVM, model FX-3; In Vivo Metric Systems, Anaheim, CA) and in studies III and IV, a 4 or 6 mm ultrasound flow probe (T106, Transonic systems Inc., Ithaca, NY, USA) together with a snare occluder were placed around the SMA. After splenectomy, the portal vein was cannulated via the splenic vein. A tonometer (Tonometrics Inc., Hopkinton, MA, USA) was introduced into the intestinal lumen 80 cm distal from the ligament of Treitz for the measurement of intramucosal pH. A catheter was placed into the urinary bladder.

4.3. Experimental design

In studies I and II, after a stabilization period of 60 minutes, the SMA occluder was adjusted to reduce the SMA blood flow stepwise by 40 %, 70 % and finally 100 % from the baseline. Each occlusion level was maintained for 60 minutes. Following the total occlusion of 60 minutes, the occluder was released and the measurements were continued for an additional 60 minutes before the animal was sacrificed. The animals received only maintenance fluid therapy of 0.9 % saline infused at a rate of 5 ml/kg/hr.

In studies III and IV, during a stabilization period of at least 30 min, PCWP was adjusted to 10 mmHg by means of hydroxyethyl starch (Plasmafucin, Kabi Pharmacia, Halden, Norway) and acetated Ringer's solution (Ringersteril, Orion, Espoo, Finland) infusion in a proportion of 1:1. In the ischemic groups, the SMA blood flow was reduced with a snare occluder and the flow was stabilized to 30 % from the baseline during a 15-minute period. After the SMA blood flow stabilized to the target level, the occluder was left untouched for 120 minutes. In the sham groups, the occluder was placed around the SMA but the SMA blood flow was not reduced after the stabilization period and the measurements were continued up to 120 min. After the stabilization period, the animals in the control arms received only basic fluid therapy (0.9 % saline 5 ml/kg/hr). In the

fluid therapy arms, PCWP was maintained at 10 mmHg throughout the experiment by administration of hydroxyethyl starch and acetated Ringer's solution in the proportion of 1:1. In the dobutamine treatment arms, dobutamine hydrochloride was infused at a dose of 5 μg/kg/min for 15 minutes after the SMA flow had stabilized, thereafter the dose was increased to 10 μg/kg/min. Basic fluid therapy was maintained similarly to the control arms. In the combined dobutamine-fluid therapy arms, in addition to dobutamine, PCWP was maintained at 10 mmHg by fluid therapy similarly to the fluid treatment arms. At 120 min, the snare occluder was removed in all study groups, and the experiment was continued for another 60 min.

The study protocol in all studies was approved by the Review Board of Animal Experiments of Kuopio University. The care and handling of the animals were in accord with National Institutes of Health guidelines.

4.4. Hemodynamic measurements

Systemic and pulmonary hemodynamics were recorded continuously and calculated as one minute median values of data collected at 10 second intervals. The mean value of the 10 minute periods (I, II), and of the 5 minute periods (III, IV) preceding each cardiac output and PCWP measurements were used for analysis except for the first data points after reperfusion of the SMA, where a 3 minute mean value was used (I). Cardiac output was determined with the thermodilution method as the average of three repeated measurements using 10 ml bolus injections of 0.9 % saline at room temperature. The cardiac index was calculated dividing the cardiac output by the weight of the animal. SVRI was calculated as follows: SVRI = (MAP-MCVP)/CI.

In studies I and II, the continuous SMA blood flow signal was recorded through an amplifier (IVM, Model BA 201, In Vivo Metric Systems, Anaheim, USA) fed to an instrumentation tape recorder (Racal Store 7 DS, Racal Recorders Ltd, Southampton, England) and displayed on the screen of a cat-

hode ray oscilloscope. The SMA blood flow was estimated off-line using the recorded blood flow signal. This was performed by integrating the area under the blood flow signal over time. Because of the study set-up (gradual SMA occlusion), we were not able to occlude the SMA blood flow at regular intervals to assess zero flow calibration. Therefore, our SMA blood flow values during the study should not be considered as exact measurements, but as estimations of SMA blood flow between the baseline and total SMA occlusion. In studies III and IV, the SMA blood flow was measured with an ultrasound flow probe (T106, Transonic systems Inc., Ithaca, NY, USA).

4.5. Oxygen delivery and consumption

Blood samples were aspirated from the carotid artery, pulmonary artery and portal vein. A blood gas analyzer and an oximeter (ABL 500, OS3, Radiometer, Copenhagen, Denmark) were used to determine the blood gas values and oxygen saturation values of the samples corrected for the temperature. Oxygen delivery was measured as the product of cardiac output and arterial oxygen content and oxygen consumption as the product of cardiac output and arterial-venous oxygen content gradient. Oxygen contents were calculated as 1.39 x hemoglobin concentration x oxygen saturation + dissolved oxygen. Oxygen extraction was derived from oxygen consumption and oxygen delivery.

4.6. Tonometric measurements

The tonometer was filled with 0.9 % saline. After 30 minutes of equilibration, the PCO_2 of the sample and simultaneous arterial blood gas values were determined using the blood gas analyzer (ABL 500, Radiometer, Copenhagen, Denmark). Intramucosal pH was calculated with the modified Henderson-Hasselbach equation: $pH=6.1 + log ([HCO_3^-]/(PCO_2 \times 0.03))$ using the arterial bicarbonate concentration and the saline PCO_2, adjusted for the 30 minutes

time of equilibrium (Fiddian-Green et al 1983). Intramucosal-arterial and intramucosal-portal venous PCO_2 gradients were calculated from the corrected tonometric PCO_2 and simultaneous arterial and portal venous PCO_2 values.

4.7. Blood lactate concentrations

Blood lactate concentrations were measured from portal vein and arterial blood samples and determined by the enzymatic method (Boehringer Mannheim Total Entsymatic Test-Combination Cat. no 256 773, EPOS analyzer 5060, Eppendorf Gerätebau, Hamburg, Germany). Portal venous-arterial lactate gradient was calculated. In study I, an increase above mean + 2SD of the baseline was considered as an indicator for the development of intestinal ischemia. Intramucosal pH, PCO_2 and intramucosal-portal venous PCO_2 gradient were assessed at the corresponding time point (I).

4.8. Serum and urine creatinine concentrations

In study IV, serum and urine creatinine values were measured with Jaffe method without deproteinization (HiCo Creatinine, Cat. no 1040 847, Boehringer Mannheim, Hamburg, Germany) using a Hitachi 717 Automatic Analyzer (Hitachi Ltd., Japan) (Wilson et al 1987). C_{cr} was calculated as: C_{cr} (ml/s) = (V * U-crea * 1000) / (T * S-crea); where V is urine volume (ml), U-crea is urine creatinine concentration (mmol/l), T is time (min) and S-crea is serum creatinine concentration (μmol/l).

4.9. Statistical methods

In studies I and II, the effect of time at the different time points was analyzed with Friedman and Wilcoxon tests. A least mean square linear test was used for univariate regression analysis. In studies III and IV, the animals were

randomized blockwise with a full factorial design into eight treatment groups
(Figure 2). The differences between the baseline values were compared with

Controls

Fluid treatment (PCWP 10 mmHg)

Ischemic
(N=24)

Dobutamine treatment (10 μg/min/kg)

Fluid and dobutamine treatment

Controls

Fluid treatment (PCWP 10 mmHg)

Sham
(N=24)

Dobutamine treatment (10 μg/min/kg)

Fluid and dobutamine treatment

Figure 2. Treatment groups

one-way analysis of variance. The effect of time within the study groups was
analyzed with paired sample t-test. Differences between the groups during the
study were compared with multivariate analysis of variance for repeated
measurements using dependent variable, grouping factors
(ischemia/reperfusion, fluid, dobutamine) and within-subject factor (time). The
effect of ischemia-reperfusion was regarded as significant if the ischemia-
reperfusion-time interaction comparing ischemic and sham control groups was
significant. The effects of fluid treatment and ischemia-reperfusion were

regarded as significant if the ischemia-reperfusion-fluid-time interaction or the fluid-time interaction comparing ischemic and sham control and fluid treated groups were significant. The effects of dobutamine treatment and ischemia-reperfusion were regarded as significant if the ischemia-reperfusion-dobutamine-time interaction or the dobutamine-time interaction comparing ischemic and sham control and dobutamine treated groups were significant. The effects of fluid-dobutamine treatment and ischemia-reperfusion were regarded as significant if the ischemia-reperfusion-fluid-dobutamine-time interaction or the fluid-dobutamine-time interaction comparing all study groups were significant. A p-value < 0.05 was considered statistically significant. The results are expressed as mean $\pm$ SEM.
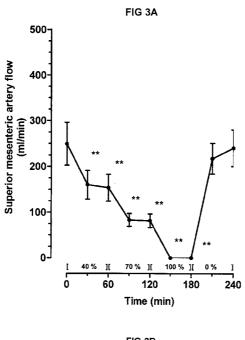
5. RESULTS

5.1. Development of intestinal ischemia during gradual reduction of superior mesenteric artery flow (I)

Q_{SMA} values at baseline, 40 % occlusion and 70 % occlusion were 249 ± 47 ml/min, 154 ± 30 ml/min and 82 ± 15 ml/min, respectively (Figure 3A). After the release of the occlusion, Q_{SMA} returned close to the baseline level, but a higher proportion of cardiac output was delivered to the SMA region as compared to the baseline (10.2 ± 1.4 % vs. 5.5 ± 0.7 %, p<0.01).

An increase in portal venous-arterial lactate gradient above mean + 2SD of baseline was observed at 93 min corresponding to 69 ± 7 % SMA occlusion (Figure 3B). At this point, intramucosal pH had decreased to 6.93 ± 0.06 (p<0.01 vs baseline), intramucosal PCO_2 had increased to 16.6 ± 1.5 kPa and intramucosal-portal venous PCO_2 gradient to 8.9 ± 1.5 kPa (p<0.05 vs baseline)(Figure 4A-C).

The portal venous lactate level increased from 4.6 ± 0.7 mmol/l to 6.4 ± 0.5 mmol/l during the SMA occlusion, reached its peak value 5 minutes after the reperfusion (8.7 ± 0.8 mmol/L, p<0.05 vs baseline), and decreased towards the end of the experiment (Figure 3B). The portal venous-arterial lactate gradient increased during the SMA flow reduction (p<0.01 at the end of the SMA occlusion vs baseline) and reached the peak value 5 minutes after the release of the vascular occlusion (3.3 ± 0.5 mmol/L, p<0.05 vs baseline). Thereafter, it decreased during the reperfusion, but remained above the baseline value until the end of the experiment.

Intramucosal pH decreased from 7.18 ± 0.04 to 6.81 ± 0.04 (p<0.01 vs baseline) at the end of the SMA occlusion, and remained below the baseline value after the SMA reperfusion (Figure 4A, Table 3). Intramucosal PCO_2 increased from 12.4 ± 1.3 kPa at baseline to 21.2 ± 1.8 kPa at the end of SMA occlusion (p<0.01), and decreased to 15.5 ± 1.7 kPa at the end of the

FIG 3A

FIG 3B

Figure 3. Effect of gradual occlusion and reperfusion of superior mesenteric artery on (A) superior mesenteric artery blood flow and (B) portal venous-arterial lactate gradient. * = $p < 0.05$: ** = $p < 0.01$ vs baseline (0 min). [Occlusion level shown above the x-axis].

Figure 4. Effect of gradual occlusion and reperfusion of superior mesenteric artery on (A) intramucosal pH, (B) arterial, mixed venous, portal venous and intramucosal pCO_2 values, (C) intramucosal-arterial, intramucosal-portal venous, portal venous-arterial, and mixed venous-arterial pCO_2 gradients, (D) portal pH and (E) splanchnic oxygen extraction. * = $p < 0.05$, ** = $p < 0.01$ vs baseline (0 min). [Occlusion level shown above the x-axis].

Table 3. Hemodynamics, tonometry and blood gas variables during graded superior mesenteric artery occlusion

	Baseline	End of ischemia	P
Mean arterial pressure (mmHg)	79 ± 3	104 ± 5	0.0022
Heart rate (beats/min)	124 ± 5	173 ± 11	0.0022
Cardiac index (ml/min/kg)	161 ± 12	114 ± 8	0.0060
PAOP (mmHg)	4.0 ± 1.0	3.0 ± 1.0	NS
Hemoglobin (g/l)	104 ± 3	112 ± 3	0.0022
SMA flow (ml/min/kg)	8.7 ± 1.5	0 ± 0	0.0022
Intramucosal pH	7.18 ± 0.04	6.81 ± 0.04	0.0033
Lactate gradient (mmol/l)	0.02 ± 0.07	2.32 ± 0.47	0.0044
O_2-extraction$_s$	0.44 ± 0.03	0.60 ± 0.03	0.0209
pH_i	7.18 ± 0.04	6.81 ± 0.04	0.0033
pH_A	7.42 ± 0.01	7.44 ± 0.01	NS
pH_V	7.38 ± 0.01	7.39 ± 0.01	NS
pH_s	7.36 ± 0.01	7.25 ± 0.03	0.0152
PCO_{2i} (kPa)	12.4 ± 1.3	21.2 ± 1.8	0.0076
pCO_{2A} (kPa)	5.2 ± 0.2	4.8 ± 0.1	NS
pCO_{2V} (kPa)	6.0 ± 0.2	5.9 ± 0.1	NS
pCO_{2s} (kPa)	6.6 ± 0.3	8.2 ± 0.6	0.0209
a-HCO_3^- (mmol/l)	25.4 ± 1.0	25.2 ± 0.9	NS
v-HCO_3^- (mmol/l)	24.8 ± 1.0	25.1 ± 0.9	NS
s-HCO_3^- (mmol/l)	25.7 ± 1.0	21.5 ± 1.0	0.0152
a-BE (mmol/l)	0.9 ± 1.2	0.3 ± 1.0	NS
v-BE (mmol/l)	1.2 ± 1.2	1.6 ± 1.0	NS
s-BE (mmol/l)	2.8 ± 1.1	-0.7 ± 1.0	0.0284

Abbrevations: PAOP = pulmonary artery occluded pressure; SMA = superior mesenteric artery; lactate gradient = portal venous-arterial lactate gradient; pH_i = intramucosal pH; a = arterial; s = splanchnic/portal vein; v = mixed vein; BE=base excess; NS = not significant

reperfusion (Figure 4B, Table 3). Accordingly, the intramucosal-arterial PCO_2 gradient (p<0.01), the intramucosal-portal venous PCO_2 gradient (p<0.01), and the portal venous-arterial PCO_2 gradient (p<0.01) all increased during the SMA occlusion (Figure 4C).

The portal venous pH decreased during the SMA flow reduction (p<0.05 at the end of ischemia vs baseline) with a more pronounced drop at five minutes after the SMA reperfusion (Figure 4D, Table 3). Later during the reperfusion, portal venous pH started to increase, but remained below the baseline value.

Splanchnic oxygen extraction increased from 0.44 ± 0.03 to 0.60 ± 0.03 (p<0.05 vs baseline) towards the end of the SMA occlusion (Figure 4E, Table 3). After reperfusion, there was a rapid drop in the splanchnic oxygen extraction.

5.2. Systemic hemodynamics and oxygen transport during the development of intestinal ischemia (I,II)

The cardiac index decreased gradually throughout the experiment (p<0.01 vs baseline)(Figure 5A). HR increased significantly (p<0.01) at 30 minutes after the total SMA occlusion and remained above the baseline value during the whole reperfusion period (Figure 5B). MAP and SVRI increased towards the end of SMA occlusion with the peak at 30 minutes after the total occlusion (Figure 5C,D). After the release of the SMA occlusion, a rapid decrease in the MAP and SVRI values were observed. MPAP during the occlusion and reperfusion did not differ significantly from the baseline. PCWP decreased gradually from 4 ± 1 mmHg at baseline to 3 ± 1 mmHg at the end of SMA occlusion and further decreased to 2 ± 1 mmHg at the end of the reperfusion period (p<0.05).

