Haemodynamic Management in Liver Surgery

Lena Sand Bown

Department of Anaesthesiology
and Intensive Care Medicine
Institute of Clinical Sciences
at Sahlgrenska Academy
University of Gothenburg

UNIVERSITY OF GOTHENBURG

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lena.sand@vgregion.se

To my family

Abstract

Liver resection surgery is a potentially curative treatment for liver tumours. The liver is a highly vascular organ, and substantial intra-operative blood loss is common. Increased blood loss negatively impacts both postoperative outcome and long-term survival.

A low central venous pressure (CVP) has been suggested in order to reduce blood loss during liver surgery. The rationale is that low CVP reflects lower pressure in the hepatic venous system, which in turn reduces the driving force causing bleeding when the liver tissues are transected. Together with fluid restriction, strategies to achieve a low CVP (LCVP) include patient tilt (head up or down), zero PEEP, nitroglycerine, diuretics and neuraxial anaesthesia. Vasopressin reduces portal pressure in patients with portal hypertension and has been shown to reduce blood loss in liver transplantation. LCVP management in liver surgery is associated with reduced blood loss and may increase the risk of organ of hypo-perfusion.

Aims

To investigate the effect of patient position (tilt), nitroglycerine, PEEP and vasopressin on portal and hepatic venous pressures and systemic haemodynamics. To assess the effect of vasopressin on portal and hepato-splanchnic blood flows. To determine whether pressure changes in the superior vena cava are reflected in the hepatic venous system. To retrospectively evaluate the effects of a new anaesthetic management protocol involving low CVP and goal directed therapy (GDT/LCVP) in liver resection surgery.

Methods

We used tip-manometer catheters to directly measure changes in hepatic venous and portal pressures during 10° tilt (head up and down), nitroglycerine infusion, and alterations in PEEP. The effect of low-to-moderate doses of vasopressin on hepatic venous and portal flow and pressure was assessed with conventional fluid-filled catheters in these vessels, collection of samples for blood gas analysis and the application of Fick's principle. The effects on systemic haemodynamics were also assessed. Patient data were obtained and compared from two cohorts, before and after the introduction of GDT/LCVP.

Results

Patient tilt led to substantial changes in CVP and mean arterial pressure (MAP), but only minor effects on hepatic pressures. Increased PEEP resulted in small increases in hepatic and central venous pressures. Nitroglycerine caused a parallel decrease in systemic and hepatic venous pressures. Cardiac output decreased. With the addition of head down tilt, MAP, cardiac output and CVP increased. Hepatic venous pressure increased marginally, but did not return to baseline. Vasopressin had no effect on hepatic pressures, but led to decreases in portal and hepato-splanchnic blood flow. After the introduction of LCVP/GDT management, median intra-operative haemorrhage decreased by almost a litre, with no increase in post-operative complications.

Conclusions

Changes in CVP reflect changes in hepatic venous pressure in the supine position, but not during patient tilt. Tilting is not effective in reducing hepatic venous pressures. Nitroglycerine reduces the hepatic and portal venous pressures, but adverse central hemodynamic effects may limit its application. Vasopressin reduces portal and hepatic blood flow with only minor effect on pressures. Introducing goal-directed therapy with a low CVP protocol led to a large reduction in intra-operative blood loss compared to previous anaesthetic management techniques.

Summary in Swedish
Populärvetenskaplig sammanfattning

Leverresektion är en möjlig botande behandlingsmetod för patienter med levercancer. Vid leverkirurgi är det viktigt att reducera blodförlust och därigenom behovet av blodtransfusion, vilket anses kunna minska komplikationer i efterförloppet och öka långtidsöverlevnad. Ett flertal studier har påvisat minskad blödning när trycket i övre hålvenen, det centrala ventrycket (CVT) har hållits lågt vilket avspeglar trycket i lever-venerna. Det har varit oklart hur ett lågt CVT skall åstadkommas på ett adekvat och bra sätt. Åtgärder så som vätskerestriktion, lägesförändring av patienten, användning av kärlvidgande läkemedel (nitroglycerin), vattendrivande läkemedel och ryggbedöv-ning (epidural), i kombination med kirurgiska tekniker, har föreslagits för att sänka CVT och levervenstryck och för att därigenom minska blodförlust vid leverkirurgi.

I delarbete I och II har vi studerat effekten av lägesförändring (huvudänden upp alternativt ner), ett kärlvidgande läkemedel (nitroglycerin) samt effekten av utand-ningstryck (PEEP), på tryck i porta- och leverven i relation till CVT. Resultaten visade att tryck i porta- och leverven ändrades minimalt vid lägesförändringar, medan CVT sjönk vid höjning av huvudänden och steg vid sänkning av huvudänden. Därtill med-förde lägesförändring med huvudänden upp en sänkning av blodtrycket. Ökning av PEEP gav en liten ökning av levervenstryck, vilket får sättas i relation till eventuell positiv effekt på patientens lungfunktion. Vid tillförsel av nitroglycerin sjönk CVT, porta- och levervenstryck parallellt. Som bieffekt gav nitroglycerin lågt blodtryck samt minskad hjärtminutvolym. Vid lägesförändring med huvudänden ner i kombination med nitroglycerin bibehölls ett lägre levervenstryck, jämfört med utgångsvärdet, med förbättrad hjärtminutvolym samt blodtryck.

I delarbete III har vi undersökt effekten av en låg dos vasopressin på flöde och tryck i lever- och portaven. Vasopressin har en sammandragande effekt i magtarmkanalens kärlbädd och används kliniskt för att minska portatryck hos patienter med levercirrhos (skrumplever). Man har även visat att vasopressin har medfört minskad blodförlust hos patienter som genomgått levertransplantation. Hos patienter med normal leverfunktion och portatryck medförde vasopressin inte någon trycksänkande effekt på porta- och levervenstryck men en påtaglig minskning av blodflödet i lever och magtarmcirku-lationen, utan ogynnsam effekt på systemcirkulationen. Enligt tidigare studier kan denna flödesminskning leda till minskad levervolym. Om det bara är tryck i levern som har betydelse för blödning i samband med leverkirurgi så kommer inte vaso-

pressin att medföra minskad blödning, men om en minskad blodvolym i levern har betydelse, så skulle vasopressin kunna leda till mindre blödning vid kirurgi.

För att försöka minska blödning vid leveroperationer på vår klinik, införde vi 2011 en regimförändring vilket innebar målstyrd behandling med låg-CVT. Detta för att minska blodförlust men samtidigt optimera blodcirkulation, andningsfunktion, koagulation samt njurfunktion, hos patienter som genomgår leverkirurgi. I delarbete IV gjordes retrospektivt en analys av denna förändring. Vi jämförde 39 patienter från 2010 (innan förändring) med 41 patienter från 2012 (efter förändring). Vår nya regim medförde att vätsketillförsel under operationen minskade och behovet av kärlaktiva läkemedel ökade. Därtill resulterade förändringen i att blodförlusten minskade med nästan en liter (-40 %) per patient utan att vi fann några signifikant negativa postoperativa förändringar.

Sammanfattningsvis har denna avhandling visat att levervenstryck inte påverkas av lägesförändring även om CVP ändras. Nitroglycerin kan effektivt sänka porta- och levervenstryck men kan ge cirkulatorisk instabilitet hos en del patienter vilket delvis kan åtgärdas med sänkning av huvudändan. Vasopressin sänker inte tryck men blodflöde i levern och om detta minskar blödning vid kirurgi hos patienter med normal leverfunktion behöver belysas i ytterligare studier. Målstyrd behandling med låg-CVT har medfört en minskad blodförlust vid leverkirurgi.

List of papers

This thesis is based on the following papers, which
will be referred to in the text by their Roman numerals.

I. Sand L, Rizell M, Houltz E, Karlsen K, Wiklund J, Odenstedt Hergès H, Stenqvist O, Lundin S. **Effect of patient position and PEEP on hepatic, portal and central venous pressures during liver resection.** *Acta Anaesthesiol Scand 2011; 55: 1106–1112.*

II. Sand L, Lundin S, Rizell M, Wiklund J, Stenqvist O, Houltz E. **Nitroglycerine and patient position effect on central, hepatic and portal venous pressures during liver surgery.** *Acta Anaesthesiol Scand 2014; 58: 961–967.*

III. Sand Bown L, Ricksten S-E, Houltz E, Einarsson H, Söndergaard S, Rizell M, Lundin S. **Vasopressin-induced changes in splanchnic blood flow and hepatic and portal venous pressures in liver resection.** *Accepted for publication in Acta Anaesthesiol Scand 2015.*

IV. Sand Bown L, Wolmesjö N, Ricksten S-E, Rizell M, Lundborg C, Lundin S, Söndergaard S. **Goal-directed haemodynamic bundled therapy reduces bleeding in liver resection.** *Submitted manuscript.*