Systemic oxygen delivery and oxygen consumption decreased early and progressively during the experiment (Figure 6A,B). After the release of the

FIG 5A

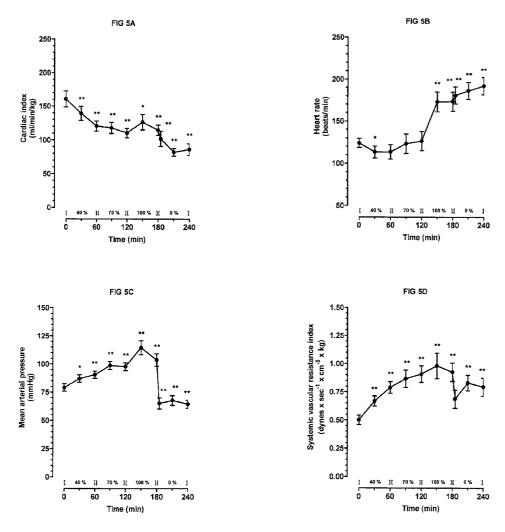
FIG 5B

FIG 5C

FIG 5D

Figure 5. Effect of gradual occlusion and reperfusion of the superior mesenteric artery on (A) cardiac index, (B) heart rate, (C) mean arterial pressure and (D) systemic vascular resistance index. * = p<0.05; ** = p<0.01 vs baseline (0 min).[Occlusion level shown above the x-axis].
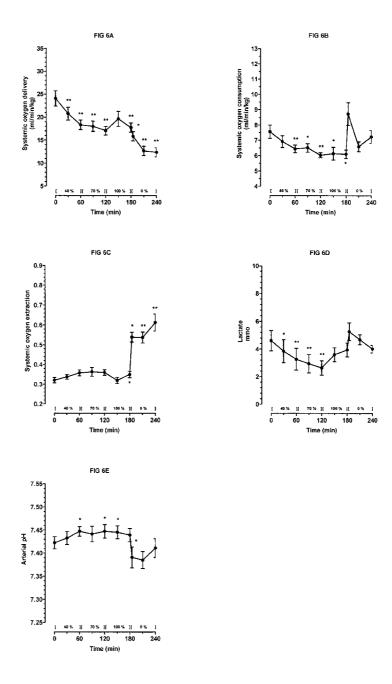
Figure 6. Effect of gradual occlusion and reperfusion of the superior mesenteric artery on (A) systemic oxygen delivery, (B) systemic oxygen consumption, (C) systemic oxygen extraction, (D) arterial lactate and (E) arterial pH. * = $p<0.05$; ** = $p<0.01$ vs baseline (0 min). [Occlusion level shown above the x-axis]
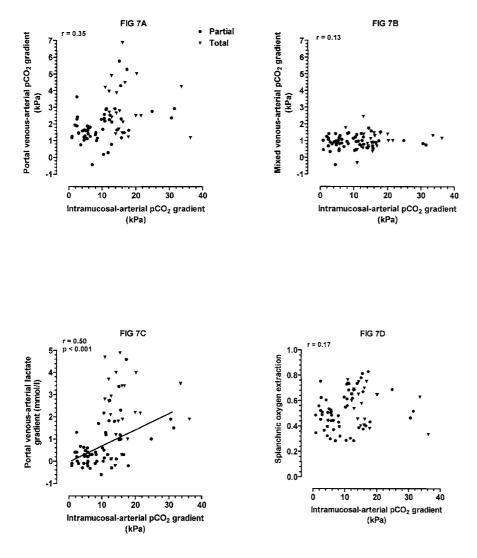
Figure 7. The relation between intramucosal -arterial PCO_2 gradient and (A) portal venous-arterial PCO_2 gradient, (B) mixed venous-arterial PCO_2 gradient, (C) portal venous-arterial lactate gradient and (D) splanchnic oxygen extraction during gradual SMA occlusion.

FIG8A

r = 0.75
p < 0.001

● Partial
▼ Total

FIG 8B

r = 0.79
p < 0.001

FIG 8C

r = 0.10

FIG 8D

r = 0.14

Portal venous-arterial PCO_2 gradient (kPa)

Portal venous-arterial lactate gradient (mmol/l)

Splanchnic oxygen extraction

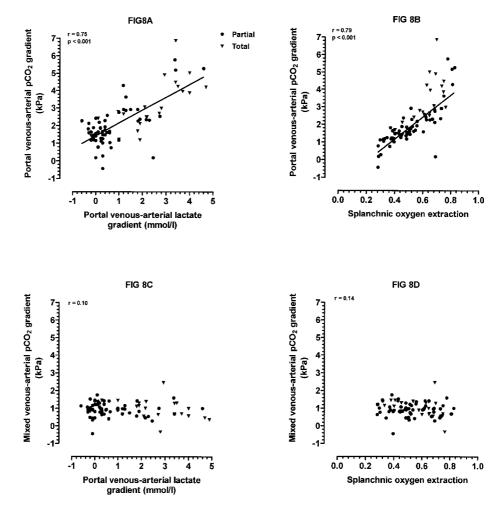Mixed venous-arterial PCO_2 gradient (kPa)

Figure 8. The relation between portal venous-arterial PCO_2 gradient and (A) portal venous-arterial lactate gradient and (B) splanchnic oxygen extraction and between mixed venous-arterial PCO_2 gradient and (C) portal venous-arterial lactate gradient and (D) splanchnic oxygen extraction during gradual SMA occlusion.

SMA occlusion, a temporary increase in systemic oxygen consumption was observed, however at the end of the experiment, oxygen consumption had declined almost back to the baseline value. During the ischemia, only minor changes were observed in the systemic oxygen extraction, whereas during the

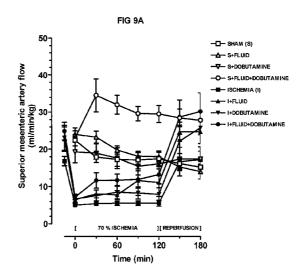reperfusion it increased significantly (p<0.05 vs baseline) (Figure 6C).

Systemic arterial lactate level decreased during the partial ischemia, started to increase at 30 minutes after the total ischemia and reached its peak value (5.3 ± 0.6 mmol/l) 5 minutes after the release of the vascular occlusion (Figure 6D).

Arterial pH increased during the ischemia (p<0.05 vs baseline), whereas five minutes after the reperfusion it decreased significantly below the baseline value (p<0.05) and increased thereafter (Figure 6E).

In a univariate regression analysis, the intramucosal-arterial PCO_2 gradient correlated only poorly or did not correlate at all with portal venous-arterial PCO_2 gradient (r=0.35, p<0.01), mixed venous-arterial PCO_2 gradient (r=0.13), portal venous-arterial lactate gradient (r=0.50, p<0.001), or with intestinal oxygen extraction (r=0.17) (Fig. 7A-D). The portal venous-arterial PCO_2 gradient correlated with the portal venous-arterial lactate gradient (r=0.75, p<0.001), and with the splanchnic oxygen extraction (r=0.79, p<0.001) (Fig. 8A,B). The mixed venous-arterial PCO_2 gradient did not correlate with the portal venous-arterial lactate gradient (r=0.10) or with splanchnic oxygen extraction (r=0.14) (Figure 8C,D).

5.3. Effects of dobutamine and fluid therapy on systemic and regional hemodynamics and oxygen transport during intestinal ischemia (III)

Baseline values did not differ between the study groups. SMA blood flow and the proportion of Q_{SMA} of CO decreased in all ischemic groups at the start of the SMA occlusion (Figure 9AB). Subsequently, Q_{SMA} increased to the end of the ischemic period in the dobutamine-fluid treated group (p<0.05), whereas the proportion of Q_{SMA} of CO remained unchanged. During the reperfusion, Q_{SMA} and the proportion of Q_{SMA} of CO returned to baseline in all groups. Ischemia or reperfusion did not modify the treatment effects on Q_{SMA} or on the proportion of Q_{SMA} of CO. Fluid treatment increased Q_{SMA} (p<0.05), and dobutamine decreased the proportion of Q_{SMA} of CO compared to control groups (p<0.05 for both) during the ischemic period. Other treatments did not influence Q_{SMA} or
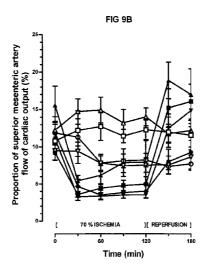
FIG 9A

FIG 9B

Figure 9. Effect of 70 % occlusion and reperfusion of the superior mesenteric artery on (A) superior mesenteric artery blood flow and (B) the proportion of SMA blood flow of cardiac output. [Occlusion level shown above the x-axis].
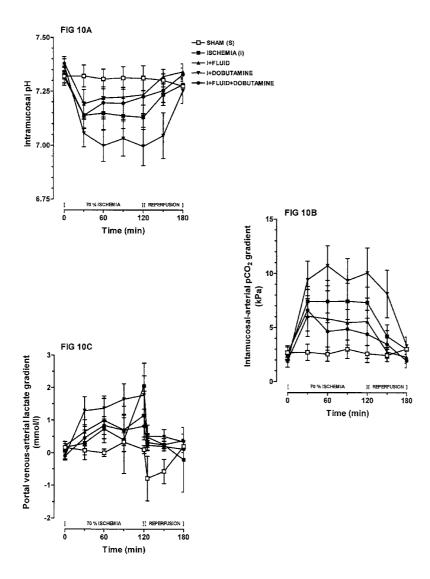
Figure 10. Effect of 70 % occlusion and reperfusion of the superior mesenteric artery on (A) intramucosal pHi, (B) intramucosal-arterial PCO_2 gradient, and (C) portal venous-arterial lactate gradient.[Occlusion level shown above the x-axis].

Table 4. **Regional tissue oxygenation at baseline (0 min), at the end of ischemia (120 min) and at reperfusion (180 min) in the eight different treatment groups**

Time (min)	0	120	180
Intramucosal pH			
Control			
Sham	7.32 ± 0.04	7.31 ± 0.06	7.27 ± 0.04
Ischemia	7.33 ± 0.02	7.13 ± 0.06 *	7.28 ± 0.04 #
Fluid treatment			
Sham	7.36 ± 0.03	7.35 ± 0.03	7.27 ± 0.06
Ischemia	7.38 ± 0.02	7.23 ± 0.09	7.34 ± 0.04
Dobutamine			
Sham	7.35 ± 0.05	7.33 ± 0.03	7.31 ± 0.01
Ischemia	7.37 ± 0.04	6.99 ± 0.09 **	7.25 ± 0.06 #
Dobutamine + fluid			
Sham	7.38 ± 0.03	7.38 ± 0.01	7.37 ± 0.01
Ischemia	7.32 ± 0.03	7.22 ± 0.08	7.33 ± 0.03
pCO_2 gradient (kPa)			
Control			
Sham	2.7 ± 0.7	2.6 ± 0.8	3.0 ± 0.7
Ischemia	2.0 ± 0.5	7.3 ± 1.4 *	3.0 ± 0.8 ##
Fluid treatment			
Sham	1.7 ± 0.4	1.9 ± 0.3	3.5 ± 1.3
Ischemia	1.9 ± 0.1	5.5 ± 2.2	2.3 ± 0.5
Dobutamine			
Sham	2.1 ± 0.7	2.1 ± 0.6	2.3 ± 0.3
Ischemia	1.8 ± 0.5	10.1 ± 2.3 *	2.8 ± 0.9 #
Dobutamine + fluid			
Sham	1.9 ± 0.5	1.2 ± 0.3	1.6 ± 0.3
Ischemia	2.6 ± 0.6	4.4 ± 2.2	1.9 ± 0.6
Lactate gradient (mmol/l)			
Control			
Sham	0.2 ± 0.1	0.1 ± 0.1	0.2 ± 0.2
Ischemia	0.2 ± 0.1	2.0 ± 0.7 *	0.2 ± 1.0
Fluid treatment			
Sham	0.2 ± 0.1	0.0 ± 0.1	0.4 ± 0.3
Ischemia	0.2 ± 0.1	1.1 ± 0.7	0.4 ± 0.2
Dobutamine			
Sham	0.2 ± 0.1	0.5 ± 0.1 *	0.2 ± 0.1 #
Ischemia	0.1 ± 0.1	1.8 ± 0.6 *	0.3 ± 0.1 #
Dobutamine + fluid			
Sham	0.3 ± 0.2	0.3 ± 0.2	0.1 ± 0.2
Ischemia	0.1 ± 0.1	0.8 ± 0.3 *	0.1 ± 0

* vs baseline, # vs end of ischemia; *# $p < 0.05$; **## $p < 0.01$.

Table 5. Systemic hemodynamics at baseline (0 min), at the end of ischemia (120 min) and at reperfusion (180 min) in the eight different treatment groups

Time (min)	0			120			180		
CI (ml/kg/min)									
Control									
Sham	212	±	13	148	±	20 [*]	139	±	17
Ischemia	193	±	25	122	±	15	109	±	7
Fluid treatment									
Sham	183	±	23	121	±	21 [**]	104	±	13
Ischemia	150	±	12	150	±	32	174	±	31
Dobutamine									
Sham	202	±	12	221	±	38	212	±	43
Ischemia	206	±	20	214	±	25	184	±	22 [#]
Dobutamine + fluid									
Sham	197	±	15	369	±	29 [***]	366	±	18
Ischemia	223	±	21	360	±	39 [**]	359	±	32
MAP (mmHg)									
Control									
Sham	90	±	2	109	±	7 [*]	103	±	9
Ischemia	94	±	4	107	±	1 [*]	98	±	5
Fluid treatment									
Sham	92	±	4	127	±	9 [**]	124	±	4
Ischemia	105	±	7	123	±	5 [**]	121	±	9
Dobutamine									
Sham	93	±	6	98	±	8	95	±	9
Ischemia	106	±	7	93	±	10	76	±	14
Dobutamine + fluid									
Sham	100	±	4	115	±	4	120	±	4
Ischemia	100	±	3	117	±	5 [*]	114	±	5
HR (beats/min)									
Control									
Sham	109	±	6	101	±	11	106	±	11
Ischemia	102	±	10	80	±	7	100	±	11 [#]
Fluid treatment									
Sham	104	±	4	89	±	5 [*]	89	±	7
Ischemia	79	±	3	85	±	9	97	±	10
Dobutamine									
Sham	135	±	28	149	±	11	149	±	8
Ischemia	101	±	5	176	±	17 [**]	159	±	10
Dobutamine + fluid									
Sham	98	±	4	151	±	13 [*]	168	±	6
Ischemia	103	±	9	152	±	12 [**]	147	±	10
PCWP (mmHg)									
Control									
Sham	9	±	0	3	±	1 [***]	2	±	0 [#]
Ischemia	10	±	0	3	±	1 [***]	1	±	1 [##]
Fluid treatment									
Sham	10	±	0	10	±	1	11	±	1
Ischemia	10	±	1	9	±	0	10	±	0
Dobutamine									
Sham	9	±	0	1	±	0 [***]	1	±	1
Ischemia	10	±	0	1	±	0 [***]	1	±	1
Dobutamine + fluid									
Sham	10	±	0	10	±	1	11	±	0
Ischemia	10	±	0	10	±	0	8	±	1 [##]

Cardiac index (CI), mean arterial pressure (MAP), heart rate (HR), pulmonary capillary wedge pressure (PCWP); * vs baseline, # vs end of ischemia; *# $p < 0.05$, **## $p < 0.01$, *** $p < 0.001$.

Table 6. Systemic oxygen delivery, systemic oxygen consumption and systemic oxygen extraction at baseline (0 min), at the end of ischemia (120 min) and at reperfusion (180 min) in the eight different treatment groups

Time (min)	0	120	180
DO_2 (ml/min/kg)			
Control			
Sham	23.5 ± 2.0	20.8 ± 3.1	19.2 ± 2.8
Ischemia	21.6 ± 3.0	17.5 ± 2.3	15.5 ± 1.0
Fluid treatment			
Sham	19.7 ± 2.5	15.6 ± 2.8 *	12.8 ± 1.7
Ischemia	17.4 ± 0.4	18.1 ± 4.0	19.5 ± 3.6
Dobutamine			
Sham	23.3 ± 1.0	29.3 ± 4.2	27.4 ± 4.6
Ischemia	23.1 ± 2.1	27.7 ± 3.0	24.0 ± 2.4 #
Dobutamine + fluid			
Sham	20.6 ± 1.9	36.3 ± 2.4 ***	34.7 ± 4.1
Ischemia	23.7 ± 2.5	35.8 ± 3.9 **	34.6 ± 1.6
VO_2 (ml/min/kg)			
Control			
Sham	6.4 ± 0.5	6.5 ± 0.5	5.8 ± 0.8
Ischemia	5.4 ± 0.7	5.4 ± 0.3	5.3 ± 0.3
Fluid treatment			
Sham	5.2 ± 0.7	5.0 ± 0.7	4.8 ± 0.7
Ischemia	5.2 ± 0.5	5.9 ± 0.4	6.7 ± 0.7
Dobutamine			
Sham	6.7 ± 0.4	8.1 ± 0.4 *	8.8 ± 0.8
Ischemia	4.6 ± 1.1	7.9 ± 0.4	7.7 ± 0.4
Dobutamine + fluid			
Sham	5.9 ± 0.3	8.8 ± 0.5 **	6.2 ± 1.9
Ischemia	6.0 ± 0.4	8.4 ± 0.5 **	8.6 ± 0.5
Oxygen extraction			
Control			
Sham	0.27 ± 0.01	0.33 ± 0.04	0.34 ± 0.04
Ischemia	0.26 ± 0.02	0.33 ± 0.04	0.35 ± 0.03
Fluid treatment			
Sham	0.28 ± 0.04	0.34 ± 0.04 *	0.38 ± 0.02
Ischemia	0.30 ± 0.02	0.38 ± 0.04	0.38 ± 0.03
Dobutamine			
Sham	0.29 ± 0.02	0.30 ± 0.04	0.35 ± 0.04
Ischemia	0.21 ± 0.05	0.31 ± 0.05	0.33 ± 0.04
Dobutamine + fluid			
Sham	0.30 ± 0.03	0.25 ± 0.01	0.22 ± 0.05
Ischemia	0.26 ± 0.02	0.25 ± 0.03	0.26 ± 0.03

Systemic oxygen delivery (DO_2), systemic oxygen consumption (VO_2). * vs baseline, # vs ischemic baseline. *# $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

the proportion of Q_{SMA} of CO during the ischemic and reperfusion periods.

Intramucosal pH decreased at the start of the ischemia in all ischemic groups (Figure 10A). During the ischemic period, it remained below the baseline value in the control ($p<0.05$) and dobutamine ($p<0.01$) treated ischemic groups, and at the end of the ischemic period, the ischemic control group presented with significantly lower intramucosal pH than the sham control group (7.13 ± 0.06 vs 7.31 ± 0.06, $p<0.05$)(Figure 10A, Table 4). Dobutamine alone in the ischemic group reduced the intramucosal pH value further to 6.99 ± 0.09 ($p<0.05$ compared to ischemic control group), whereas other treatments did not influence it. The intramucosal-arterial PCO_2 gradient increased at the start of ischemia in the ischemic control animals ($p<0.05$) and in ischemic animals treated with dobutamine ($p<0.01$), and at the end of the ischemic period, it was higher in the ischemic control group compared to the sham control group (7.3 ± 1.4 vs 2.6 ± 0.8 kPa, $p<0.01$) (Figure 10B, Table 4). None of the treatments had any significant effect on intramucosal-arterial PCO_2 gradient. The portal venous-arterial lactate gradient increased at the start of the ischemia in the dobutamine treated ischemic animals ($p<0.05$), and at the end of the ischemic period it was higher as compared to baseline in control, dobutamine and dobutamine-fluid treated ischemic groups ($p<0.05$ for all) (Figure 10C, Table 4). Dobutamine alone in the ischemic group resulted in a higher portal venous-arterial lactate gradient compared to the ischemic control group ($p<0.05$). The portal venous-arterial lactate gradients did not differ from each other in the other treatment groups. Reperfusion increased the intramucosal pH and decreased the intramucosal-arterial PCO_2 gradient in control ($p<0.05$ and $p<0.01$, respectively) and dobutamine ($p<0.05$ for both) treated ischemic groups, and decreased the portal venous-arterial lactate gradient in the dobutamine treated ischemic group ($p<0.05$).

The cardiac index increased in animals treated with the dobutamine-fluid combination ($p<0.01$) (Table 5). MAP increased in the control ($p<0.05$), fluid

(p<0.01) and dobutamine-fluid (p<0.05) treated groups, and HR increased in the dobutamine and dobutamine-fluid treated groups (p<0.01 for both). PCWP decreased in the control group and in animals treated with dobutamine alone (p<0.001 for both). SMA occlusion and reperfusion did not modify the treatment effects on systemic hemodynamics. Fluid treatment had no significant influence on CI. Dobutamine resulted in an increase in CI compared to control animals (p<0.05). The effect of dobutamine was further enhanced when it was combined with fluid therapy; CI in this group was higher compared to animals receiving fluid or dobutamine on their own (p<0.05 for both). SV, MAP and HR did not differ between the treatment groups. PCWP decreased in the control groups compared to the fluid treated groups (p<0.001) and dobutamine alone decreased this parameter further (p<0.05 vs control groups). Reperfusion resulted in a decrease in CI in the dobutamine treated group and an increase in HR in the control group (p<0.05 for both). PCWP decreased in control and dobutamine-fluid treated groups (p<0.01 for both). PCWP was higher in fluid treated groups (p<0.01) and lower in the dobutamine treated groups (p<0.01) than in the control groups. Furthermore, PCWP in the dobutamine-fluid treated groups was higher than in the animals receiving dobutamine on its own (p<0.01).

Systemic oxygen delivery and consumption increased in the dobutamine-fluid treated groups (p<0.01 for both), whereas systemic oxygen extraction did not change (Table 6). Neither ischemia nor reperfusion changed the treatment influence on systemic oxygen transport. Dobutamine treated animals had higher systemic oxygen delivery compared to their controls (p<0.05), whereas other treatments had no significant effect on oxygen delivery. Systemic oxygen consumption and systemic oxygen extraction were similar in all treatment groups. Reperfusion decreased the systemic oxygen delivery in the dobutamine treated group (p<0.05) and did not influence systemic oxygen consumption and oxygen extraction. The decrease in systemic oxygen delivery was higher in the dobutamine treated groups than in control groups

(p<0.01) or in the dobutamine-fluid treated groups (p<0.05). Systemic oxygen consumption increased in the dobutamine treated groups compared to their controls, in which it decreased (p<0.01). The oxygen extraction also decreased in the dobutamine treated groups compared to dobutamine-fluid treated animals (p<0.05).

5.4. Effects of dobutamine and fluid therapy on renal function during intestinal ischemia (IV)

During the ischemic period diuresis increased and serum and urine creatinine concentrations decreased in fluid (p<0.01, p<0.01 and p<0.05, respectively) and dobutamine-fluid (p<0.01, p<0.001 and p<0.001, respectively) treated ischemic groups (Table 7). Ischemia as such did not influence renal function or diuresis. All fluid treated groups had lower serum creatinine values during SMA occlusion than control groups (p<0.001). With respect to diuresis, urine creatinine level or creatinine clearance, the treatment groups did not differ from each other during the ischemic period.

After SMA reperfusion, diuresis decreased in the ischemic control group (p<0.05) and in ischemic animals treated with dobutamine alone (p<0.01). In addition, the urine creatinine level increased in the dobutamine treated ischemic group (p<0.05), and creatinine clearance decreased in the ischemic control group (p<0.01). Reperfusion as such did not have any influence on renal function or diuresis. None of the treatments had any significant impact on renal function or diuresis during reperfusion.

Table 7. Renal function at baseline (0 min), at the end of ischemia (120 min) and at reperfusion (180 min) in the eight different treatment groups

Time (min)	0			120			180		
Diuresis (ml/kg/hr)									
Control									
Sham	11	±	7	10	±	3	4	±	1 [#]
Ischemia	5	±	2	7	±	2	1	±	0 [#]
Fluid treatment									
Sham	9	±	4	12	±	3	12	±	2
Ischemia	9	±	4	18	±	4 [**]	14	±	7
Dobutamine									
Sham	8	±	3	7	±	2	2	±	1 [#]
Ischemia	19	±	7	9	±	2	1	±	0 [##]
Dobutamine + fluid									
Sham	14	±	7	17	±	3	11	±	2 [#]
Ischemia	3	±	1	16	±	4 [**]	10	±	2
S-creatinine (μmol/l)									
Control									
Sham	67	±	3	69	±	3	70	±	3
Ischemia	87	±	8	87	±	8	88	±	8
Fluid treatment									
Sham	81	±	6	75	±	5 [*]	73	±	4
Ischemia	84	±	5	77	±	5 [**]	74	±	6
Dobutamine									
Sham	78	±	1	78	±	2	80	±	2
Ischemia	67	±	4	70	±	3	74	±	4
Dobutamine + fluid									
Sham	75	±	4	67	±	5 [**]	68	±	5
Ischemia	78	±	4	65	±	4 [***]	65	±	4
U-creatinine (mmol/l)									
Control									
Sham	3.2	±	1.1	2.4	±	0.9	3.0	±	0.9
Ischemia	5.4	±	1.7	3.0	±	0.8	5.0	±	1.0
Fluid treatment									
Sham	4.1	±	1.4	1.7	±	0.7	1.2	±	0.4
Ischemia	5.3	±	1.8	0.9	±	0.2 [*]	1.7	±	0.8
Dobutamine									
Sham	6.5	±	2.3	3.6	±	1.4	5.8	±	1.6 [#]
Ischemia	3.5	±	1.9	2.4	±	1.1	5.9	±	1.8 [#]
Dobutamine + fluid									
Sham	2.4	±	0.5	1.0	±	0.2 [*]	1.0	±	0.2
Ischemia	5.3	±	0.7	1.0	±	0.2 [***]	1.5	±	0.5
Creatinine clearance (ml/min)									
Control									
Sham	83.7	±	14.8	93.6	±	20.3	47.9	±	10.9 [#]
Ischemia	79.5	±	29.0	82.3	±	12.6	32.8	±	7.7 [##]
Fluid treatment									
Sham	106.5	±	36.4	94.8	±	38.6	77.5	±	21.6
Ischemia	108.3	±	36.9	91.3	±	19.0	62.6	±	10.4
Dobutamine									
Sham	113.8	±	13.8	104.5	±	24.0	57.9	±	13.2
Ischemia	87.1	±	9.3	86.4	±	15.5	56.1	±	17.8
Dobutamine + fluid									
Sham	111.3	±	15.5	98.2	±	12.8	66.5	±	8.9 [#]
Ischemia	106.3	±	30.2	100.2	±	19.9	77.3	±	7.8

* vs baseline, # vs end of ischemia; *# $p<0.05$, **## $p<0.01$, *** $p<0.001$

6. DISCUSSION

6.1. Development of intestinal ischemia during gradual reduction of superior mesenteric artery flow (I)

Detection of reduced splanchnic perfusion early enough to prevent tissue hypoxia is a challenge in clinical practice since hypoperfusion of the splanchnic region has been suggested to contribute to the development of multiple organ failure (Carrico et al 1986, Deitch 1992). The blood lactate level has been claimed to be a good marker and may even be the predominant indicator of intestinal ischemia (Lange and Jackel 1994, Mizock and Falk 1992). In this study, the development of intestinal ischaemia was evaluated by an increase in the portal venous-arterial lactate gradient. In parallel with the increase in the portal venous-arterial lactate gradient, the intramucosal pH decreased and tonometric PCO_2 , tonometric-portal venous PCO_2 gradient and splanchnic oxygen extraction increased, all of which are variables mirroring the development of intestinal ischemia. The critical time point for the increase in the portal venous-arterial lactate above mean + 2SD of the baseline value occurred at 33 min from the start of the corresponding 70 % SMA occlusion level. At this time point also significant changes in intramucosal pH and tonometric-portal venous pCO_2 gradient were observed. This is in close agreement with Grum et al. (Grum et al 1984), who reported that tonometrically detected intramucosal pH decreased and was dependent on the regional oxygen consumption, when oxygen delivery was decreased by 60 % from the baseline.

Acid-base balance, oxygen delivery, consumption and extraction as well as the blood lactate concentration have been suggested to provide useful information about tissue perfusion (Bakker et al 1996, Dhainaut et al 1990, Schlichting and Lyberg 1995), it has also been reported that information obtained from systemic and pulmonary artery hemodynamics and blood

samples cannot be used to detect intestinal ischaemia evoked by a five hour total SMA occlusion in pigs (Schlichting and Lyberg 1995). Mixed venous hypercarbia and increased systemic venous-arterial PCO_2 gradient have been found to be markers of systemic hypoperfusion during systemic hypoperfusion, reflecting the changes in cardiac output (Adrogue et al 1989, Bowles et al 1992, Halmagyi et al 1970, Mathias et al 1988, Mecher et al 1990). Thus, it has been suggested that the systemic mixed venous-arterial PCO_2 gradient might be also useful for detecting an oxygen supply/demand mismatch during systemic hypoperfusion (Bowles et al 1992). The splanchnic region receives 20-30 % of cardiac output and accounts for a slightly higher proportion of the total body metabolic activity and oxygen consumption at rest. Therefore, it seems reasonable to assume that intestinal ischemia with concomitant mild hypovolemia should impact on the mixed venous-arterial PCO_2 gradient. The intramucosal pH has been found to be a clinically feasible method for the detection of regional intestinal hypoperfusion in several studies (Antonsson et al 1990, Antonsson et al 1993, Fiddian-Green et al 1986, Gutierrez et al 1992b, Montgomery et al 1990). However, the intramucosal-arterial PCO_2 gradient has been claimed to be an even better indicator of tissue hypoperfusion than intramucosal pH or the intramucosal-arterial pH gradient (Schlichtig et al 1996). In addition, the intramucosal-portal venous PCO_2 gradient has also been reported to increase when intestinal oxygen delivery was decreased by systemic hypoperfusion (Schlichtig and Bowles 1994).

In the present study, intramucosal-arterial PCO_2 gradient and intramucosal-portal venous PCO_2 gradient both were sensitive at detecting regional splanchnic hypoperfusion, though the portal venous-arterial PCO_2 gradient correlated better with splanchnic lactate production (Bakker et al 1992, Benjamin et al 1987, Martin et al 1985) and splanchnic oxygen extraction (Benjamin et al 1987, Lundberg et al 1990, Mathias et al 1988) than the intramucosal-arterial PCO_2 gradient. The dilution of these ischemic markers by the blood received from the other parts of the splanchnic region may explain the

poor correlation between them and the intramucosal-arterial PCO_2 gradient. Whether these correlations would have been better below the critical extraction ratio, remains unresolved, because the whole splanchnic oxygen extraction ratio was measured in this study instead of the oxygen extraction ratio of the splanchnic area perfused by SMA.

The regional PCO_2 gradients were able to detect regional splanchnic hypoperfusion, but mixed venous PCO_2 and systemic mixed venous-arterial PCO_2 gradient did not reveal the defect. As intramucosal-arterial PCO_2 gradient increases in parallel with the decrease in SMA blood flow, the venous outflow from that region also decreases causing the PCO_2 outflow to decline. Portal flow is reduced in parallel to the reduction of SMA flow causing a dilutional effect of the blood from the rest of the splanchnic region and decreasing PCO_2. When portal flow is decreased, the hepatic arterial buffer response attempts to compensate and maintain liver blood flow, which then increases hepatic venous blood flow and thus decreases PCO_2.