Table of Contents

Abbreviations

Δ	(delta) changes
AKI	acute kidney injury
ANOVA	analysis of variance
AVP	vasopressin
BL	baseline
C	control
C1 and C2	control periods
CI	cardiac index
CO	cardiac output
CVC	central venous catheter
CVP	central venous pressure
EBL	estimated blood loss
ECG	electrocardiogram
ERA	enhanced recovery after surgery
GDT	goal directed therapy
GFR	glomerular filtration rate
HABR	hepatic arterial buffer response
HR	heart rate
HT	hypertension
HVP	hepatic venous pressure
i.v.	intravenous
IVC	inferior vena cava
L	litre
LCVP	low central venous pressure
MAC	minimum alveolar concentration
MAP	mean arterial pressure
NG	nitroglycerine
PA	pulmonary artery
PEEP	positive end expiratory pressure
PiCCO	pulse contour cardiac output
PVP	portal venous pressure
Qhspl	hepato-splanchnic blood flow
Qpv	portal venous blood flow
Qspl	splanchnic venous blood flow

RIFLE	Risk, Injury, Failure, Loss of kidney function and End stage kidney disease
SaO2	arterial oxygen saturation
SD	standard deviation
SEM	standard error of the mean
ShvO2	hepatic venous oxygen saturation
SpvO2	portal venous oxygen saturation
SPSS	statistic package for the social sciences
SV	stroke volume
SvO2	central venous oxygen saturation
SVR	systemic vascular resistance
U	units

Introduction

Liver resection surgery is a potentially curative treatment for selected primary and metastatic liver tumours. An increasing number of patients with significant comorbidities are undergoing liver resection, the most frequent indications for surgery being colorectal cancer metastases, hepatocellular carcinoma and cholangiocarcinoma.[1,2]

The liver is a highly vascular organ, and substantial blood loss is common during liver surgery.[3-5] Intra-operative blood loss has been negatively correlated with both postoperative outcome and long-term survival.[6,7] Furthermore, it has been suggested that blood loss and the number of blood units transfused may be an independent prognostic risk factor for tumour recurrence.[6,8]

Intra-operative blood loss has been positively correlated with central venous pressure (CVP)[5,9,10] and pressure in the inferior caval vein (IVC).[11] CVP measured in the superior caval vein has been used as a surrogate for IVC, hepatic vein or hepatic post-sinusoidal pressure. A variety of strategies have been developed to either reduce inflow to and/or facilitate outflow from the hepatic vascular bed in order to reduce intra-hepatic vascular pressure. These strategies include surgical techniques such as vascular inflow and outflow occlusions and anaesthetic techniques, such as low central venous pressure (LCVP) anaesthetic management.[4,12,13] Although a low CVP in liver surgery is associated with reduced blood loss, it may also increase the risk of complications such as air embolism and inadequate organ perfusion leading to organ dysfunction, for example acute renal failure.[14-17]
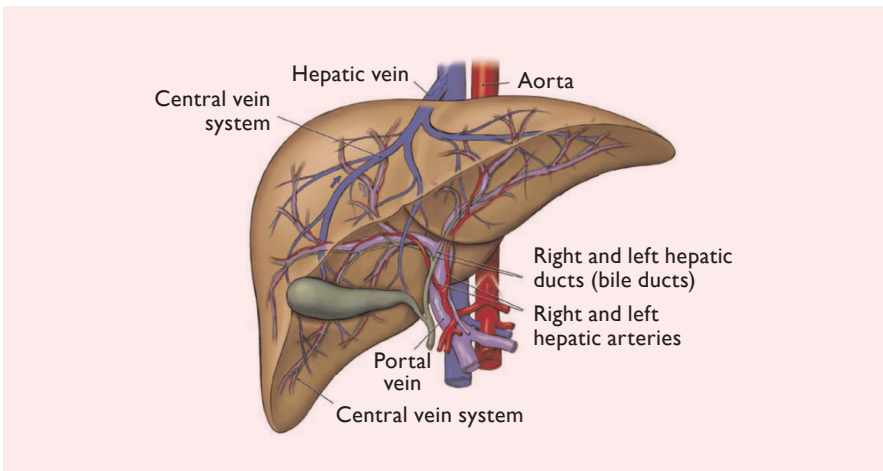

Figure 1. Internal anatomy of the liver.[18] Reproduced with permission from the publisher.

Circulatory physiology of the liver

The liver receives about 25–30% of cardiac output (CO), 800–1200 mL/min, through a unique dual supply, with 75% of total hepatic flow supplied by the portal vein and 25% by the hepatic artery (Figures 1 and 2). The hepatic blood flow is regulated by both extrinsic (neural and humoral) and intrinsic (pressure-flow, metabolic and the hepatic artery buffer response (HABR)) mechanisms.[18] The HABR mechanism involves an increase in hepatic arterial flow in response to a reduction in portal venous flow, in order to maintain hepatic oxygenation. This increase is mediated by an increase in adenosine concentration in the space of Disse, which is triggered by a reduction of portal flow (Figure 3). The more oxygen-rich hepatic arterial blood can compensate for a reduction of up to 50% of portal flow.[19,20]

The splanchnic organs contain around 15–20%[21] of the body's total blood volume with the majority of the blood present in veins (70%).[22] The liver serves as an important blood reservoir with much of its volume being composed of blood.[21] In response to sympatho-adrenal activation, up to one litre of blood may be transferred into the systemic circulation within 30 seconds.[20] Conversely, in the case of fluid overload, the hepato-splanchnic circulation has the capacity to accommodate large volumes of blood. Due to the high compliance of the hepato-splanchnic veins, this can occur without a significant increase in transmural pressure.[21,22]

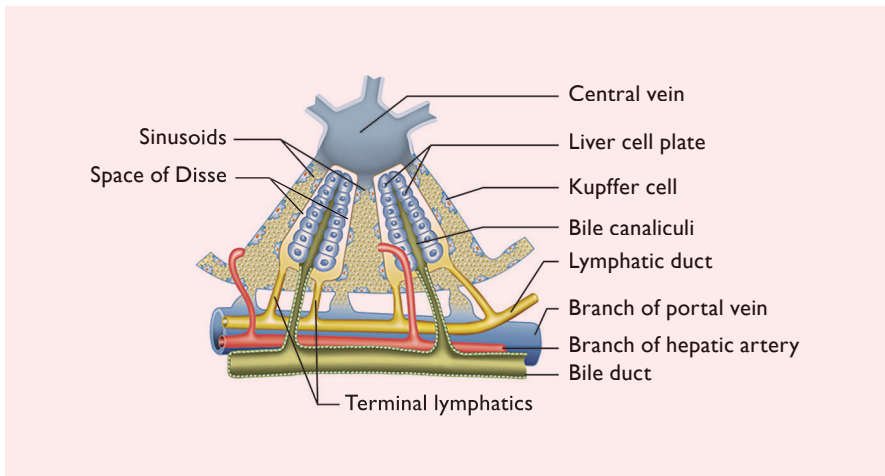

Figure 3. Basic structure of a liver lobule.[24]
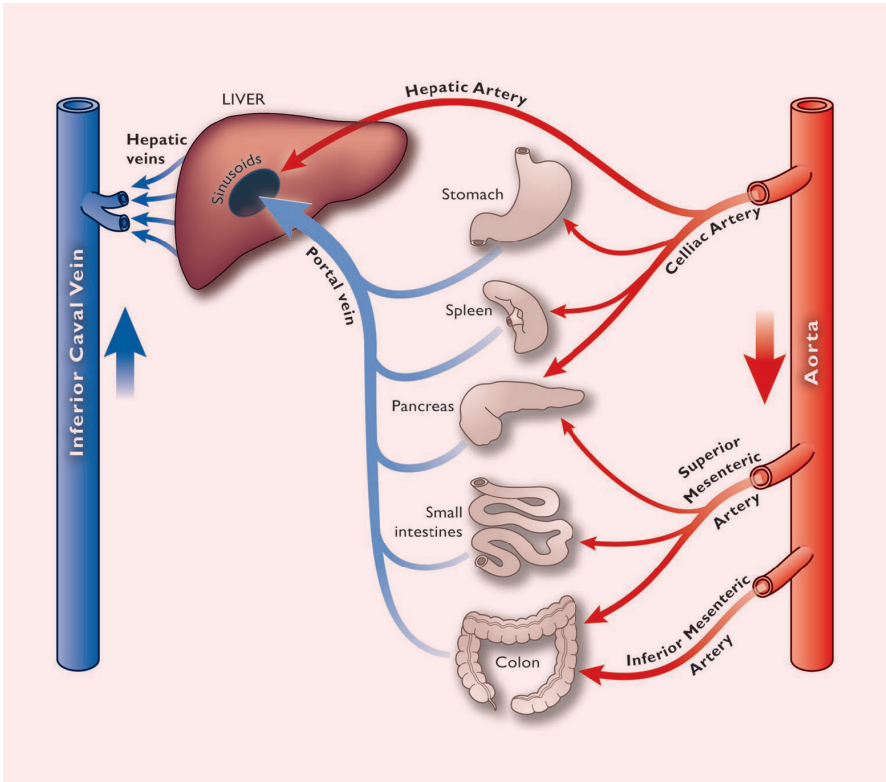Reproduced with permission from the publisher (Elsevier).