Arterial lactate started to increase after the induction of total ischemia, but it was not able to detect the development of intestinal ischemia earlier, even though portal venous arterial lactate values had increased. This is in line with previous reports, in which intestinal ischemia caused by total SMA occlusion lasting from 30 minutes to 120 minutes increased systemic and regional blood lactate (Jonas et al 1996, Nutz et al 1987). One explanation is that the increased lactate metabolism in the liver is able to compensate for the increased intestinal lactate production and this prevents the development of systemic lactatemia and acidosis. This suggestion is further supported by the findings of Jakob et al. (Jakob et al 2000), who showed that reduced SMA blood flow increased the portal venous lactate values. However, this increase in the influx of lactate to liver was compensated for by the increase in liver lactate uptake leading to normal systemic lactate values. This is also in line with the findings of Rasmussen et al. (Rasmussen and Haglund 1992), who were not able to measure any increase in systemic lactate concentrations

during septic shock in spite of clearly decreased splanchnic perfusion. Another possibility is that portal vein flow was reduced during the gradual SMA occlusion. As a consequence, although the portal venous lactate concentration increased, the cumulative amount of lactate entering the systemic circulation was not changed until the SMA occlusion was complete, when the lactate production was sufficiently great to overwhelm hepatic uptake and to increase systemic lactate values.

Intestinal hypoperfusion and ischemia have been reported in different experiments during peritonitis, hemorrhage, cardiac tamponade and endotoxemia (Antonsson et al 1995, Bailey et al 1986, Bailey et al 1987b, Fink et al 1991, McNeill et al 1970, Rasmussen and Haglund 1992). All these experiments produce systemic hypoperfusion in addition to splanchnic hypoperfusion, but do not allow an examination of the systemic effects of splachnic hypoperfusion. In our study, isolated SMA occlusion was used to produce intestinal ischaemia. This allowed us to evaluate the systemic influence of splanchnic hypoperfusion. However, although this experiment is suitable for this purpose, an isolated SMA occlusion is rather uncommon in clinical practice though it may occur in patients with large emboli or severe atherosclerotic disease. Although our study shows that intestinal ischaemia may develop without any systemic signs of tissue hypoperfusion, the clinical relevance of this finding should be interpreted with caution.

6.2. Systemic hemodynamics and oxygen transport during the development of intestinal
ischemia (I,II)

The changes in systemic hemodynamics during the intestinal ischemia were nonspecific and associated with the developing hypovolemia caused by the loss of intravascular fluid into the peritoneal cavity (Haglind et al 1981, Kangwalklai et al 1973, Tjiong et al 1974). In spite of clear evidence of hypovolemia, in the

present study an increase in mean arterial blood pressure was observed, which is opposite to previous studies (Haglund et al 1978, Norlén et al 1978, Redfors et al 1984). The reason for the mean blood pressure increase remains unclear but it confirms that normal blood pressure cannot be used to exclude significant hypovolemia. Even though the hemodynamic changes were minor during the ischemic period, more pronounced changes were observed during the reperfusion, most probably attributable to the release of cardiotoxic and acidic metabolites (Lundgren and Haglund 1978b) together with a worsening hypovolemia due to the decrease in cardiac output. This together with the deteriorating hypovolemia caused by redistribution of the reduced circulating blood volume back into the intestinal circulation and an uncoupling of the vasoregulative systems leading to a reduced mean arterial blood pressure after the reperfusion.

Systemic oxygen delivery and consumption decreased with the reduction of the SMA flow and cardiac output, whereas the systemic oxygen extraction remained unchanged and arterial pH increased during the SMA occlusion. However, after the reperfusion, even though systemic oxygen delivery followed the course of cardiac output, the systemic oxygen consumption showed a transient increase. This may be due to the combined effects of recovery from the oxygen-debt and the activation of inflammatory mediators.

6.3. Effects of dobutamine and fluid therapy on systemic and regional hemodynamics and oxygen transport during intestinal ischemia (III)

Fluid therapy and vasoactive agents have been used to increase oxygen delivery and consumption to supranormal levels in attempts to decrease the risk of multiple organ failure (Durham et al 1996, Heyland et al 1996, Shoemaker et al 1988). Although increased cardiac output by vasoactive agents usually increases splanchnic blood flow, the actual effects of vasoactive agents on

intestinal mucosal perfusion have been inconsistent (Giraud and MacCannell 1984, Immink et al 1976, Vernon et al 1992).

In our study, dobutamine infusion alone evoked the most severe metabolic signs of intestinal ischemia, characterized by the lowest intramucosal pH and the highest portal venous-arterial lactate gradient during partial superior mesenteric artery occlusion. In addition, dobutamine, even when given with fluids, did not offer any advantage as compared to fluid treatment alone. The results from other studies are confusing. Dobutamine has either increased (Gutierrez et al 1994, Silverman and Tuma 1992), decreased (Parviainen et al 1995, Silverman and Tuma 1992) or had no effect on (Uusaro et al 1997) gastric intramucosal pH. After cardiac surgery, gastric intramucosal pH decreased or has remained unchanged despite the increased splanchnic blood flow suggesting that dobutamine may interfere with splanchnic vasoregulation and cause a local mismatch between splanchnic oxygen supply and demand despite the increased regional blood flow (Parviainen et al 1995, Uusaro et al 1997). Nonetheless, in septic patients, gastric intramucosal pH has increased in response to dobutamine treatment (Gutierrez et al 1996, Silverman and Tuma 1992).

In our study, dobutamine increased cardiac output and the effect was enhanced when dobutamine was combined with fluid therapy. Although dobutamine did not change SMA flow, dobutamine did decrease the fractional SMA flow, suggesting that changes in systemic hemodynamics (cardiac output) cannot be used to predict changes in regional blood flow (SMA flow). The decreased fractional SMA flow should not have influenced intramucosal pH unless local metabolic demands had simultaneously increased. In addition, dobutamine may cause redistribution of blood flow within the splanchnic bed or in the intestinal wall as has been demonstrated with other vasoactive agents (Shepherd et al 1984). Even though splanchnic blood flow generallyincreases in parallel with cardiac output after administration of inotropic drugs, the response of intestinal mucosal perfusion to vasoactive agents has been

reported to be more variable. In experimental studies, dopamine, norepinephrine, epinephrine reduced intestinal mucosal blood flow (Giraud and MacCannell 1984, Immink et al 1976), whereas the effects of dobutamine were dependent on the balance between its alpha-mediated vasoconstrictory and beta-mediated vasodilatatory properties (Vernon et al 1992). Dobutamine alone or in combination with fluid therapy has been found to increase intestinal mucosal perfusion (Bersten et al 1992, De Backer et al 1996, Fink et al 1991, Neviere et al 1997, Secchi et al 1997, Vincent et al 1987), although there are also reports which show no improvement in the intestinal perfusion (Germann et al 1997, Nordin et al 1996).

Since dobutamine has both alpha- and beta-agonist properties (Ruffolo 1987), it would be expected to increase the local metabolic demands. In our study, the increase of SMA blood flow in response to the potential increase in the metabolic demands was limited. Accordingly, local acidosis would be expected to become intensified. Although the effect of dobutamine on splanchnic metabolic demand is small (Reinelt et al 1997), it may still have intensified mucosal acidosis. It is also possible that the intestinal ischemia associated with hypovolemia may lead to blood flow redistribution which cannot be corrected by dobutamine. Since hypovolemia is a strong vasoconstrictory stimulus (Edouard et al 1994), it is possible that the alpha-adrenergic properties of dobutamine may have enhanced intestinal vasocontriction in those animals not receiving fluid resuscitation.

6.4. Effects of dobutamine and fluid therapy on renal function during intestinal ischemia (IV)

Inadequate tissue perfusion resulting in intestinal ischemia contributes to the pathogenesis of multiple organ failure in critically ill patients (Carrico et al 1986, Deitch et al 1987, Gutierrez et al 1992b). In addition, the risk for multiple organ failure can be reduced by increasing oxygen delivery to supranormal levels

using fluid therapy and vasoactive agents (Durham et al 1996, Hayes et al 1994, Heyland et al 1996, Shoemaker et al 1988). The effects of intestinal ischemia alone and combined with vasoactive therapy on renal function are only poorly understood (LaNoue et al 1996, Rothenbach et al 1997)

In our study, partial intestinal ischemia did not influence renal function since renal function in animals with SMA occlusion and sham operated animals did not differ from each other. However, reperfusion of SMA blood flow in ischemia, but interestingly also in sham operated animals, resulted in a deterioration of renal function characterized by a decrease in diuresis and creatinine clearance and an increase in the urine creatinine concentration, which was most obvious in those animals treated without fluid therapy. Treatment had also significant effects on renal function. Fluid treatment increased diuresis and reduced serum and urine creatinine concentrations. On the contrary, animals treated with dobutamine alone showed a tendency (although non-significant) towards a decrease in diuresis and an increase in serum and urine creatinine concentrations.

In our study, partial SMA occlusion did not influence renal function. LaNoue et al. (LaNoue et al 1996) measured renal blood flow with microspheres and a Doppler flow probe in a total ischemia and reperfusion model. They observed that intestinal ischemia reduced renal blood flow as measured by their Doppler flow probe but not by microspheres without influencing tissue ATP levels or inulin clearance. In addition, they found that reperfusion decreased more significantly renal blood flow and renal tissue ATP levels. This is in line with our study: diuresis and creatinine clearance remained stable during the SMA occlusion, whereas during the reperfusion they tended to decrease in all study groups. However, the deterioration of renal function during the reperfusion could be alleviated with fluid therapy but not with dobutamine treatment alone.

Intestinal ischemia reperfusion injury releases cardiotoxic factors decreasing myocardial contractility and reducing renal blood flow (Horton and White 1991). Although, in our study we did detect a decrease in cardiac output during total

intestinal blood flow occlusion and reperfusion (I), we also noted that partial SMA occlusion and reperfusion did not decrease cardiac output sufficiently to account for the effects on diuresis and creatinine clearance. Baroreflex-mediated sympathetic activity and elevated circulating catecholamine levels may result in renal vasoconstriction, and the kidney itself may respond to pathologic states by generating potent paracrine vasoconstrictors (LaNoue et al 1996, Rothenbach et al 1997). It is also known that ischemia reperfusion injury activates inflammatory mediators such as complement and neutrophils, and also evokes the release of local proinflammatory and vasoactive agents including eicosanoids and nitric oxide as well as cytokines which can cause both local and remote organ damage (Caty et al 1990, Schmeling et al 1989, Turnage et al 1994, Turnage et al 1995a, Turnage et al 1995b, Turnage et al 1995c). These may partly explain the changes in renal function noted in our study.

The impairment of renal function associated with SMA occlusion and reperfusion was observed both in the ischemic groups and in sham operated animals. This is in agreement with the results of LaNoue et al. (LaNoue et al 1996), who reported decreased renal blood flow also in their sham group and explained this finding by evaporative fluid loss; in their study saline infusion preserved renal blood flow in the sham groups. In our study also the basic fluid treatment of 5 ml 0.9% saline/kg/hour during the developing hypovolemia may have contributed to the impairment of renal function. However, this is not the only explanation because we found decreased diuresis and creatinine clearance in all sham operated animals, e.g. also in animals treated with fluid-dobutamine combination i.e. animals who showed no evidence of hypovolemia. Their pulmonary wedge pressure was kept constant and their cardiac output was increased. One cannot account for the changes in renal function by the deterioration of systemic hemodynamics. One explanation could be some reflexes, originating from the SMA area, which are activated by the manipulation

of the occluder and trigger the changes in renal function during reperfusion since the occluder was also removed from the sham animals..

It has been suggested that dobutamine releases vasopressin with its concomitant antidiuretic effect mediated in response to the drug's beta-adrenergic stimulation (Westman and Järnberg 1986). However, this is not supported by the findings of our study; dobutamine did not influence diuresis or creatinine clearance during partial intestinal hypoperfusion. On the other hand, the importance of adequate fluid therapy was demonstrated by the fact that fluid treatment alone or combined with dobutamine therapy increased diuresis and decreased serum and urine creatinine concentrations.

In healthy volunteers, dobutamine has been found to decrease the renal fraction of cardiac output without influencing renal vascular resistance and renal blood flow (Biro et al 1988, Westman and Järnberg 1986). In contrast, other experimental studies have claimed that dobutamine increases renal blood flow and reduces renal vascular resistance (Biro et al 1988, Fiser et al 1988). In addition, the effect of dobutamine on renal function in different clinical settings has been very inconsistent. In critically ill patients, dobutamine has increased creatinine clearance without influencing diuresis (Duke et al 1994). In chronic congestive heart failure, dobutamine has been reported to increase creatinine clearance and diuresis (Baumann et al 1990). Low dose dobutamine did not effect urine output and serum creatinine levels after cardiopulmonary bypass in children (Wenstone et al 1991) and after major vascular surgery in adults (Westman and Järnberg 1987). In a clinical sepsis study, dobutamine did increase diuresis without influencing creatinine clearance (Levy et al 1999). On the contrary, in experimental sepsis, dobutamine alone or combined with fluid therapy decreased kidney perfusion (Bersten et al 1992, Haywood et al 1991). Finally, in rats, dobutamine did not increase renal excretory function during sepsis (Palsson et al 1997). Based on previous reports and our results we conclude that the effects of dobutamine seem to vary between different species

and between disease states, and that our results should be evaluated only in the context of intestinal ischemia.

One limitation of our study is that our setup does not allow the direct measurement of renal blood flow. Thus, we used diuresis and creatinine clearance as the prime measures of renal function even though renal damage can be examed also by other methods assaying the levels of beta2-microglobulin, retinol binding protein, microalbuminuria or the level of lactate dehydrogenase (Hauet et al 2000, Sezai et al 1997, Thakkar et al 1998). On the other hand, we wanted to use measures of renal function which would be relevant to in clinical situation. However, it is clear that the direct measurement of renal blood flow would have increased the value of this study.

7. SUMMARY AND CONCLUSIONS

The present experimental study evaluated the systemic and regional effects of progressive intestinal ischemia caused by graded occlusion of the SMA with the intention of answering four questions: 1. to determine the level of superior mesenteric artery flow reduction that can cause intestinal ischemia, 2. to investigate whether the assessment of systemic hemodynamics and oxygen transport can be used in detecting the development of intestinal ischemia, 3. to evaluate the effects of dobutamine and fluid therapy on systemic and regional hemodynamics and oxygen transport during intestinal ischemia, and 4. to study the effects of dobutamine and fluid therapy on renal function during intestinal ischemia.

SMA blood flow was decreased by 40%, 70% and 100% and thereafter the occlusion was released in 12 pigs. The development of intestinal ischemia defined as an increase in portal venous-arterial lactate gradient above mean + 2SD of the baseline occurred at 33 minutes after a corresponding 70% SMA occlusion. This was associated with a decrease in intramucosal pH and portal venous pH and an increase in the intramucosal-arterial pCO_2 gradient and splanchnic oxygen extraction. Systemic and regional hemodynamics and oxygen transport variables were monitored continuously but no specific changes related to intestinal ischemia were observed. In another 24 ischemic pigs, SMA blood flow was reduced to 30% from baseline for 120 min, and thereafter released. An additional 24 pigs (sham group) served as non-ischemic controls. The animals were further assigned into four treatment arms: controls, fluid therapy, dobutamine therapy and fluid + dobutamine therapy. Intestinal ischemia did not modify the effects of fluid or dobutamine therapy on systemic hemodynamics and oxygen transport. Although dobutamine did have

positive effects on systemic hemodynamics on its own, it worsened intestinal tissue perfusion during partial SMA occlusion. The combination of fluid and dobutamine therapy did not improve tissue perfusion over that achieved with fluid treatment alone. An impairment of renal function was observed during the reperfusion period of the experiment. The impairment was most obvious in the control groups and in animals treated with dobutamine alone.

Based on the present study it can be concluded that:

1. intestinal ischemia evaluated by the increase in portal venous-arterial lactate gradient above mean + 2SD of baseline developed at 70 % occlusion level.

2. changes in systemic hemodynamics, oxygen transport variables and PCO_2 gradients were not able to detect the development of intestinal ischemia.

3. dobutamine had positive effects on systemic hemodynamics which were further enhanced by fluid therapy. However, dobutamine, when administered alone, worsened the intestinal ischemia caused by superior mesenteric artery occlusion. The deterioration of mucosal perfusion was mirrored by the decreased intramucosal pH and increased portal venous-arterial lactate gradient. Intestinal ischemia did not modify the effects of fluid or dobutamine therapy on systemic hemodynamics and oxygen transport.

4. an impairment of renal function was observed during the reperfusion period of the experiment. The changes in renal function were modest during fluid treament. Dobutamine alone decreased diuresis and increased serum and urine creatinine concentrations.

8. REFERENCES

Adrogue HJ, Rashad MN, Gorin AB, Yacoub J, Madias NE. Assessing acid-base status in circulatory failure. Differences between arterial and central venous blood. N Engl J Med 1989; 320:1312-1316.

Aliabadi-Wahle S, Choe EU, Flint LM, Ferrara JJ. Post-treatment dopexamine infusions partially reverse reductions in cranial mesenteric blood flow and mucosal oxygenation induced by hypoxia in newborn piglets. Am Surg 1999; 65:548-553.

Andersson R, Parsson H, Isaksson B, Norgren L. Acute intestinal ischemia. A 14-year retrospective investigation. Acta Chir Scand 1984; 150:217-221.

Antonsson JB, Boyle CC3, Kruithoff KL, Wang HL, Sacristan E, Rothschild HR, Fink MP. Validation of tonometric measurement of gut intramural pH during endotoxemia and mesenteric occlusion in pigs. Am J Physiol 1990; 259:G519-23.

Antonsson JB, Engstrom L, Rasmussen I, Wollert S, Haglund UH. Changes in gut intramucosal pH and gut oxygen extraction ratio in a porcine model of peritonitis and hemorrhage. Crit Care Med 1995; 23:1872-1881.

Antonsson JB, Haglund UH. Gut intramucosal pH and intraluminal PO_2 in a porcine model of peritonitis or haemorrhage. Gut 1995; 37:791-797.

Antonsson JB, Kuttila K, Niinikoski J, Haglund UH. Subcutaneous and gut tissue perfusion and oxygenation changes as related to oxygen transport in experimental peritonitis. Circ Shock 1993; 41, 261-267.

Astiz ME, Rackow EC, Kaufman B, Falk JL, Weil MH. Relationship of oxygen delivery and mixed venous oxygenation to lactic acidosis in patients with sepsis and acute myocardial infarction. Crit Care Med 1988; 16:655-658.

Atallah MM, Saied MM, el-Diasty TA, Gray PA, Park GR. Renal effect of dopexamine hydrochloride in patients with chronic renal dysfunction. Urol Res 1992; 20:419-424.

Azar G, Love R, Choe E, Flint L, Steinberg S. Neither dopamine nor dobutamine reverses the depression in mesenteric blood flow caused by positive end-expiratory pressure. J Trauma 1996; 40:679-685.

Bailey RW, Bulkley GB, Hamilton SR, Morris JB, Haglund UH. Protection of the small intestine from nonocclusive mesenteric ischemic injury due to cardiogenic shock. Am J Surg 1987; 153:108-116.

Bailey RW, Bulkley GB, Hamilton SR, Morris JB, Smith GW. Pathogenesis of nonocclusive ischemic colitis. Ann Surg 1986; 203:590-599.

Bakker J, Coffernils M, Leon M, Gris P, Vincent JL. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. Chest 1991; 99:956-962.

Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg 1996; 171:221-226.

Bakker J, Vincent JL, Gris P, Leon M, Coffernils M, Kahn RJ. Veno-arterial carbon dioxide gradient in human septic shock. Chest 1992; 101:509-515.

Bams JL, Kolkman JJ, Roukens MP, Douma DP, Loef BG, Meuwissen SG, Groeneveld AB. Reliable gastric tonometry after coronary artery surgery: need

for acid secretion suppression despite transient failure of acid secretion. Intensive Care Med 1998; 24:1139-1143.

Bastien O, Piriou V, Aouifi A, Evans R, Lehot JJ. Effects of dopexamine on blood flow in multiple splanchnic sites measured by laser Doppler velocimetry in rabbits undergoing cardiopulmonary bypass. Br J Anaesth 1999; 82:104-109.

Baum TD, Wang H, Rothschild HR, Gang DL, Fink MP. Mesenteric oxygen metabolism, ileal mucosal hydrogen ion concentration, and tissue edema after crystalloid or colloid resuscitation in porcine endotoxic shock: comparison of Ringer's lactate and 6% hetastarch. Circ Shock 1990; 30:385-397.

Baumann G, Felix SB, Filcek SA. Usefulness of dopexamine hydrochloride versus dobutamine in chronic congestive heart failure and effects on hemodynamics and urine output. Am J Cardiol 1990; 65:748-754.

Bellomo R, Cole L, Ronco C. Hemodynamic support and the role of dopamine. Kidney Int Suppl 1998; 66:S71-S74.

Bellomo R, Kellum JA, Wisniewski SR, Pinsky MR. Effects of norepinephrine on the renal vasculature in normal and endotoxemic dogs. Am J Respir Crit Care Med 1999; 159:1186-1192.

Benjamin E, Paluch TA, Berger SR, Premus G, Wu C, Iberti TJ. Venous hypercarbia in canine hemorrhagic shock. Crit Care Med 1987; 15:516-518.

Bergofsky EH. Determination of tissue O_2 tensions by hollow visceral tonometers: Effect of breathing enriched O_2 mixtures. J Clin Invest 1964; 43:193-200.

Bersten AD, Hersch M, Cheung H, Rutledge FS, Sibbald WJ. The effect of various sympathomimetics on the regional circulations in hyperdynamic sepsis. Surgery 1992; 112:549-561.

Bersten AD, Rutten AJ. Renovascular interaction of epinephrine, dopamine, and intraperitoneal sepsis. Crit Care Med 1995; 23:537-544.

Biffl WL, Moore EE. Splanchnic ischaemia/reperfusion and multiple organ failure. Br J Anaesth 1996; 77:59-70.

Bigam DL, Barrington KJ, Jirsch DW, Cheung PY. Effects of a continuous epinephrine infusion on regional blood flow in awake newborn piglets. Biol Neonate 1998; 73:198-206.

Biro GP, Douglas JR, Keon WJ, Taichman GC. Changes in regional blood flow distribution induced by infusions of dopexamine hydrochloride or dobutamine in anesthetized dogs. Am J Cardiol 1988; 62:30C-36C.

Blumenfeld JD, Vaughan JrED. Renal physiology. In: Walsh PC, Retik AB, Vaughan JrED, Wein AJ, editors. Campbell's Urology. Philadelphia: W.B.Saunders Company, 1998: 263-313.

Blunt M, Young P, Ridley S. A comparison of the effects of dopexamine and prostacyclin in systemic inflammatory response syndrome. Anaesthesia 1999; 54:313-319.

Bock HA. Pathophysiology of acute renal failure in septic shock: from prerenal to renal failure. Kidney Int Suppl 1998; 64:S15-S18.

Bohlen HG. Intestinal tissue PO_2 and microvascular responses during glucose exposure. Am J Physiol 1980; 238:H164-H171.

Boldt J, Heesen M, Muller M, Pabsdorf M, Hempelmann G. The effects of albumin versus hydroxyethyl starch solution on cardiorespiratory and circulatory variables in critically ill patients. Anesth Analg 1996; 83:254-261.

Boldt J, Mueller M, Menges T, Papsdorf M, Hempelmann G. Influence of different volume therapy regimens on regulators of the circulation in the critically ill. Br J Anaesth 1996; 77:480-487.

Booker PD, Pozzi M. A placebo-controlled study of the effects of dopexamine on gastric mucosal perfusion in infants undergoing hypothermic cardiopulmonary bypass. Br J Anaesth 2000; 84:23-27.

Bowles SA, Schlichtig R, Kramer DJ, Klions HA. Arteriovenous pH and partial pressure of carbon dioxide detect critical oxygen delivery during progressive hemorrhage in dogs. J Crit Care 1992; 7:95-105.

Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. Jama 1993; 270:2699-2707.

Boyd O, Mackay CJ, Lamb G, Bland JM, Grounds RM, Bennett ED. Comparison of clinical information gained from routine blood-gas analysis and from gastric tonometry for intramural pH. Lancet 1993; 341: 142-146.

Breslow MJ, Miller CF, Parker SD, Walman AT, Traystman RJ. Effect of vasopressors on organ blood flow during endotoxin shock in pigs. Am J Physiol 1987; 252:H291-H300.

Bron KM, Redman HC. Splanchnic artery stenosis and occlusion. Incidence, arteriographic and clinical manifestations. Radiology 1969; 92:323-328.

Brown RA, Chiu CJ, Scott HJ, Gurd FN. Ultrastructural changes in the canine ileal mucosal cell after mesenteric arterial occlusion. Arch Surg 1970; 101:290-297.

Brundin T, Wahren J. Influence of a mixed meal on splanchnic and interscapular energy expenditure in humans. Am J Physiol 1991; 260:E232-E237.

Buckley NM, Brazeau P, Gootman PM, Frasier ID. Renal circulatory effects of adrenergic stimuli in anesthetized piglets and mature swine. Am J Physiol 1979; 237:H690-H695.

Bulkley GB, Kvietys PR, Parks DA, Perry MA, Granger DN. Relationship of blood flow and oxygen consumption to ischemic injury in the canine small intestine. Gastroenterology 1985; 89:852-857.

Bulkley GB, Zuidema GD, Hamilton SR, O'Mara CS, Klacsmann PG, Horn SD. Intraoperative determination of small intestinal viability following ischemic injury: a prospective, controlled trial of two adjuvant methods (Doppler and fluorescein) compared with standard clinical judgment. Ann Surg 1981; 193:628-637.

Cain SM. Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. J Appl Physiol 1977; 42:228-234.

Cain SM, Curtis SE. Systemic and regional oxygen uptake and delivery and lactate flux in endotoxic dogs infused with dopexamine. Crit Care Med 1991; 19:1552-1560.

Calvet X, Baigorri F, Duarte M, Saura P, Royo C, Joseph D, Mas A, Artigas A. Effect of ranitidine on gastric intramucosal pH in critically ill patients. Intensive Care Med 1998; 24:12-17.

Carrico CJ, Meakins JL, Marshall JC, Fry D, Maier RV. Multiple-organ-failure syndrome. Arch Surg 1986; 121:196-208.

Caty MG, Guice KS, Oldham KT, Remick DG, Kunkel SI. Evidence for tumor necrosis factor-induced pulmonary microvascular injury after intestinal ischemia-reperfusion injury. Ann Surg 1990; 212:694-700.

Chintala MS, Lokhandwala MF, Jandhyala BS. Protective effects of dopexamine hydrochloride in renal failure after acute haemorrhage in anaesthetized dogs. J Auton Pharmacol 1990; 10 Suppl 1:s95-102.

Chiu CJ, McArdle AH, Brown R, Scott HJ, Gurd FN. Intestinal mucosal lesion in low-flow states. I. A morphological, hemodynamic, and metabolic reappraisal. Arch Surg 1970; 101:478-483.

Christiansen JS, Pedersen MM, Schmitz A, Christensen CK, Christensen T, Mogensen CE. Low-dose dopamine infusion, renal haemodynamics and urinary albumin excretion rate in insulin-dependent diabetics and in normal man. Scand J Clin Lab Invest 1988; 48:679-683.

Creteur J, De Backer D, Vincent JL. A dobutamine test can disclose hepatosplanchnic hypoperfusion in septic patients. Am J Respir Crit Care Med 1999; 160:839-845.

Croft RJ, Menon GP, Marston A. Does 'intestinal angina' exist? A critical study of obstructed visceral arteries. Br J Surg 1981; 68:316-318.

Dahn MS, Lange P, Lobdell K, Hans B, Jacobs LA, Mitchell RA. Splanchnic and total body oxygen consumption differences in septic and injured patients. Surgery 1987; 101:69-80.

Dalton JM, Gore DC, Makhoul RG, Fisher MR, DeMaria EJ. Decreased splanchnic perfusion measured by duplex ultrasound in humans undergoing small volume hemorrhage. Crit Care Med 1995; 23:491-497.

Dawson AM, Trenchard D, Guz A. Small bowel tonometry: Assessment of small gut mucosal oxygen tension in dog and man. Nature Lond 1965; 206:943-944.

Day NP, Phu NH, Mai NT, Bethell DB, Chau TT, Loc PP, Chuong LV, Sinh DX, Solomon T, Haywood G, Hien TT, White NJ. Effects of dopamine and epinephrine infusions on renal hemodynamics in severe malaria and severe sepsis. Crit Care Med 2000; 28:1353-1362.

De Backer D, Zhang H, Manikis P, Vincent JL. Regional effects of dobutamine in endotoxic shock. J Surg Res 1996; 65:93-100.

Deitch EA. Multiple organ failure. Pathophysiology and potential future therapy. Ann Surg 1992; 216: 117-134.

Deitch EA, Berg R, Specian R. Endotoxin promotes the translocation of bacteria from the gut. Arch Surg 1987; 122:185-190.

Deitch EA, Bridges W, Baker J, Ma JW, Ma L, Grisham MB, Granger DN, Specian RD, Berg R. Hemorrhagic shock-induced bacterial translocation is reduced by xanthine oxidase inhibition or inactivation. Surgery 1988; 104:191-198.

DeLaurier GA, Ivey RK, Johnson RH. Peritoneal fluid lactic acid and diagnostic dilemmas in acute abdominal disease. Am J Surg 1994; 167:302-305.

Desjars P, Pinaud M, Bugnon D, Tasseau F. Norepinephrine therapy has no deleterious renal effects in human septic shock. Crit Care Med 1989; 17:426-429.

Dhainaut JF, Edwards JD, Grootendorst AF, Nightingale P, Pinsky MR, Reinhart K, Shoemaker WC, Vincent JL. Practical aspects of oxygen transport: conclusions and recommendations of the Roundtable Conference. Intensive Care Med 1990; 16:S179-S180.

Diebel LN, Robinson SL, Wilson RF, Dulchavsky SA. Splanchnic mucosal perfusion effects of hypertonic versus isotonic resuscitation of hemorrhagic shock. Am Surg 1993; 59:495-499.

Doglio GR, Pusajo JF, Egurrola MA, Bonfigli GC, Parra C, Vetere L, Hernandez MS, Fernandez S, Palizas F, Gutierrez G. Gastric mucosal pH as a prognostic index of mortality in critically ill patients. Crit Care Med 1991; 19:1037-1040.

Duke GJ, Briedis JH, Weaver RA. Renal support in critically ill patients: low-dose dopamine or low-dose dobutamine? Crit Care Med 1994; 22:1919-1925.

Duranteau J, Sitbon P, Teboul JL, Vicaut E, Anguel N, Richard C, Samii K. Effects of epinephrine, norepinephrine, or the combination of norepinephrine and dobutamine on gastric mucosa in septic shock. Crit Care Med 1999; 27:893-900.

Durham RM, Neunaber K, Mazuski JE, Shapiro MJ, Baue AE. The use of oxygen consumption and delivery as endpoints for resuscitation in critically ill patients. J Trauma 1996; 41:32-39.

Edouard AR, Degremont AC, Duranteau J, Pussard E, Berdeaux A, Samii K. Heterogeneous regional vascular responses to simulated transient hypovolemia in man. Intensive Care Med 1994; 20:414-420.

Ernst O, Asnar V, Sergent G, Lederman E, Nicol L, Paris JC, L'Hermine C. Comparing contrast-enhanced breath-hold MR angiography and conventional angiography in the evaluation of mesenteric circulation. AJR Am J Roentgenol 2000; 174:433-439.