Figure 2. Schematic representation of the splanchnic circulation.[23]
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Historical background

The first successful liver resection was performed in 1886 on a 30-year-old woman. The patient required re-operation due to haemorrhage later the same day but survived. Because of the high risk of perioperative bleeding in liver resection surgery, this procedure remained rare until the 1950's when surgical techniques to regulate hepatic inflow/outflow improved. Knowledge of liver anatomy and in particular the arrangement of the liver segments also contributed to improved surgical outcomes. Despite this, liver surgery during the 1950's and 1960's was still regarded as very high risk, with significant blood loss and mortality rates of around 50%.[25]

Even during the 1970's mortality rates were reported to vary between 13–20%, with the main contributing factors being haemorrhage and postoperative liver failure. Perioperative blood loss was often in excess of 10 litres. Over the last 25 years, perioperative outcomes have steadily improved due to improved surgical knowledge of anatomically based resections (Figure 4) and refinement in intraoperative management, which has led to significantly reduced perioperative blood loss. The 30-day mortality rate today is between 2–3%.[25,26]

During the late 1980's and early 1990's, the low CVP (LCVP) approach to anaesthesia for liver resection evolved at several centres, as an alternative to the previous standard approach, which involved volume loading prior to surgery. The hypothesis was that volume loading leads to an increase in CVP, which in turn is transmitted to the hepatic and sinusoidal veins leading to an increased hepatic venous pressure (HVP) and increased bleeding at the parenchymal resection site. It was therefore hypothesised, that if CVP were reduced, control of haemorrhage would be easier. With the LCVP technique, which involved pharmacological interventions and no volume loading preoperatively to actively reduce CVP during parenchymal transection, bleeding could be reduced.[25]

In 1997, Johnson showed a linear correlation between the inferior caval venous pressure and blood loss during liver surgery.[11] In 1998, Jones et al. reported a prospective study examining 100 patients undergoing liver resection.[9] Blood loss was significantly lower in patients with a CVP less than 5 mmHg compared to those with a CVP in excess of 5 mmHg (200 mL vs 1000 mL). In a retrospective study of almost 500 patients, Melendez reported a median blood loss of less than 700 mL during liver resection surgery managed with the LCVP technique.[5] Several studies have subsequently evaluated the LCVP anaesthetic technique in combination with different surgical inflow and outflow controls.[12,13,27]
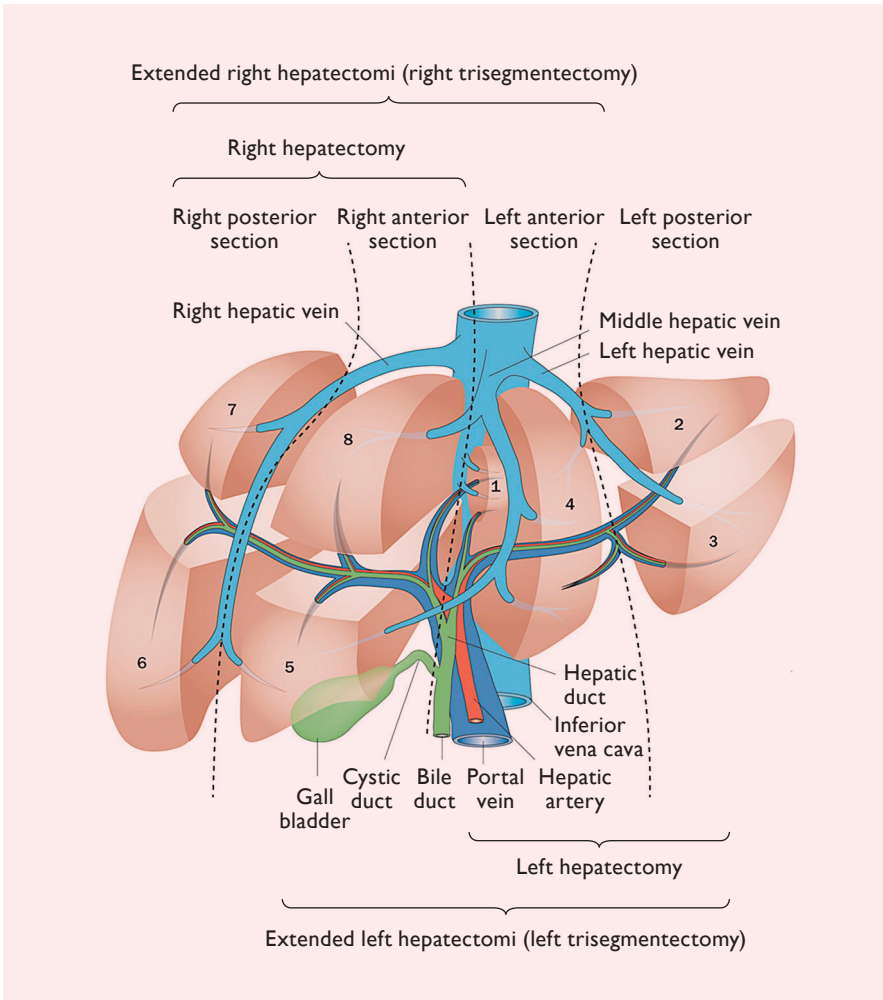
Figure 4. Segmental liver anatomy and hepatic segments during liver resection.[18]
Figure adapted with permission from the publisher (UpToDate).

The low CVP anaesthetic technique

Prior to the resection phase, CVP is actively lowered to less than 5 mmHg,[5,9] while simultaneously maintaining a diuresis of over 25 mL/h, a systolic blood pressure over 90 mmHg and a minimum haemoglobin value of 7–10 g/dL depending on the patient's clinical condition.[5] To achieve the desired CVP goal, fluid restriction together with interventions such as diuretics, vasodilators (nitroglycerine),[10] epidural anaesthesia/ analgesia,[28] alteration in patient position[5,10,29] and phlebotomy[30] are used in different combinations.

Avoidance of PEEP has also been recommended as a part of the LCVP concept since PEEP is thought to increase intra-thoracic pressure, which in turn may be transmitted to the central and hepatic veins.[21]

Conflicting recommendations regarding alterations in patient position have been proposed to decrease CVP and hepatic venous pressures. Jones[9] and Soonawalla[29] have recommended head up tilt whereas Johnson has recommended head down tilt,[11] and Rees the horizontal position.[28]

Although several observational studies have found a correlation with CVP and blood loss,[5,28,31] only one randomized controlled study has demonstrated a reduction in blood loss in liver resection surgery with the LCVP anaesthetic technique.[10]

Other interventions to reduce the intrahepatic pressure and blood loss

Vasopressin acts on V1 receptors in the mesenteric circulation causing an elevated splanchnic arterial resistance and a reduction in the portal venous blood flow. It is used for treatment of patients with portal hypertension and vasopressin has been demonstrated to reduce the portal pressure and blood loss from oesophageal varices in this patient group.[32] In patients with portal hypertension undergoing liver transplantation, vasopressin has been shown to significantly reduce portal venous pressure and flow without decreasing cardiac output or intestinal perfusion.[33] Vasopressin has also been shown to reduce blood loss after liver transplantation.[34] Terlipressin, a synthetic analogue of vasopressin, has been shown to reduce blood loss and the incidence of acute kidney injury after liver transplantation.[35,36]

In liver resection surgery, where the majority of the patients have a normal portal pressure, vasopressin treatment has not been included in the LCVP anaesthetic technique where the main purpose is to lower the CVP and the hepatic venous pressures. Whether vasopressin can be used to lower portal and venous pressures in this group of patients has not been investigated. However, in an animal study, vasopressin has been shown to improve outcome in blunt liver trauma.[17,37,38]

Liver resection surgery and the kidney

Although several liver centres practice the LCVP technique, its application is not universal,[17] and concerns have been raised about possible postoperative morbidity arising from hypo-perfusion of abdominal organs, especially the kidney.[14] The incidence of postoperative renal failure after liver resection surgery varies between studies.[5,10,39]

Goal directed therapy with low CVP during liver surgery

At Sahlgrenska University Hospital, Gothenburg, the first liver resection was performed in 1967. Today, close to 100 liver resections are performed annually. Before the introduction of the LCVP technique in 2011, the average blood loss was high, at 2–2.5 litres. Patients were managed with conventional haemodynamic targets, a liberal fluid regime and without cardiac output monitoring.

Based on our own studies,[40,41] other published clinical observations/key studies[5,10] and after thorough consultation with our surgical colleagues, we introduced a new haemodynamic strategy for liver resection surgery in 2011. The main aim was to reduce blood loss during surgery. The new management strategy, named the goal directed therapy with low CVP anaesthetic technique (GDT/LCVP), with goal directed therapy for the cardiovascular, respiratory, renal and coagulation systems, was implemented to achieve the above stated goal without increasing postoperative morbidity. Haemodynamic goals were a mean arterial pressure over 65 mmHg (in patients without cardiac disease), a cardiac index over 2.5 L/min/m^2 and a diuresis over 0.5 mL/kg/h, in addition to the aim of reducing CVP to 5 mmHg or below, or lowering the baseline value by 1/3, prior to the resection phase. Guidelines for crystalloid/colloid volume resuscitation, vasoactive and inotropic agents, ventilator settings, diuretics and haemostatic agents were recommended to achieve these goals.

Aims

In patients undergoing liver resection surgery, the aims were:

- To assess the relationship between central-, hepatic- and portal venous pressures (CVP, HVP and PVP) in the horizontal, head up and head down position. To determine if CVP reflects the actual pressure in the liver vascular bed when body position is changed (Study I).

- To evaluate the effect of PEEP on hepatic and systemic haemodynamics (Study I).

- To study the effect of nitroglycerine on hepatic- and portal pressures in relation to CVP and cardiac output in the horizontal and head down position (Study II).

- To investigate the effect of vasopressin on central-, hepatic- and portal venous pressures and to evaluate vasopressin-induced changes in splanchnic and hepato-splanchnic blood flow and systemic haemodynamics (Study III).

- To compare the perioperative outcome for two cohorts of patients (2010/2012) undergoing liver resection surgery, before and after the introduction of goal directed therapy with low CVP (Study IV).

Patients and Methods

Ethical approval

The Gothenburg Regional Ethical Review Board approved the protocols. In Studies I–III, written informed consent was obtained during preoperative evaluation, before enrolment in the studies. The nature of the studies and the risks involved were presented both orally and in written form. In Study IV, patient consent was not deemed necessary due the retrospective nature of this study.

Patients

Studies I–III: Patients undergoing liver resection due to primary liver cancer, gallbladder cancer, cholangiocarcinoma or liver metastases were recruited in Studies I (10 patients), II (13 patients) and III (12 patients).

Study IV: Patients undergoing open liver resection due to a metastatic malignancy were studied. Data from 39 patients in a cohort from 2010 (liberal group) and 41 patients in a cohort from 2012 (GDT/LCVP) were analysed and compared.

Anaesthetic technique

Patients on β-blocking agents prior to surgery received their prescribed dose preoperatively. Anaesthesia was induced with an intravenous bolus of sodium pentothal 3–5 mg/kg (Studies I and II) or propofol 1–2 mg/kg (Studies III–IV), together with fentanyl 2–3 μg/kg. Rocuronium 0.6 mg/kg was used to facilitate tracheal intubation. Anaesthesia was maintained with isoflurane (Studies I–II) or sevoflurane (Study III) at a minimum alveolar concentration (MAC) of 1.0 delivered in an O_2/air mixture during the experimental procedure. In Study IV anaesthesia was maintained with sevoflurane in an O_2/air mixture together with intermittent fentanyl 1–2 μg/kg or a remifentanil, target-controlled infusion (3–8 ng/mL). An epidural catheter was inserted preoperatively in all patients and was activated postoperatively except in Study IV in the 2012 (GDT/LCVP) cohort when the epidural analgesia/anaesthesia was activated preoperatively at the discretion of the anaesthetist using "Breivik's mixture" (bupivacaine (1 mg/mL), fentanyl (2 μg/mL) and adrenaline (2 μg/mL).

Monitoring and measurements

Pulse oximetry, spirometry, capnography, ECG, mean arterial pressure (MAP) and CVP were continuously measured and stored. The pressure transducers used for MAP and CVP (CODAN pvb Critical Care GmbH, Forstinning, German) were zeroed and

positioned at the right atrial level (the phlebostatic axis) using a laser spirit level.

In Studies I and II, cardiac output was measured using a pulmonary artery catheter (Swan-Ganz CCOmbo Pulmonary Artery Catheter, Edwards Life Sciences LLC, Irwine, CA, USA), with bolus thermodilution (10 mL iced saline boluses in triplicate). Pulmonary artery pressure recordings confirmed the correct position of the catheter. MAP was measured via a cannula in the radial artery and CVP was monitored via the proximal port of the pulmonary artery catheter. When altering patient position, the pressure transducers were readjusted to the right atrial level.

In Studies III and IV, cardiac output was measured using a PiCCO catheter (PULSION Medical Systems, Feldkirchen, Germany) inserted in the femoral artery and calibrated by bolus thermodilution (20 mL iced saline boluses in triplicate via the tri-lumen central venous catheter). MAP was measured via the femoral artery catheter and CVP via the central venous catheter inserted in the right internal jugular vein. Stroke volume (SV) and systemic vascular resistance (SVR) were subsequently calculated (Study III).

Measurement of hepato-splanchnic pressures

The catheters used for measurement of hepatic and portal venous pressures in Studies I–III were inserted surgically. The catheter tip for measurement of HVP was positioned in the hepatic vein outflow region, 2–3 cm from the inferior caval vein. The catheter tip for measurement of PVP was positioned in the portal vein.

To improve accuracy during alterations in patient position in Studies I and II, PVP and HVP recordings were made using tip manometer catheters (Millar Instruments Inc. Houston, USA). These catheters have a miniaturised transducer located in the catheter tip (Figure 5). In comparison to fluid filled catheters these have the advantage of measuring absolute pressure. The tip manometer contains a piezoelectric element and the pressure signal is converted to an electrical signal in the associated hardware. In order to detect zero drift during the experimental procedure, the tip manometers were zeroed by immersion one cm below the surface of a body temperature saline bath before and after pressure measurements.

In Study III, single lumen fluid-filled central venous catheters (Arrow, 16 Ga, Int., Inc., Reading, PA, USA) were used, instead of tip manometry, as alterations of body position were not performed. This enabled concurrent blood gas analysis from the portal and hepatic veins. The pressure transducers (CODAN pvb Critical Care GmbH, Forstinning, Germany) were zeroed and positioned at the right atrial level using a laser spirit level.
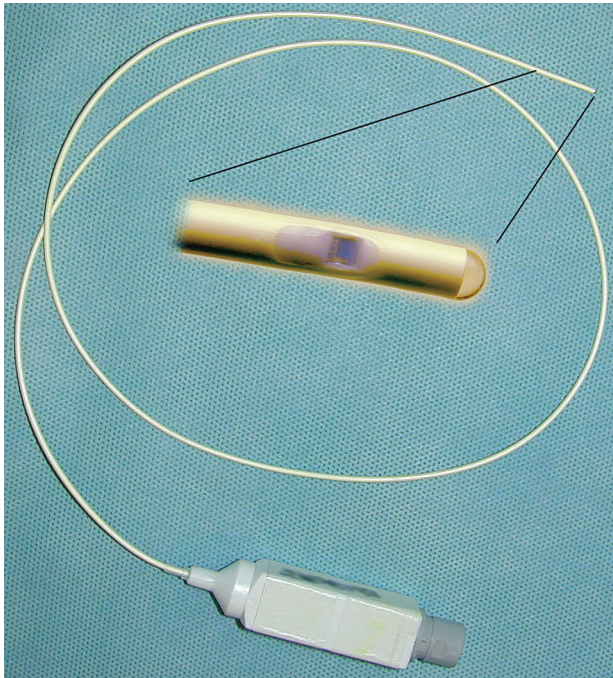
Figure 5. Tip pressure transducer (Millar MPC-500 70cm, 5F) was used to avoid calibration, damping and resonance phenomena, inherent in fluid filled catheters.

Calculation of hepato-splanchnic blood flow changes (Study III)

Portal and hepatic-splanchnic blood flow changes during vasopressin infusion were estimated using Fick's principle during steady state conditions, assuming unchanged splanchnic organ oxygen consumption during the intervention. Changes (Δ) in portal venous (Qpv) blood flow and changes in total hepato-splanchnic blood flow (Qhspl) were calculated from the arterial and portal blood gases before (pre) and during (post) vasopressin infusion, using the following equations derived from Fick´s equation:[42]

1) $\Delta Qpv\ (Qpv\%) = Qpv^{(post)}/Qpv^{(pre)} = \{SaO_2^{(pre)}-SpvO_2^{(pre)})/(SaO_2^{(post)}-SpvO_2^{(post)}\} \times 100$

2) $\Delta Qhspl\ (Qhspl\%) = Qhspl^{(post)}/Qhspl^{(pre)} = \{SaO_2^{(pre)}-ShvO_2^{(pre)})/(SaO_2^{(post)}-ShvO_2^{(post)}\} \times 100$

SaO_2 is arterial oxygen saturation, $SpvO_2$ is portal venous oxygen saturation and $ShvO_2$ is hepatic venous oxygen saturation (Figure 6).
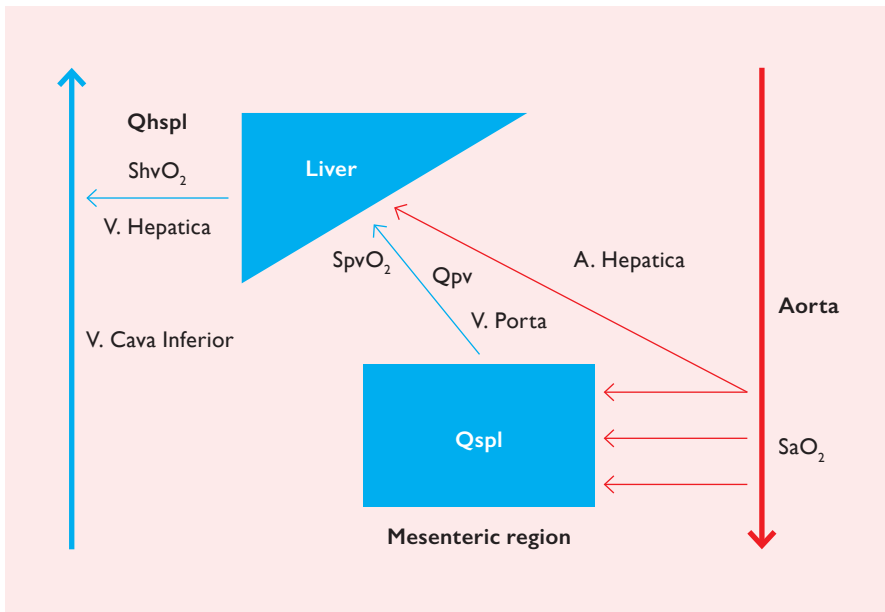
Figure 6. Schematic illustration of the hepato-splanchnic circulation.