Ferrara JJ, Dyess DL, Peeples GL, Christenberry DP, Roberts WS, Tacchi EJ, Swafford AN, Ardell JL, Powell RW. Effects of dopamine and dobutamine on regional blood flow distribution in the neonatal piglet. Ann Surg 1995; 221:531-540.

Fiddian-Green RG, Baker S. Predictive value of the stomach wall pH for complications after cardiac operations: comparison with other monitoring. Crit Care Med 1987; 15:153-156.

Fiddian-Green RG, McGough E, Pittenger G, Rothman E. Predictive value of intramural pH and other risk factors for massive bleeding from stress ulceration. Gastroenterology 1983; 85:613-620.

Fiddian-Green RG, Pittenger G, Whitehouse WMJ. Back-diffusion of CO_2 and its influence on the intramural pH in gastric mucosa. J Surg Res 1982; 33:39-48.

Fiddian-Green RG, Amelin PM, Herrmann JB, Arous E, Cutler BS, Schiedler M, Wheeler HB, Baker S. Prediction of the development of sigmoid ischemia on the day of aortic operations. Indirect measurements of intramural pH in the colon. Arch Surg 1986; 121:654-660.

Fink MP, Kaups KL, Wang HL, Rothschild HR. Maintenance of superior mesenteric arterial perfusion prevents increased intestinal mucosal permeability in endotoxic pigs. Surgery 1991; 110:154-160.

Fink MP, Nelson R, Roethel R. Low-dose dopamine preserves renal blood flow in endotoxin shocked dogs treated with ibuprofen. J Surg Res 1985; 38:582-591.

Fiser DH, Fewell JE, Hill DE, Brown AL. Cardiovascular and renal effects of dopamine and dobutamine in healthy, conscious piglets. Crit Care Med 1988; 16(4):340-345.

Friedman G, Berlot G, Kahn RJ, Vincent JL. Combined measurements of blood lactate concentrations and gastric intramucosal pH in patients with severe sepsis. Crit Care Med 1995; 23:1184-1193.

Gärdebäck M, Settergren G. Dopexamine and dopamine in the prevention of low gastric mucosal pH following cardiopulmonary by-pass. Acta Anaesthesiol Scand 1995; 39:1066-1070.

Gärdebäck M, Settergren G, Ohquist G, Tiren C. Effect of dopexamine on calculated low gastric intramucosal pH following valve replacement. Acta Anaesthesiol Scand 1995; 39:599-604.

Germann R, Haisjackl M, Schwarz B, Deusch E, Meusburger S, Gruber E, Pajk W, Hausdorfer H, Bonatti J, Furtner B, Ulmer H, Hasibinder W. Inotropic treatment and intestinal mucosal tissue oxygenation in a model of porcine endotoxemia. Crit Care Med 1997; 25:1191-1197.

Giraud GD, MacCannell KL. Decreased nutrient blood flow during dopamine- and epinephrine-induced intestinal vasodilation. J Pharmacol Exp Ther 1984; 230:214-220.

Goldberg LI. Cardiovascular and renal actions of dopamine: potential clinical applications. Pharmacol Rev 1972; 24:1-29.

Good J, Frost G, Oakley CM, Cleland JG. The renal effects of dopamine and dobutamine in stable chronic heart failure. Postgrad Med J 1992; 68 Suppl 2:S7-11.

Gordon IL, Wesley R, Wong DH, Ingegno MD, Spivak B, Wilson SE. Effect of dopamine on renal blood flow and cardiac output. Arch Surg 1995; 130:864-868.

Granger DN, Richardson PD, Kvietys PR, Mortillaro NA. Intestinal blood flow. Gastroenterology 1980; 78:837-863.

Gray PA, Bodenham AR, Park GR. A comparison of dopexamine and dopamine to prevent renal impairment in patients undergoing orthotopic liver Transplantation. Anaesthesia 1991; 46:638-641.

Groeneveld AB, Vermeij CG, Thijs LG. Arterial and mixed venous blood acid-base balance during hypoperfusion with incremental positive end-expiratory pressure in the pig. Anesth Analg 1991; 73:576-582.

Grum CM, Fiddian-Green RG, Pittenger GL, Grant BJ, Rothman ED, Dantzker DR. Adequacy of tissue oxygenation in intact dog intestine. J Appl Physiol 1984; 56:1065-1069.

Gump FE, Price JBJ, Kinney JM. Whole body and splanchnic blood flow and oxygen consumption measurements in patients with intraperitoneal infection. Ann Surg 1970; 171:321-328.

Gutierrez G, Bismar H, Dantzker DR, Silva N. Comparison of gastric intramucosal pH with measures of oxygen transport and consumption in critically ill patients. Crit Care Med 1992; 20:451-457.

Gutierrez G, Clark C, Brown SD, Price K, Ortiz L, Nelson C. Effect of dobutamine on oxygen consumption and gastric mucosal pH in septic patients. Am J Respir Crit Care Med 1994; 150:324-329.

Gutierrez G, Palizas F, Doglio G, Wainsztein N, Gallesio A, Pacin J, Dubin A, Schiavi E, Jorge M, Pusajo J, Klein F, San Roman E, Dorfman B, Shottlender J, Giniger R. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. Lancet 1992; 339:195-199.

Guzman JA, Kruse JA. Gut mucosal-arterial PCO_2 gradient as an indicator of splanchnic perfusion during systemic hypo- and hypercapnia. Crit Care Med 1999; 27:2760-2765.

Ha HK, Rha SE, Kim AY, Auh YH. CT and MR diagnoses of intestinal ischemia. Semin Ultrasound CT MR 2000; 21:40-55.

Habre W, Beghetti M, Roduit C, Girardin E, Vallotton M, Friedli B, Berner M.Haemodynamic and renal effects of dopexamine after cardiac surgery in children. Anaesth Intensive Care 1996; 24:435-439.

Haglind E, Haglund U, Lundgren O, Schersten T. Graded intestinal vascular obstruction. IV. An analysis of the pathophysiology in the development of refractory shock. Circ Shock 1981; 8:635-646.

Haglund U, Bulkley GB, Granger DN. On the pathophysiology of intestinal ischemic injury. Clinical review. Acta Chir Scand 1987; 153:321-324.

Haglund U, Hulten L, Ahren C, Lundgren O. Mucosal lesions in the human small intestine in shock. Gut 1975; 16:979-984.

Haglund U, Myrvold H, Lundgren O. Cardiac and pulmonary function in regional intestinal shock. Arch Surg 1978; 113:963-969.

Halmagyi DF, Kennedy M, Varga D. Hidden hypercapnia in hemorrhagic hypotension. Anesthesiology 1970; 33:594-601.

Hamed AT, Ginos JZ, Ekas RDJ, Jandhyala BS, Lokhandwala MF. Renal hemodynamics in hemorrhagic hypotension: studies on the effects of pre- and postjunctional dopamine receptor agonists. J Cardiovasc Pharmacol 1983; 5:207-212.

Hauet T, Gibelin H, Richer JP, Godart C, Eugene M, Carretier M. Influence of retrieval conditions on renal medulla injury: evaluation by proton NMR spectroscopy in an isolated perfused pig kidney model. J Surg Res 2000; 93:1-8.

Hayes JK, Luo X, Wong KC, McJames S, Tseng CK. Effects of dobutamine, norepinephrine and epinephrine on intramucosal pH and hemodynamics of dogs during endotoxic shock. Acta Anaesthesiol Sin 1998; 36:113-126.

Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994; 330:1717-1722.

Haywood GA, Tighe D, Moss R, al-Saady N, Foshola TO, Riley SP, Pearson I, Webb A, McKenna WJ, Bennett ED. Goal directed therapy with dobutamine in a porcine model of septic shock: effects on systemic and renal oxygen transport. Postgrad Med J 1991; 67 Suppl 1:S36-S39.

Heinonen PO, Jousela IT, Blomqvist KA, Olkkola KT, Takkunen OS. Validation of air tonometric measurement of gastric regional concentrations of CO_2 in critically ill septic patients. Intensive Care Med 1997; 23:524-529.

Heyland DK, Cook DJ, King D, Kernerman P, Brun Buisson C. Maximizing oxygen delivery in critically ill patients: a methodologic appraisal of the evidence. Crit Care Med 1996; 24:517-524.

Horton JW, Walker PB. Small-volume hypertonic saline dextran resuscitation from canine endotoxin shock. Ann Surg 1991; 214:64-73.

Horton JW, White DJ. Cardiac contractile injury after intestinal ischemia-reperfusion. Am J Physiol 1991; 261:H1164-H1170.

Hunter GC, Guernsey JM. Mesenteric ischemia. Med Clin North Am 1988; 72:1091-1115.

Immink WF, Beijer HJ, Brouwer FA, Charbon GA. Norepinephrine and isoprenaline induced changes of peripheral blood flow acceleration caused by changes of cardiac inotropy. Pflugers Arch 1976; 365:119-127.

Jakob SM, Merasto-Minkkinen M, Tenhunen JJ, Heino A, Alhava E, Takala J. Prevention of systemic hyperlactatemia during splanchnic ischemia. Shock 2000; 14:123-127.

Jamison M, Widerhorn J, Weber L, Campese V, Vasquez J, Hovanessian L, Rahimtoola SH, Elkayam U. Central and renal hemodynamic effects of a new agonist at peripheral dopamine- and beta-2 adrenoreceptors (dopexamine) in patients with heart failure. Am Heart J 1989; 117:607-614.

Javle P, Yates J, Kynaston HG, Parsons KF, Jenkins SA. Hepatosplanchnic haemodynamics and renal blood flow and function in rats with liver failure. Gut 1998; 43:272-279.

Jonas J, Schwarz S, Alebrahim-Dehkordy A. Behavior of the lactate level in occlusion and reperfusion of the right superior mesenteric artery. An animal experiment study. Langenbecks Arch Chir 1996; 381:1-6.

Juste RN, Panikkar K, Soni N. The effects of low-dose dopamine infusions on haemodynamic and renal parameters in patients with septic shock requiring treatment with noradrenaline. Intensive Care Med 1998; 24:564-568.

Juvonen PO, Tenhunen JJ, Heino AA, Merasto M, Paajanen HE, Alhava EM, Takala JA. Splanchnic tissue perfusion in acute experimental pancreatitis. Scand J Gastroenterol 1999; 34:308-314.

Järvinen O, Laurikka J, Salenius J-P, Tarkka M. Acute intestinal ischaemia: A review of 214 cases. Ann Chir Gynaecol 1994; 83:22-25.

Kainuma M, Nakashima K, Sakuma I, Kawase M, Komatsu T, Shimada Y, Nimura Y, Nonami T. Hepatic venous hemoglobin oxygen saturation predicts liver dysfunction after hepatectomy. Anesthesiology 1992; 76:379-386.

Kairaluoma MI, Karkola P, Heikkinen D, Huttunen R, Mokka RE, Larmi TK. Mesenteric infarction. Am J Surg 1977; 133:188-193.

Kaisers U, Pappert D, Langrehr JM, Undi H, Neuhaus P, Rossaint R. Dopamine, dopexamine and dobutamine in liver transplant recipients: a comparison of their effects on hemodynamics, oxygen transport and hepatic venous oxygen saturation. Transpl Int 1996; 9:214-220.

Kaleya RN, Boley SJ. Acute mesenteric ischemia. Crit Care Clin 1995; 11:479-512.

Kampp M, Lundgren O, Nilsson NJ. Extravascular shunting of oxygen in the small intestine of the cat. Acta Physiol Scand 1968; 72:396-403.

Kangwalklai K, Saadat S, Bella E, Enquist IF. Space studies during occlusion of the superior mesenteric artery and upon its release. Surg Gynecol Obstet 1973; 137:263-266.

Karzai W, Lotte A, Gunnicker M, Vorgrimler Karzai UM, Priebe HJ. Dobutamine increases oxygen consumption during constant flow cardiopulmonary bypass. Br J Anaesth 1996; 76:5-8.

Kiefer P, Tugtekin I, Wiedeck H, Bracht H, Geldner G, Georgieff M, Radermacher P. Effect of a dopexamine-induced increase in cardiac index on splanchnic hemodynamics in septic shock. Am J Respir Crit Care Med 2000; 161:775-779.

Kirchhoff K, Leuwer M, Thum P, Bornscheuer A, Piepenbrock S. Different effects of dopamine and dopexamine on the isolated perfused rat kidney. Br J Anaesth 1999; 83:898-902.

Kleen M, Habler O, Hutter J, Podtschaske A, Tiede M, Kemming G, Corso C, Batra S, Keipert P, Faithfull S, Messmer K. Effects of hemodilution on splanchnic perfusion and hepatorenal function. I. Splanchnic perfusion. Eur J Med Res 1997; 2:413-418.

Knolmayer TJ, Bowyer MW, Egan JC, Asbun HJ. The effects of pneumoperitoneum on gastric blood flow and traditional hemodynamic measurements. Surg Endosc-Ultrasound Interv 1998; 12:115-118.

Koikkalainen K, Kohler R. Stenosis and occlusion in the coeliac and mesenteric arteries. A comparative angiographic and clinical study. Ann Chir Gynaecol Fenn 1971; 60:9-24.

Kolkman JJ, Zwarekant LJ, Boshuizen K, Groeneveld AB, Steverink PJ, Meuwissen SG. Type of solution and PCO_2 measurement errors during tonometry. Intensive Care Med 1997; 23:658-663.

Krupski WC, Selzman CH, Whitehill TA. Unusual causes of mesenteric ischemia. Surg Clin North Am 1997; 77:471-502.

Kulka PJ, Tryba M. Inotropic support of the critically ill patient. A review of the agents. Drugs 1993; 45:654-667.

Kuttila K, Perttila J, Vanttinen E, Niinikoski J. Tonometric assessment of sigmoid perfusion during aortobifemoral reconstruction for arteriosclerosis. Eur J Surg 1994; 160:491-495.

Kwaan JH, Connolly JE. Prevention of intestinal infarction resulting from mesenteric arterial occlusive disease. Surg Gynecol Obstet 1983; 157(4):321-324.

Landow L, Phillips DA, Heard SO, Prevost D, Vandersalm TJ, Fink MP. Gastric tonometry and venous oximetry in cardiac surgery patients. Crit Care Med 1991; 19:1226-1233.

Lange H, Jackel R. Usefulness of plasma lactate concentration in the diagnosis of acute abdominal disease. Eur J Surg 1994; 160:381-384.

LaNoue JLJ, Turnage RH, Kadesky KM, Guice KS, Oldham KT, Myers SI. The effect of intestinal reperfusion on renal function and perfusion. J Surg Res 1996; 64:19-25.

Laustsen J, Jensen BV, Jelnes R, Egeblad K, Balslev IB. The value of sigmoideoscopy in the diagnosis of ischemic colitis following aortic reconstruction. Int Angiol 1990; 9:117-119.

Leier CV. Regional blood flow responses to vasodilators and inotropes in congestive heart failure. Am J Cardiol 1988; 62:86E-93E.

Leier CV, Heban PT, Huss P, Bush CA, Lewis RP. Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. Circulation 1978; 58:466-475.

Lemaire LC, van Lanschot JJ, Stoutenbeek CP, van Deventer SJ, Wells CL, Gouma DJ. Bacterial translocation in multiple organ failure: cause or epiphenomenon still unproven. Br J Surg 1997; 84:1340-1350.

Leung FW, Morishita T, Livingston EH, Reedy T, Guth PH. Reflectance spectrophotometry for the assessment of gastroduodenal mucosal perfusion. Am J Physiol 1987; 252:G797-G804.

Levey AS, Madaio MP, Perrone RD. Laboratory assessment of renal disease: Clearance, urinanalysis, and renal biopsy. In: Brenner BM, Rector FC, editors. The Kidney. Philadelphia: W.B. Saunders Company, 1991: 919-968.

Levy B, Nace L, Bollaert PE, Dousset B, Mallie JP, Larcan A. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. Intensive Care Med 1997; 23:282-287.