Experimental procedure, Studies I–III

The investigations were performed after the dissection phase, prior to the liver resection phase. Steady state conditions were defined as stable heart rate, arterial and venous pressures during a period of maintained anaesthesia depth without surgical stimulation. Measurements were made five minutes after stable values were established.

Effect of body position and PEEP on portal, hepatic and central venous pressure (Study I)

The effect of body position and two PEEP levels (5 and 10 cm H_2O) on hepatic, portal and central venous pressures as well as systemic haemodynamics, were studied in sequence, with the patients in (1) horizontal position, (2) 10° head-down and (3) 10° head-up position (Figure 7).

Figure 7. The experimental protocol for Study I. The red arrows indicate measuring points for pressure recordings of portal-, hepatic- and central- venous pressures, mean arterial pressure and measurements of cardiac output with thermodilution.

Effect of nitroglycerine and patient position on hepatic pressure and systemic haemodynamics (Study II)

The effect of nitroglycerine (NG) infusion and patient position on hepatic, portal, and central venous pressures as well as systemic haemodynamics were studied in a sequence, with measurements made at: (1) baseline in horizontal position (BL), (2) in horizontal position with NG infusion (1 mg/mL) lowering MAP to 60 mmHg, (3) with maintained NG infusion and the patient positioned 10° head down and finally (4) after termination of NG infusion with maintained, head down tilt position (-NG) (Figure 8).
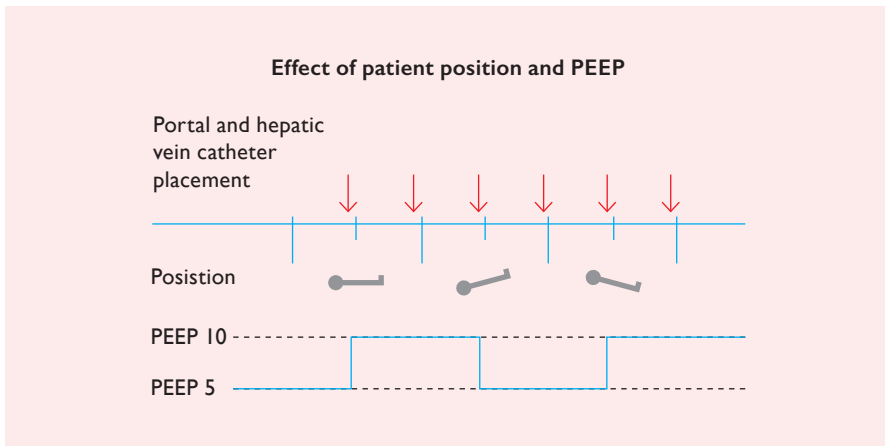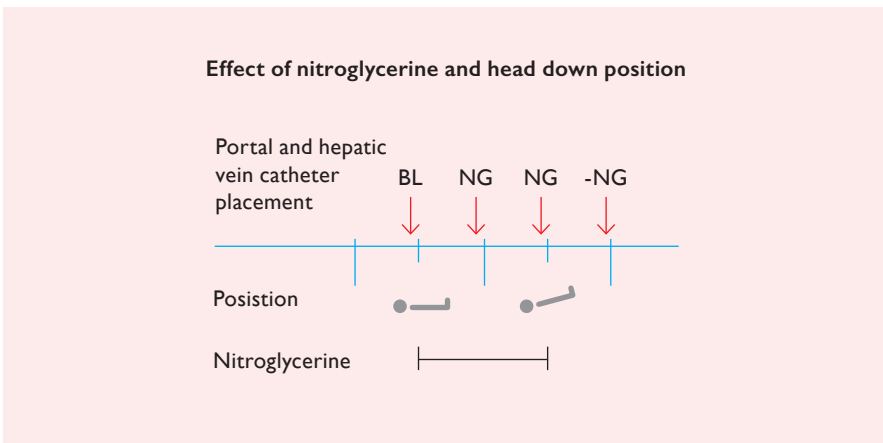

Figure 8. The experimental protocol for Study II. The red arrows indicating measuring points for pressure recordings of portal-, hepatic- and central- venous pressures, mean arterial pressure and measurements of cardiac output with thermodilution. BL, baseline; NG, nitroglycerine; -NG, no nitroglycerine.

Effect of vasopressin on regional and systemic haemodynamics

The effects of vasopressin on hepatic, portal, central venous pressures and systemic and hepato-splanchnic haemodynamics were analysed at two doses of vasopressin: 2.4 and 4.8 U/h, after a steady state period of 10 minutes followed by two 15 minute control periods, C1 and C2 (Figure 9). Each dose was administered for 15 minutes. At each measuring point blood samples from the arterial, central, portal and hepatic venous catheters were obtained for calculation of changes in portal and hepato-splanchnic blood flow, see figure 6. For evaluation of splanchnic or renal hypoperfusion, blood samples for lactate were obtained and the arterial-portal venous lactate gradient was calculated. Serum creatinine was analysed 48 hours and seven days after surgery.

Effect of vasopressin on hepatic pressures and flow

Portal and hepatic vein catheter placement

| C1 | C2 | 2.4 | 4.8 |

| 0 | 15 | 30 | 45 |

VP 2.4 U/h   VP 4.8 U/h

Measuring points
- *Pressure recording: PVP, HVP, CVP, MAP*
- *Thermodilution PICCO: CO, SVR*
- *Blood samples: saturation, s-lactate (arterial, central, portal, hepatic)*
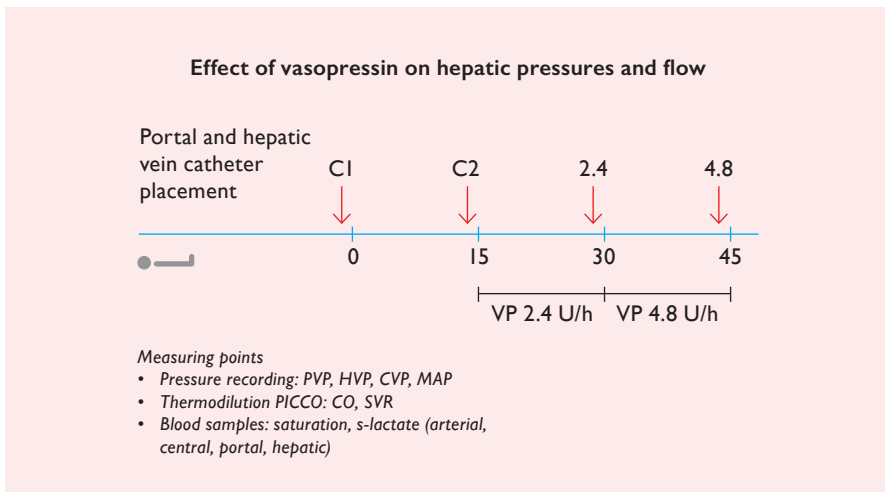
Figure 9. Schematic representation of the experimental procedure for Study III. The red arrows indicate pressure recordings (PVP, HVP, CVP, MAP), cardiac output measurement by thermodilution and simultaneous determination of oxygen saturation and serum lactate (arterial, central, portal, hepatic). C1, control period 1; C2, control period 2; VP, vasopressin; U/h, units/hour.