Levy B, Bollaert PE, Lucchelli JP, Sadoune LO, Nace L, Larcan A. Dobutamine improves the adequacy of gastric mucosal perfusion in epinephrine-treated septic shock. Crit Care Med 1997; 25:1649-1654.

Levy B, Nace L, Bollaert PE, Dousset B, Mallie JP, Larcan A. Comparison of systemic and regional effects of dobutamine and dopexamine in norepinephrine-treated septic shock. Intensive Care Med 1999; 25:942-948.

Lherm T, Troche G, Rossignol M, Bordes P, Zazzo JF. Renal effects of low-dose dopamine in patients with sepsis syndrome or septic shock treated with catecholamines. Intensive Care Med 1996; 22:213-219.

Locke R, Hauser CJ, Shoemaker WC. The use of surface oximetry to assess bowel viability. Arch Surg 1984; 119:1252-1256.

Lundberg J, Lundberg D, Norgren L, Ribbe E, Thorne J, Werner O. Intestinal hemodynamics during laparotomy: effects of thoracic epidural anesthesia and dopamine in humans. Anesth Analg 1990; 71:9-15.

Lundgren O. Physiology of the intestinal circulation. In: Marston A, Bulkley GB, Fiddian Green RG, Haglund U, editors. Splanchnic ischemia and multiple organ failure. St Louis: CV Mosby, 1989: 29-40.

Lundgren O, Haglund U. On the chemical nature of the blood borne cardiotoxic material released from the feline small bowel in regional shock. Acta Physiol Scand 1978; 103:59-70.

Lundgren O, Haglund U. The pathophysiology of the intestinal countercurrent exchanger. Life Sci 1978; 23:1411-1422.

MacCannell KL, Giraud GD, Hamilton PL, Groves G. Haemodynamic responses to dopamine and dobutamine infusions as a function of duration of infusion. Pharmacology 1983; 26:29-39.

MacGregor DA, Butterworth JF, Zaloga CP, Prielipp RC, James R, Royster RL. Hemodynamic and renal effects of dopexamine and dobutamine in patients with reduced cardiac output following coronary artery bypass grafting. Chest 1994; 106:835-841.

Madorin WS, Martin CM, Sibbald WJ. Dopexamine attenuates flow motion in ileal mucosal arterioles in normotensive sepsis. Crit Care Med 1999; 27:394-400.

Magilligan DJJ, Teasdall R, Eisinminger R, Peterson E. Mixed venous oxygen saturation as a predictor of cardiac output in the postoperative cardiac surgical patient. Ann Thorac Surg 1987; 44:260-262.

Mäkisalo HJ, Korsback CH, Soini HO, Heino A, Hockerstedt KA. Correction of hemorrhagic shock-induced liver hypoxia with whole blood, Ringer's solution or with hetastarch. Res Exp Med (Berl) 1989; 189:397-407.

Maningas PA. Resuscitation with 7.5% NaCl in 6% dextran-70 during hemorrhagic shock in swine: effects on organ blood flow. Crit Care Med 1987; 15:1121-1126.

Marik PE. Gastric intramucosal pH. A better predictor of multiorgan dysfunction syndrome and death than oxygen-derived variables in patients with sepsis. Chest 1993; 104:225-229.

Marik PE, Lorenzana A. Effect of tube feedings on the measurement of gastric intramucosal pH. Crit Care Med 1996; 24:1498-1500.

Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. Jama 1994; 272:1354-1357.

Marin C, Eon B, Saux P, Aknin P, Gouin F. Renal effects of norepinephrine used to treat septic shock patients. Crit Care Med 1990; 18:282-285.

Marnitz U, Dauberschmidt R, Mrochen H. The value of blood lactate determination in the postoperative phase. Anaesthesiol Reanim 1994; 19:103-109.

Martin C, Papazian L, Perrin G, Saux P, Gouin F. Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? Chest 1993; 103:1826-1831.

Martin GB, Carden DL, Nowak RM, Tomlanovich MC. Comparison of central venous and arterial pH and PCO_2 during open-chest CPR in the canine model. Ann Emerg Med 1985; 14:529-533.

Mathias DW, Clifford PS, Klopfenstein HS. Mixed venous blood gases are superior to arterial blood gases in assessing acid-base status and oxygenation during acute cardiac tamponade in dogs. J Clin Invest 1988; 82:833-838.

Maynard ND, Bihari DJ, Dalton RN, Smithies MN, Mason RC. Increasing splanchnic blood flow in the critically III. Chest 1995; 108:1648-1654.

McKinsey JF, Gewertz BL. Acute mesenteric ischemia. Surg Clin North Am 1997; 77:307-318.

McNeill JR, Stark RD, Greenway CV. Intestinal vasoconstriction after hemorrhage: roles of vasopressin and angiotensin. Am J Physiol 1970; 219:1342-1347.

Meakins JL, Marshall JC. The gastrointestinal tract: the 'motor' of MOF. Arch Surg 1986; 121:197-201.

Mecher CE, Rackow EC, Astiz ME, Weil MH. Venous hypercarbia associated with severe sepsis and systemic hypoperfusion. Crit Care Med 1990; 18:585-589.

Meier-Hellmann A, Bredle DL, Specht M, Hannemann L, Reinhart K. Dopexamine increases splanchnic blood flow but decreases gastric mucosal pH in severe septic patients treated with dobutamine. Crit Care Med 1999; 27:2166-2171.

Meier-Hellmann A, Bredle DL, Specht M, Spies C, Hannemann L, Reinhart K. The effects of low-dose dopamine on splanchnic blood flow and oxygen uptake in patients with septic shock. Intensive Care Med 1997; 23:31-37.

Meier-Hellmann A, Reinhart K. Effects of catecholamines on regional perfusion and oxygenation in critically ill patients. Acta Anaesthesiol Scand Suppl 1995; 107:239-248.

Meier-Hellmann A, Reinhart K, Bredle DL, Specht M, Spies CD, Hannemann L. Epinephrine impairs splanchnic perfusion in septic shock. Crit Care Med 1997; 25:399-404.

Meier-Hellmann A, Specht M, Hannemann L, Hassel H, Bredle DL, Reinhart K. Splanchnic blood flow is greater in septic shock treated with norepinephrine than in severe sepsis. Intensive Care Med 1996; 22:1354-1359.

Miller PR, Meredith JW, Chang MC. Randomized, prospective comparison of increased preload versus inotropes in the resuscitation of trauma patients: effects on cardiopulmonary function and visceral perfusion. J Trauma 1998; 44:107-113.

Mizock BA, Falk JL. Lactic acidosis in critical illness. Crit Care Med 1992; 20:80-93.

Montgomery A, Almqvist P, Arvidsson D, Lindgren S, Haglund U. Early detection of gastrointestinal mucosal ischemia in porcine E. coli sepsis. Acta Chir Scand 1990; 156:613-620.

Montgomery A, Hartmann M, Jonsson K, Haglund U. Intramucosal pH measurement with tonometers for detecting gastrointestinal ischemia in porcine hemorrhagic shock. Circ Shock 1989; 29:319-327.

Morales J, Kibsey P, Thomas PD, Poznansky MJ, Hamilton SM. The effects of ischemia and ischemia-reperfusion on bacterial translocation, lipid peroxidation, and gut histology: studies on hemorrhagic shock in pigs. J Trauma 1992; 33:221-226.

Mousdale S, Clyburn PA, Mackie AM, Groves ND, Rosen M. Comparison of the effects of dopamine, dobutamine, and dopexamine upon renal blood flow: a study in normal healthy volunteers. Br J Clin Pharmacol 1988; 25:555-560.

Murray MJ, Gonze MD, Nowak LR, Cobb CF. Serum D(-)-lactate levels as an aid to diagnosing acute intestinal ischemia. Am J Surg 1994; 167:575-578.

Nelson DP, Samsel RW, Wood LD, Schumacker PT. Pathological supply dependence of systemic and intestinal O_2 uptake during endotoxemia. J Appl Physiol 1988; 64:2410-2419.

Neveu H, Kleinknecht D, Brivet F, Loirat P, Landais P. Prognostic factors in acute renal failure due to sepsis. Results of a prospective multicentre study. The French Study Group on Acute Renal Failure. Nephrol Dial Transplant 1996; 11:293-299.

Neviere R, Chagnon JL, Vallet B, Lebleu N, Marechal X, Mathieu D, Wattel F, Dupuis B. Dobutamine improves gastrointestinal mucosal blood flow in a porcine model of endotoxic shock. Crit Care Med 1997; 25:1371-1377.

Neviere R, Mathieu D, Chagnon JL, Lebleu N, Wattel F. The contrasting effects of dobutamine and dopamine on gastric mucosal perfusion in septic patients. Am J Respir Crit Care Med 1996; 154:1684-1688.

Nicoloff AD, Williamson WK, Moneta GL, Taylor LM, Porter JM. Duplex ultrasonography in evaluation of splanchnic artery stenosis. Surg Clin North Am 1997; 77:339-355.

Noldge GF, Priebe HJ, Bohle W, Buttler KJ, Geiger K. Effects of acute normovolemic hemodilution on splanchnic oxygenation and on hepatic histology and metabolism in anesthetized pigs. Anesthesiology 1991; 74:908-918.

Nordin AJ, Mäkisalo H, Hockerstedt KA. Failure of dobutamine to improve liver oxygenation during resuscitation with a crystalloid solution after experimental haemorrhagic shock. Eur J Surg 1996;
162:973-979.

Norlén K, Rentzhog L, Wikstrom S. Regional and central hemodyanamics during segmental ischemia of the small intestine in the rat. Eur Surg Res 1978; 10:246-258.

Nutz V, Sommer JH, Schultze-Petzold J. Hyperlactacidemia in intestinal ischemia. II. Experimental principles. Langenbecks Arch Chir 1987; 370:69-78.

O'Neill PJ, Cobb LM, Ayala A, Morrison MH, Chaudry IH. Aggressive fluid resuscitation following intestinal ischemia-reperfusion in immature rats prevents metabolic derangements and down regulates interleukin-6 release. Shock 1994; 1:381-387.

O'Neill PJ, Cobb LM, Steigman CK, Chaudry IH. Prevention of secondary cardiovascular instability after intestinal ischemia and reperfusion improves survival. Am J Physiol 1993; 264:R622-R629.

Oi Y, Aneman A, Svensson M, Ewert S, Dahlqvist M, Haljamae H. Hypertonic saline-dextran improves intestinal perfusion and survival in porcine endotoxin shock. Crit Care Med 2000; 28:2843-2850.

Olsen NV. Effects of dopamine on renal haemodynamics tubular function and sodium excretion in normal humans. Dan Med Bull 1998; 45:282-297.

Olsen NV, Lund J, Jensen PF, Espersen K, Kanstrup IL, Plum I, Leyssac PP. Dopamine, dobutamine, and dopexamine. A comparison of renal effects in unanesthetized human volunteers. Anesthesiology 1993; 79:685-694.

Olson D, Pohlman A, Hall JB. Administration of low-dose dopamine to nonoliguric patients with sepsis syndrome does not raise intramucosal gastric pH nor improve creatinine clearance. Am J Respir Crit Care Med 1996; 154:1664-1670.

Oster ZH, Som P, Zamora PO. Mesenteric vascular occlusion: a new diagnostic method using a radiolabeled monoclonal antibody reactive with platelets. Radiology 1989; 171:653-656.

Ottinger LW, Austen WG. A study of 136 patients with mesenteric infarction. Surg Gynecol Obstet 1967; 124:251-261.

Palsson J, Ricksten SE, Houltz E, Lundin S. Effects of dopamine, dopexamine and dobutamine on renal excretory function during experimental sepsis in conscious rats. Acta Anaesthesiol Scand 1997; 41:392-398.

Park PO, Haglund U. Regeneration of small bowel mucosa after intestinal ischemia. Crit Care Med 1992; 20:135-139.

Park PO, Haglund U, Bulkley GB, Falt K. The sequence of development of intestinal tissue injury after strangulation ischemia and reperfusion. Surgery 1990; 107:574-580.

Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, Damske BA, Parrillo JE. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 1984; 100:483-490.

Parks DA, Granger DN. Contributions of ischemia and reperfusion to mucosal lesion formation. Am J Physiol 1986; 250:G749-G753.

Parks DA, Grogaard B, Granger DN. Comparison of partial and complete arterial occlusion models for studying intestinal ischemia. Surgery 1982; 92:896-901.

Parviainen I, Ruokonen E, Takala J. Dobutamine-induced dissociation between changes in splanchnic blood flow and gastric intramucosal pH after cardiac surgery. Br J Anaesth 1995; 74:277-282.

Parviainen I, Väisänen O, Ruokonen E, Takala J. Effect of nasogastric suction and ranitidine on the calculated gastric intramucosal pH. Intensive Care Med 1996; 22:319-323.

Patel A, Kaleya RN, Sammartano RJ. Pathophysiology of mesenteric ischemia. Surg Clin North Am 1992; 72:31-41.

Pawlik W, Shepherd AP, Jacobson ED. Effect of vasoactive agents on intestinal oxygen consumption and blood flow in dogs. J Clin Invest 1975; 56:484-490.

Peitzman AB, Udekwu AO, Ochoa J, Smith S. Bacterial translocation in trauma patients. J Trauma 1991; 31:1083-1086.

Piper SN, Boldt J, Schmidt CC, Brosch C, Maleck WH, Berchtold C. Influence of dopexamine on hemodynamics, intramucosal pH, and regulators of the macrocirculation and microcirculation in patients undergoing abdominal aortic surgery. J Cardiothorac Vasc Anesth 2000; 14:281-287.

Polk HCJ, Shields CL. Remote organ failure: a valid sign of occult intra-abdominal infection. Surgery 1977; 81:310-313.

Priebe HJ, Noldge GF, Armbruster K, Geiger K. Differential effects of dobutamine, dopamine, and noradrenaline on splanchnic haemodynamics and oxygenation in the pig. Acta Anaesthesiol Scand 1995; 39:1088-1096.

Prough DS, Whitley JM, Taylor CL, Deal DD, DeWitt DS. Small-volume resuscitation from hemorrhagic shock in dogs: effects on systemic hemodynamics and systemic blood flow. Crit Care Med 1991; 19:364-372.

Rasmussen I, Haglund U. Early gut ischemia in experimental fecal peritonitis. Circ Shock 1992; 38:22-28.

Redfors S, Hallback DA, Haglund U, Jodal M, Lundgren O. Blood flow distribution, villous tissue osmolality and fluid and electrolyte transport in the cat small intestine during regional hypotension. Acta Physiol Scand 1984; 121:193-209.

Reilly PM, Bulkley GB. Vasoactive mediators and splanchnic perfusion. Crit Care Med 1993; 21(2 Suppl):S55-S68.

Reinelt H, Radermacher P, Fischer G, Geisser W, Wachter U, Wiedeck H, Georgieff M, Vogt J. Effects of a dobutamine-induced increase in splanchnic blood flow on hepatic metabolic activity in patients with septic shock. Anesthesiology 1997; 86:818-824.

Rhee RY, Gloviczki P. Mesenteric venous thrombosis. Surg Clin North Am 1997; 77:327-338.

Richardson PD, Withrington PG. Liver blood flow. I. Intrinsic and nervous control of liver blood flow. Gastroenterology 1981; 81:159-173.

Richer M, Robert S, Lebel M. Renal hemodynamics during norepinephrine and low-dose dopamine infusions in man. Crit Care Med 1996; 24:1150-1156.

Roayaie S, Jossart G, Gitlitz D, Lamparello P, Hollier L, Gagner M. Laparoscopic release of celiac artery compression syndrome facilitated by laparoscopic ultrasound scanning to confirm restoration of flow. J Vasc Surg 2000; 32:814-817.

Robie NW, Goldberg LI. Comparative systemic and regional hemodynamic effects of dopamine and dobutamine. Am Heart J 1975; 90:340-345.

Rodeberg DA, Chaet MS, Bass RC, Arkovitz MS, Garcia VF. Nitric oxide: an overview. Am J Surg 1995; 170:292-303.