Change of haemodynamic management during liver surgery at Sahlgrenska University Hospital

The first cohort comprised patients (n=39) subjected to open liver resection for metastatic malignancy in 2010. These patients were managed with conventional haemodynamic targets, MAP over 70 mmHg, liberal fluid use and no cardiac output monitoring. CVP was monitored but was not intentionally reduced. Intra-operative neuraxial analgesia/anaesthesia was rarely used. The second cohort (n=41) included patients undergoing open liver resection surgery for metastatic malignancy during 2012. These were managed with the GDT/LCVP anaesthetic technique. During parenchymal resection, CVP was lowered to 5 mmHg or below, or reduced by 1/3 of its initial value, by fluid restriction, use of diuretics, inotropic and vasoactive agents. Cardiac index was maintained at or above 2.5 L/min/m², MAP at or above 65 mmHg and diuresis at or above 0.5 mL/kg/h. Epidural analgesia/anaesthesia was activated at the discretion of the anaesthetist. Normovolemic haemodilution was permitted down to a haemoglobin level of 8 g/dL in patients without cardiopulmonary compromise, otherwise with a lower limit of 10–12 g/dL. Blood loss was substituted with colloids and packed red blood cells. A crystalloid solution was infused at a rate of 50–80 mL/h to maintain an adequate diuresis. No change of position was used. Lactate from blood samples were analysed and serum creatinine was obtained 48 hours and seven days postoperatively.

Data collection

In Studies I–III patient data were collected at 100 Hz to a dedicated software program (S/5 Collect 4, GE Healthcare, Helsinki, Finland). Portal and hepatic venous pressures were sampled from the tip-manometers to an A/D converter (MP100 BIOPAC Systems, Inc) at 100 Hz, which in Study III was changed to 20 Hz, and transferred to a dedicated software program (AcqKnowledge software BIOPAC Systems, Inc) for analysis.

In Study IV data were collected from each patient's medical and anaesthetic perioperative records.

Statistical analysis

Studies I–III were prospective, while Study IV was a retrospective analysis. The prospective studies were preceded by power analyses to ensure satisfactory statistical power. Power (or β) is the probability of not detecting an existing difference, as opposed to p (or α), which is the probability of incorrectly identifying a difference as real, which in reality is due to random variation.

To analyse power, an estimation of dispersion must be made. We considered dispersion in data from previous studies and entered these together with the detection limit

for the variables of interest into a web-based statistical tool (www.quantitativeskills.com). The output from this tool is the number of patients that need to be included in the study to detect differences over the detection limit with a certain power.

To compensate for inadvertent data loss, additional patients were included in each study. Data are presented as means and standard deviation, except for Study IV where a skewed distribution was described by median and quartile range.

Comparison of means in Studies I, II and III were performed using analysis of variance for repeated measurements (ANOVA). The two within-variables present in Studies I and II, were addressed by a two-way within subjects ANOVA[43], while in Study III a one-way ANOVA was used.

If a significant ANOVA was present, the analysis was continued by paired t-tests. In order to avoid mass-significance problems due to multiple comparisons a Hochberg correction was applied to the t-tests.[44] In Study III if a significant overall ANOVA was present, the analysis was continued with paired t-tests between baseline (mean of C1 and C2) and vasopressin infusion values.

In Study I, co-variation between variables was addressed by correlation analysis. In Study IV, the retrospective analysis, data were evaluated by Mann-Whitney U tests for data not considered normally distributed, and by paired t-tests for data with normal distribution. Proportions were analysed by two-proportion z-tests in this study.

The prospective studies were designed for a statistical power of 0.8 and in all studies a p-value of <0.05 was considered significant.

Results

Patients

A total number of 35 patients were primarily included in Studies I-III. Data are presented in table 1. In Study II, two patients were excluded due to a faulty tip-manometer catheter. For details relating to demographic data and diagnosis, see Papers I–III.

Table 1.
Demografics Paper I, II and III.

Paper	pat (no)	male/ female	age	prim/sec	HT	CM
I	10	6/4	67 ± 14	3/7	4	4
II	13	5/8	64 ± 10	2/11	7	7
III	12	6/6	67 ± 8	3/9	4	3

pat, patients; no, number; prim/sec, primary/secondary livercancer; HT, hypertension; CM, cardiac medication

In Study IV, 80 patients were subjected to a retrospective analysis. 39 patients underwent surgery in 2010 and 41 patients in 2012 (Table 6).

There were no differences between groups with respect to age, American Society of Anaesthesia-score (ASA), gender, preoperative serum creatinine, haemoglobin, duration of anaesthesia and surgery, duration of hospital stay, time spent at the postoperative anaesthesia care unit, resection size or incidence of postoperative infections. There were no perioperative deaths up until hospital discharge.

Effects of patient tilt

A 10° head-down tilt resulted in an increase in CVP without changes in hepatic venous or portal pressures, during anaesthesia prior to liver resection (Study I) (Figures 10, 11 and Table 2) both with and without a nitroglycerine infusion (Study II) (Figure 12 and Table 3). Tilting 10° head-up caused a substantial decrease in CVP but with no effect on hepatic venous pressures (Study I) (Figure 10, 11 and Table 2). MAP increased with head-down, and decreased with head-up tilt respectively, while changes in position caused only minor changes in cardiac output (Study I).

Effects of PEEP

Increasing PEEP from 5 to 10 cm H_2O, led to small increases in both CVP and hepatic venous pressures in the horizontal, head-up and head-down position. Cardiac output decreased (Study I) (Figure 10 and Table 2).

Table 2.
Mean values and standard deviation for studied parameters in the 10 patients included in Study 1 during changes in PEEP and body position.

	Baseline		Head down tilt		Head up tilt		ANOVA		
	Peep 5	Peep 10	Peep 5	Peep 10	Peep 5	Peep 10	Position	PEEP	P*P
MAP (mmHg)	72 ± 8	68 ± 8	76 ± 8*	74 ± 7*	63 ± 7*	61 ± 10*	0.001	0.03	0.75
CO (L/min)	6.5 ± 2.2	6.3 ± 2.1†	7.1 ± 2.4	6.8 ± 2.5†	6.7 ± 2.1	6.2 ± 1.6†	0.054	0.001	0.32
CVP (mmHg)	11 ± 3	12 ± 3§	15 ± 3***	16 ± 3***§	6 ± 4***	7 ± 3***§	0.001	0.001	0.11
HVP (mmHg)	11 ± 3	12 ± 4§	12 ± 4*	13 ± 4*	11 ± 4	12 ± 4§	0.01	0.0002	0.02
PVP (mmHg)	14 ± 3	14 ± 3	14 ± 3	15 ± 3	14 ± 2	15 ± 3†	0.52	0.05	0.43

*P < 0.05 vs baseline; **P < 0.01 vs baseline; ***P < 0.001 vs baseline
†P < 0.05 vs PEEP 5; §P < 0.001 vs PEEP 5
MAP, mean arterial pressure; CO, cardiac output; CVP, central venous pressure; HVP, hepatic venous pressure;
PVP, portal venous pressure P*P interaction between position and PEEP; ANOVA, analysis of variance
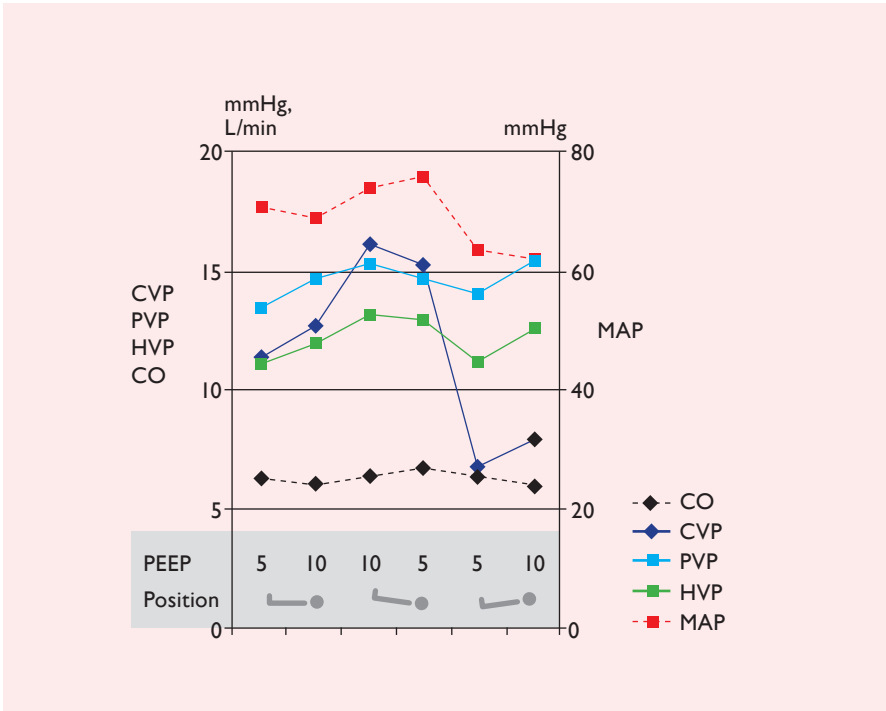
Figure 10. Changes in central-, hepatic- and portal venous pressures (CVP, HVP and PVP), mean arterial pressure (MAP) and cardiac output (CO) during alterations in patient position and PEEP.
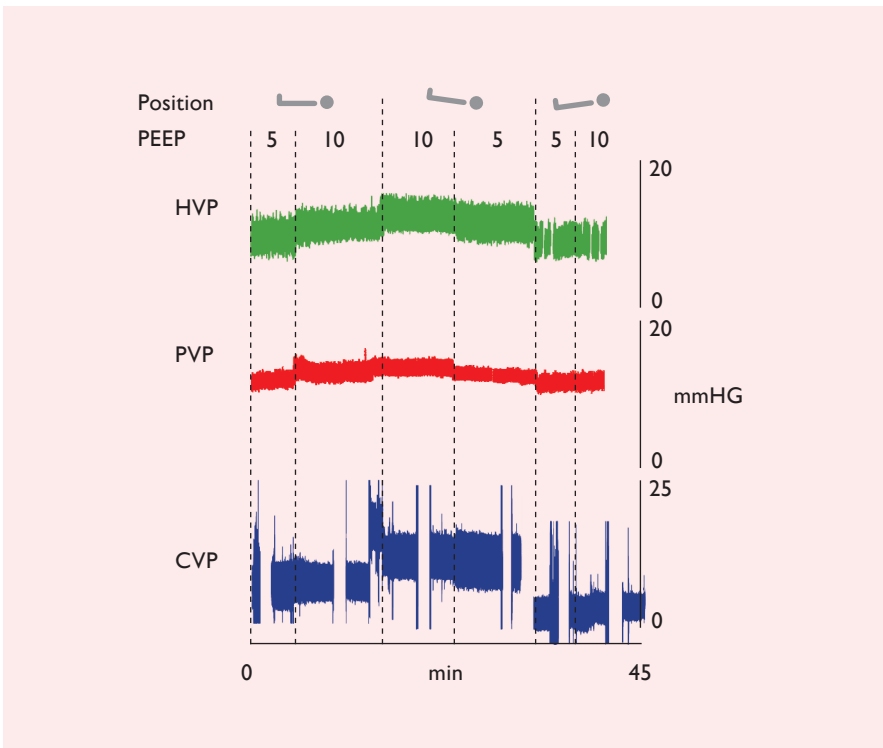
Figure 11. Measurements from a typical experiment. Changes in body position with head down tilt resulted in marked increase in CVP, while HVP and PVP remained largely stable. Tilting the patient with head up resulted in a decrease in CVP without any clear changes in HVP and PVP. An increase in PEEP from 5 to 10 cmH$_2$O, irrespective of position increased HVP, PVP and CVP with approximately 1 mmHg.