Rothenbach P, Turnage RH, Iglesias J, Riva A, Bartula L, Myers SI. Downstream effects of splanchnic ischemia-reperfusion injury on renal function and eicosanoid release. J Appl Physiol 1997; 83:530-536.

Roumen RM, Vreugde JP, Goris RJ. Gastric tonometry in multiple trauma patients. J Trauma 1994; 36:313-316.

Rowell LB, Blackmon JR, Kenny MA, Escourrou P. Splanchnic vasomotor and metabolic adjustments to hypoxia and exercise in humans. Am J Physiol 1984; 247:H251-H258.

Ruffolo RR, Jr. The pharmacology of dobutamine. Am J Med Sci 1987; 294:244-248.

Ruokonen E, Takala J, Kari A. Regional blood flow and oxygen transport in patients with the low cardiac output syndrome after cardiac surgery. Crit Care Med 1993; 21(9):1304-1311.

Ruokonen E, Takala J, Kari A, Saxen H, Mertsola J, Hansen EJ. Regional blood flow and oxygen transport in septic shock. Crit Care Med 1993; 21:1296-1303.

Ruokonen E, Uusaro A, Alhava E, Takala J. The effect of dobutamine infusion on splanchnic blood flow and oxygen transport in patients with acute pancreatitis. Intensive Care Med 1997; 23:732-737.

Sakio H, Ohtsu S, Okuda C. How should we treat intestinal ischemia?--1: Effects of dobutamine and dopamine. Masui 1994; 43:1304-1309.

Sautner T, Wessely C, Riegler M, Sedivy R, Gotzinger P, Losert U, Roth E, Jakesz R, Fugger R. Early effects of catecholamine therapy on mucosal integrity, intestinal blood flow, and oxygen metabolism in porcine endotoxin shock. Ann Surg 1998; 228:239-248.

Scannell G, Clark L, Waxman K. Regional flow during experimental hemorrhage and crystalloid resuscitation: persistence of low flow to the splanchnic organs. Resuscitation 1992; 23:217-225.

Schiffer ER, Schwieger IM, Gosteli P, Poinsot O, Mentha G, Morel DR. Systemic and splanchnic oxygen supply-demand relationship with fenoldopam, dopamine and noradrenaline in sheep. Eur J Pharmacol 1995; 286:49-60.

Schlichtig R, Bowles SA. Distinguishing between aerobic and anaerobic appearance of dissolved CO_2 in intestine during low flow. J Appl Physiol 1994; 76:2443-2451.

Schlichtig R, Cowden WL, Chaitman BR. Tolerance of unusually low mixed venous oxygen saturation. Adaptations in the chronic low cardiac output syndrome. Am J Med 1986; 80:813-818.

Schlichtig R, Mehta N, Gayowski TJ. Tissue-arterial PCO_2 difference is a better marker of ischemia than intramural pH (pHi) or arterial pH-pHi difference. J Crit Care 1996; 11:51-56.

Schlichting E, Lyberg T. Monitoring of tissue oxygenation in shock: an experimental study in pigs. Crit Care Med 1995; 23:1703-1710.

Schmeling DJ, Caty MG, Oldham KT, Guice KS, Hinshaw DB. Evidence for neutrophil-related acute lung injury after intestinal ischemia-reperfusion. Surgery 1989; 106:195-201.

Schmidt H, Secchi A, Wellmann R, Bach A, Bhrer H, Martin E. Dopexamine maintains intestinal villus blood flow during endotoxemia in rats. Crit Care Med 1996; 24:1233-1237.

Schmidt W, Hacker A, Gebhard MM, Martin E, Schmidt H. Dopexamine attenuates endotoxin-induced microcirculatory changes in rat mesentery: role of beta2 adrenoceptors. Crit Care Med 1998; 26:1639-1645.

Schneider AJ, Groeneveld AB, Teule GJ, Wesdorp RI, Thijs LG. Total body blood volume redistribution in porcine E. coli septic shock: effect of volume loading, dobutamine, and norepinephrine. Circ Shock 1991; 35:215-222.

Schwartz S, Frantz RA, Shoemaker WC. Sequential hemodynamic and oxygen transport responses in hypovolemia, anemia, and hypoxia. Am J Physiol 1981; 241:H864-H871.

Secchi A, Wellmann R, Martin E, Schmidt H. Dobutamine maintains intestinal villus blood flow during normotensive endotoxemia: an intravital microscopic study in the rat. J Crit Care 1997; 12:137-141.

Segal JM, Phang PT, Walley KR. Low-dose dopamine hastens onset of gut ischemia in a porcine model of hemorrhagic shock. J Appl Physiol 1992; 73:1159-1164.

Sezai A, Shiono M, Orime Y, Nakata K, Hata M, Yamada H, Iida M, Kashiwazaki S, Kinishita J, Nemoto M, Koujima T, Sezai Y, Saitoh T. Renal circulation and cellular metabolism during left ventricular assisted circulation: comparison study of pulsatile and nonpulsatile assists. Artif Organs 1997; 21:830-835.

Sharpe DA, Mitchel IM, Kay EA, McGoldrick JP, Munsch CM, Kay PH. Enhancing liver blood flow after cardiopulmonary bypass: the effects of dopamine and dopexamine. Perfusion 1999; 14:29-36.

Shepherd AP, Riedel GL, Maxwell LC, Kiel JW. Selective vasodilators redistribute intestinal blood flow and depress oxygen uptake. Am J Physiol 1984; 247:G377-G384.

Sherry E, Tooley MA, Bolsin SN, Monk CR, Willcox J. Effect of dopexamine hydrochloride on renal vascular resistance index and haemodynamic responses following coronary artery bypass graft surgery. Eur J Anaesthesiol 1997; 14:184-189.

Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988; 94:1176-1186.

Silva E, DeBacker D, Creteur J, Vincent JL. Effects of vasoactive drugs on gastric intramucosal pH.Crit Care Med 1998; 26:1749-1758.

Silverman HJ, Tuma P. Gastric tonometry in patients with sepsis. Effects of dobutamine infusions and packed red blood cell transfusions. Chest 1992; 102:184-188.

Sinclair DG, Houldsworth PE, Keogh B, Pepper J, Evans TW. Gastrointestinal permeability following cardiopulmonary bypass: a randomised study comparing the effects of dopamine and dopexamine.Intensive Care Med 1997; 23:510-516.

Smail N, Wang P, Cioffi WG, Bland KI, Chaudry IH. Resuscitation after uncontrolled venous hemorrhage: Does increased resuscitation volume improve regional perfusion? J Trauma 1998; 44:701-708.

Smerud MJ, Johnson CD, Stephens DH. Diagnosis of bowel infarction: a comparison of plain films and CT scans in 23 cases. AJR Am J Roentgenol 1990; 154:99-103.

Soong CV, Halliday MI, Hood JM, Rowlands BJ, Barros DS. Effect of low-dose dopamine on sigmoid colonic intramucosal pH in patients undergoing elective abdominal aortic aneurysm repair. Br J Surg 1995; 82:912-915.

Stamler A, Wang H, Weintraub RM, Hariawala MD, Fink MP, Johnson RG. Low-dose dopexamine's effect on lung and gut function after CPB in a sheep model. J Surg Res 1998; 74:165-172.

Steinberg S, Azar G, Love R, Lee R, Choe E, Flint L. Dopexamine prevents depression of mesenteric blood flow caused by positive end-expiratory pressure in rats. Surgery 1996; 120:597-601.

Stephan H, Sonntag H, Henning H, Yoshimine K. Cardiovascular and renal haemodynamic effects of dopexamine: comparison with dopamine. Br J Anaesth 1990; 65:380-387.

Studer W, Wu X. Supraceliac aortic cross-clamping and declamping. Effects of dopexamine and dopamine on systemic and mesenteric hemodynamics, metabolism and intestinal tonometry in a rat model. Acta Anaesthesiol Scand 2000; 44:241-248.

Sullivan BJ, Swallow CJ, Girotti MJ, Rotstein OD. Bacterial translocation induces procoagulant activity in tissue macrophages. A potential mechanism for end-organ dysfunction. Arch Surg 1991; 126:586-590.

Takala J. Determinants of splanchnic blood flow. Br J Anaesth 1996; 77:50-58.

Takala J, Parviainen I, Siloaho M, Ruokonen E, Hamalainen E. Saline PCO_2 is an important source of error in the assessment of gastric intramucosal pH. Crit Care Med 1994; 22:1877-1879.

Temmesfeld-Wollbruck B, Szalay A, Mayer K, Olschewski H, Seeger W, Grimminger F. Abnormalities of gastric mucosal oxygenation in septic shock: partial responsiveness to dopexamine. Am J Respir Crit Care Med 1998; 157:1586-1592.

Tenhunen JJ, Kosunen H, Alhava E, Tuomisto L, Takala JA. Intestinal luminal microdialysis: a new approach to assess gut mucosal ischemia. Anesthesiology 1999; 91:1807-1815.

Thakkar H, Lowe PA, Price CP, Newman DJ. Measurement of the kinetics of protein uptake by proximal tubular cells using an optical biosensor. Kidney Int 1998; 54:1197-1205.

Thomas TV, Mace TP, Choe EU, Flint LM, Ferrara JJ. Dopexamine Maintains Mesenteric Blood Flow During Systemic Hypoxemia in the Neonatal Piglet. J Gastrointest Surg 1997; 1:362-370.

Thoren A, Elam M, Ricksten SE. Differential effects of dopamine, dopexamine, and dobutamine on jejunal mucosal perfusion early after cardiac surgery. Crit Care Med 2000; 28:2338-2343.

Tighe D, Moss R, Haywood G, Webb A, al-Saady N, Heath F, Bennett D. Dopexamine hydrochloride maintains portal blood flow and attenuates hepatic ultrastructural changes in a porcine peritonitis model of multiple system organ failure. Circ Shock 1993; 39:199-206.

Tjiong B, Bella E, Weiner M, Enquist IF. Fluid shifts and metabolic changes during and after occlusion of the superior mesenteric artery. Surg Gynecol Obstet 1974; 139:217-221.

Turnage RH, Kadesky KM, Bartula L, Guice KS, Oldham KT, Myers SI. Splanchnic PGI2 release and "no reflow" following intestinal reperfusion. J Surg Res 1995; 58:558-564.

Turnage RH, Kadesky KM, Bartula L, Myers SI. Intestinal reperfusion up-regulates inducible nitric oxide synthase activity within the lung. Surgery 1995; 118:288-293.

Turnage RH, Kadesky KM, Bartula L, Myers SI. Pulmonary thromboxane release following intestinal reperfusion. J Surg Res 1995; 58:552-557.

Turnage RH, Magee JC, Guice KS, Myers SI, Oldham KT. Complement activation by the hydroxyl radical during intestinal reperfusion. Shock 1994; 2:445-450.

Uusaro A, Ruokonen E, Takala J. Estimation of splanchnic blood flow by the Fick principle in man and problems in the use of indocyanine green. Cardiovasc Res 1995; 30:106-112.

Uusaro A, Ruokonen E, Takala J. Splanchnic oxygen transport after cardiac surgery: evidence for inadequate tissue perfusion after stabilization of hemodynamics. Intensive Care Med 1997; 22:26-33.

Uusaro A, Russell JA, Walley KR, Takala J. Gastric-arterial PCO_2 gradient does not reflect systemic and splanchnic hemodynamics or oxygen transport after cardiac surgery. Shock 2000 ; 14:13-17.

Vahl AC, Out NJ, Kapteijn BA, Koomen AR. Nothing gained from the determinations of plasma lactate levels in the evaluation of a patient with acute abdomen. Ned Tijdschr Geneeskd 1998; 142:901-904.

Vainionpaa V, Nuutinen L, Kairaluoma M, Mokka R, Tuononen S. Haemodynamic comparison of dopamine and dobutamine in normovolaemic and hypovolaemic dogs. Acta Anaesthesiol Scand 1983; 27:490-494.

van der Linden P, Rausin I, Deltell A, Bekrar Y, Gilbart E, Bakker J, Vincent JL. Detection of tissue hypoxia by arteriovenous gradient for PCO_2 and pH in anesthetized dogs during progressive hemorrhage. Anesth Analg 1995; 80:269-275.

van Kesteren RG, Heethaar RM, Charbon GA, Heethaar J, Brouwer FA. Comparison of effects of dopamine hydrochloride and dopexamine hydrochloride on abdominal and femoral hemodynamics in anesthetized dogs. Circ Shock 1993; 40:227-233.

van Lambalgen AA, van Kraats AA, Mulder MF, van den Bos GC, Teerlink T, Thijs LG. Organ blood flow and distribution of cardiac output in dopexamine- or dobutamine-treated endotoxemic rats. J Crit Care 1993; 8:117-127.

Vaughn S, Puri VK. Cardiac output changes and continuous mixed venous oxygen saturation measurement in the critically ill. Crit Care Med 1988; 16:495-498.

Vernon DD, Garrett JS, Banner WJ, Dean JM. Hemodynamic effects of dobutamine in an intact animal model. Crit Care Med 1992; 20:1322-1329.

Vincent JL, Van der Linden P, Domb M, Blecic S, Azimi G, Bernard A. Dopamine compared with dobutamine in experimental septic shock: relevance to fluid administration. Anesth Analg 1987; 66:565-571.

Voelckel WG, Lindner KH, Wenzel V, Bonatti J, Hangler H, Frimmel C, Kunszberg E, Lingnau W. Effects of vasopressin and epinephrine on splanchnic blood flow and renal function during and after cardiopulmonary resuscitation in pigs. Crit Care Med 2000; 28:1083-1088.

Vogelzang RL, Gore RM, Anschuetz SL, Blei AT. Thrombosis of the splanchnic veins: CT diagnosis. AJR Am J Roentgenol 1988; 150:93-96.

Waller JL, Kaplan JA, Bauman DI, Craver JM. Clinical evaluation of a new fiberoptic catheter oximeter during cardiac surgery. Anesth Analg 1982; 61:676-679.

Walley KR, Friesen BP, Humer MF, Phang PT. Small bowel tonometry is more accurate than gastric tonometry in detecting gut ischemia. J Appl Physiol 1998; 85:1770-1777.

Webb AR, Moss RF, Tighe D, al Saady N, Bennett ED. The effects of dobutamine, dopexamine and fluid on hepatic histological responses to porcine faecal peritonitis. Intensive Care Med 1991; 17:487-493.

Weil MH, Rackow EC, Trevino R, Grundler W, Falk JL, Griffel MI. Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. N Engl J Med 1986; 315:153-156.

Welch M, Newstead CG, Smyth JV, Dodd PD, Walker MG. Evaluation of dopexamine hydrochloride as a renoprotective agent during aortic surgery. Ann Vasc Surg 1995; 9:488-492.

Wenstone R, Campbell JM, Booker PD, McKay R. Renal function after cardiopulmonary bypass in children: comparison of dopamine with dobutamine. Br J Anaesth 1991; 67:591-594.

Westman L, Järnberg PO. Effects of dobutamine on renal function in normal man. Acta Anaesthesiol Scand 1986; 30:72-75.

Westman L, Järnberg PO. Effects of dobutamine on haemodynamics and renal function in patients after major vascular surgery. Acta Anaesthesiol Scand 1987; 31:253-257.

Wilson C, Gupta R, Gilmour DG, Imrie CW. Acute superior mesenteric ischaemia. Br J Surg 1987; 74:279-281.

Winsö O, Biber B, Gustavsson B, Holm C, Milsom I, Niemand D. Portal blood flow in man during graded positive end-expiratory pressure ventilation. Intensive Care Med 1986; 12:80-85.

Wood PR, Lawler PG. Measurement technique and variation in intramucosal pH. Br J Anaesth 1996; 76:563-564.

Zhang H, Vincent JL. Arteriovenous differences in PCO_2 and pH are good indicators of critical hypoperfusion. Am Rev Respir Dis 1993; 148:867-871.

9. ORIGINAL PUBLICATIONS I - IV

Reprinted with permission.