Effects of nitroglycerine

In the supine posistion, a nitroglycerine (1 mg/mL) infusion titrated to a MAP of 60 mmHg caused parallel decreases of CVP, HVP and PVP. Nitroglycerine infusion decreased MAP and cardiac output in parallel with the reduction in venous pressures. Adding head-down tilt increased HVP and PVP, although not to baseline values. CVP increased to values higher than baseline. The head-down tilt increased both MAP and cardiac output, although only cardiac output returned to baseline values. Termination of the nitroglycerine infusion with the patients in a 10° head down tilt caused a further increase of all venous pressures and MAP (Study II) (Figures 12, 13 and Table 3).

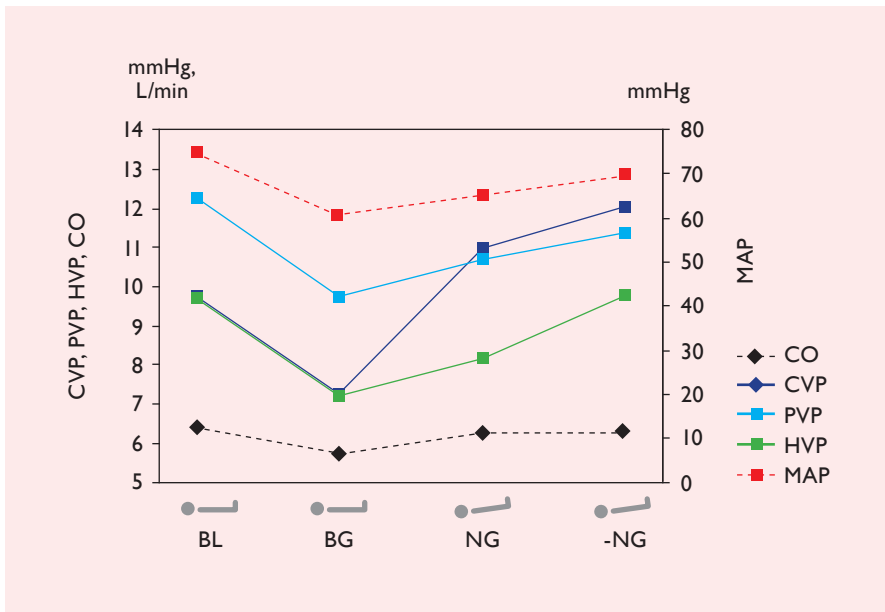**Figure 12.** Changes in central venous pressure (CVP), portal venous pressures (PVP), hepatic venous pressure (HVP), mean arterial pressure (MAP) and cardiac output (CO) during nitroglycerine (NG) infusion at baseline and at head down tilt.
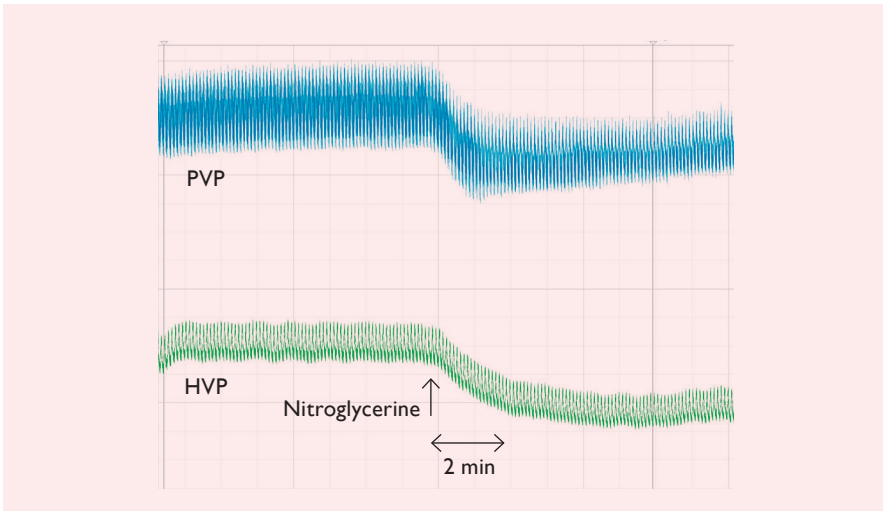
Figure 13. Changes of hepatic- and portal venous pressures (HVP and PVP) from tip-manometer recordings in one experiment where commencement of the nitroglycerine infusion resulted in marked decreases in these pressures.

Table 3.
Mean values and standard deviation for studied parameters in the patients included in the study during nitroglycerine(NG) infusion at baseline and head down tilt.

	Baseline (BL)		Head down tilt (HD)		ANOVA		
	No NG	NG	NG	No NG	NG	Position	P*P
MAP (mmHg)	75 ± 4	60 ± 5***	65 ± 5#	70 ± 4 §§	<0.001	0.8	0.004
CO (L/min)	6.3 ± 1.1	5.8 ± 1.2*	6.3 ±1###	6.2 ± 1 ns	0.02	0.14	0.0055
CVP (mmHg)	9.8 ± 2	7.2 ± 2***	11 ± 2###	12 ± 2 §§§	<0.0001	<0.0001	0.005
HVP (mmHg)	9.7 ± 2	7.2 ± 2***	8.2 ± 2###	9.8 ± 2 §§	0.0001	0.35	0.03
PVP (mmHg)	12.3 ± 2	9.7 ± 3***	10.7 ± 3##	11.4 ± 3 §§	<0.001	0.96	0.03

*$p<0.05$ vs baseline; ***$p<0.001$ vs baseline
# $p<0.05$ vs NG baseline; ## $p<0.01$ vs NG baseline; ### $p<0.001$ vs NG baseline
§§ $p<0.01$ vs NG HD tilt; §§§ $p<0.001$ vs NG HD tilt
MAP, mean arterial pressure; CO, cardiac output; CVP, central venous pressure; HVP, hepatic venous pressure; PVP, portal venous pressure P*P interaction between position and NG; ANOVA, analysis of variance

Haemodynamic Management in Liver Surgery

Effects of vasopressin

In Study III, vasopressin at two infusion rates (2.4 U/h and 4.8 U/h), led to small increases in CVP and HPV, without changes in PVP. At an infusion rate of 2.4 U/h vasopressin did not affect the central haemodynamic variables, while at 4.8 U/h slight increases in MAP and CO were observed while SVR remained unchanged. Calculation of changes in portal and total hepato-splanchnic blood flow using the modified Fick equation showed that portal blood flow decreased by $26 \pm 15\%$ at an infusion rate of 2.4 U/h and further decreased by $37 \pm 15 \%$ at the higher infusion rate, 4.8 U/h. The total hepato-splanchnic blood flow decreased by $9 \pm 8\%$ and $15 \pm 7\%$ at the two infusion rates, respectively (Tables 4, 5 and Figures 14, 15).

In Study III, we analysed arterial, central venous, portal venous and hepatic venous lactate concentrations. None of these were affected by the vasopressin infusions. The arterial-portal vein lactate gradient was also unaffected by vasopressin infusion (Table 5). Serum creatinine was 76 ± 16 μmol/L preoperatively, 78 ± 24 μmol/L after 48 hours and 65 ± 12 μmol/L after seven days ($p<0.01$ vs preoperative value).

Table 4.
Effects of vasopressin on systemic haemodynamics.

	C1	C2	AVP 2.4 U/h	AVP 4.8 U/h	ANOVA p-value
CO (l/min)	5.2 ± 0.92	5.3 ± 0.86	5.2 ± 0.76	5.5 ± 0.78*	0.02
SV (ml)	69 ± 13	69 ± 13	72 ± 11	74 ± 10*§	0.02
HR (beats/min)	76 ± 12	76 ± 12	77 ± 11	77 ± 10	0.89
MAP (mmHg)	69 ± 10	68 ± 10	72 ± 9	74 ± 10*	0.04
SVR (dynes x s x cm-5)	1083 ± 411	1063 ± 417	1150 ± 376	1107 ± 355	0.09
CVP (mmHg)	6.6 ± 1.9	6.6 ± 1.9	6.8 ± 2.0	7.2 ± 2**§	0.02

Values are presented as means ± SD
*p<0.05; **p<0.01; ***p<0.001 vs predrug control
§ p<0.05 vs AVP 2.4 U/h
AVP, vasopressin; C1, C2 pre-drug control periods; CO, cardiac output; SV, stroke volume
HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure
SVR, systemic vascular resistance

Table 5.
Effects of vasopressin on hepato-splanchnic and portal haemodynamics and lactate fluxes.

	C1	C2	AVP 2.4 U/h	AVP 4.8 U/h	ANOVA p-value
Portal venous pressure (mmHg)	10.5 ± 2.6	10.4 ± 2.6	10.3 ± 2.4	10.3 ± 2.5	0.5
Hepatic venous pressure (mmHg)	6.7 ± 1.7	6.7 ± 1.7	7.1 ± 1.7*	7.3 ± 1.9**	0.01
Portal-hepatic pressure gradient (mmHg)	3.8 ± 1.1	3.7 ± 1.1	3.2 ± 1*	3.0 ± 0.8***	0.003
Arterial oxygen saturation (%)	98.2 ± 0,5	98.2 ± 0.5	98.2 ± 0.5	98.0 ± 0.6	0.1
Central venous saturation (%)	78.9 ± 4.5	78.6 ± 4.2	79.0 ± 4.8	81.3 ± 4.3	0.05
Portal venous saturation (%)	86.6 ± 5.6	86.0 ± 6.2	82.0 ± 7.6 *	79.3 ± 7.6 ***§	0.002
Hepatic venous saturation (%)	76.3 ± 7.1	77.5 ± 6.5	73.6 ± 7.9 **	72.3 ± 9.7 **	0.015
Δ portal blood flow	1	1.0 ± 0.1	0.73 ± 0.15***	0.63 ± 0.15 ***§	<0.001
Δ hepato-splanchnic blood flow	1	1.0 ± 0.03	0.91 ± 0.08**	0.86 ± 0.07 **	0.004
Arterial lactate (mmol/l)	2.1 ± 1.2	2.1 ± 1.3	1.9 ± 1.19	2.1 ± 1.2	0.13
Central venous lactate (mmol/l)	2.1 ± 1.1	2.1 ± 1.2	2.0 ± 1.1	2.1 ± 1.1	0.4
Portal venous lactate (mmol/l)	1.9 ± 1.1	1.8 ± 1.1	1.9 ± 1.0	1.9 ± 1.1	0.75
Hepatic venous lactate (mmol/l)	1.8 ± 1.3	1.8 ± 1.3	1.7 ± 1.2	1.8 ± 1.1	0.43
Arterial portal venous lactate gradient	0.15 ± 0.27	0.24 ± 0.34	0.08 ± 0.23	0.16 ± 0.35	0.39

Values are presented as means ± SD
*p<0.05; **p<0.01; ***p<0.001 vs predrug control
§ p<0.05 vs AVP 2.4 U/h
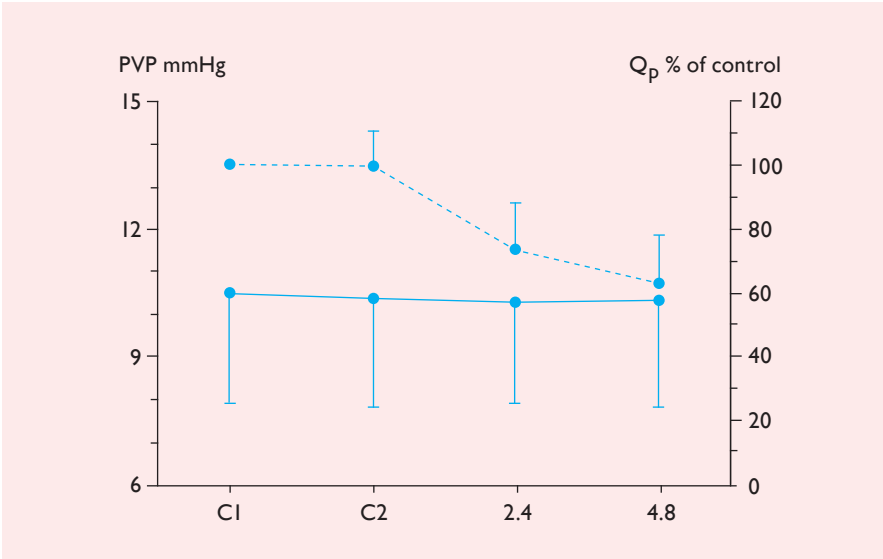*AVP, vasopressin; C1, C2 pre-drug control periods*

Figure 14. The effect of vasopressin 2.4 U/h and 4.8 U/h on hepatic venous pressure (HVP), indicated by the continuous line and changes in hepato-splanchnic blood flow (Q_{hspl}), indicated by the dotted line. C, control; 2.4, vasopressin 2.4U/h; 4.8, vasopressin 4.8 U/h.
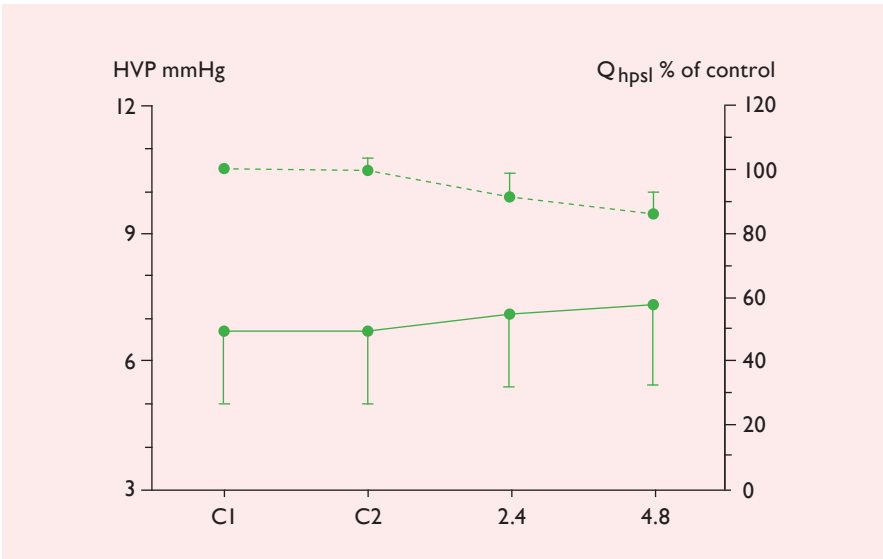

Figure 15. The effect of vasopressin 2.4 U/h and 4.8 U/h on portal venous pressure (PVP), indicated by the continuous line and changes in portal blood flow (Q_p), indicated by the dotted line. C, control; 2.4, vasopressin 2.4U/h; 4.8, vasopressin 4.8 U/h.

Effects of goal-directed management

After the introduction of the goal-directed management in liver surgery, blood loss was reduced from a median of 2320 mL interquartile range [1400, 3000] to 1406 mL [800, 2450] (Figure 16). As a corollary, intraoperative transfusions showed a tendency to decrease and intraoperative administration of colloids decreased (p< 0.001). The GDT/LCVP group received a larger volume of crystalloid fluids postoperatively (Table 6). We found increases in the intraoperative use of noradrenaline, dopamine and nitroglycerine infusions in the GDT/LCVP group vs liberal group and the use of intraoperative epidural analgesia/anaesthesia increased (p < 0.001) (Figure 18).

There were no significant differences in baseline CVP. The average CVP was significantly lower, 7.0 mmHg [6–9.8] in 2012 (GDT/LCVP) compared to 9.5 mmHg [8–12] (p < 0.03) in 2010 (liberal), see figure 17. A CVP ≤ 5 mmHg or a 1/3 reduction was reached in 22/39 patients (56%) in 2010 unintentionally vs 36/41 patients (87%) in 2012 in accordance with the GDT/LCVP concept.

Lactate, as a marker of organ hypoperfusion, did not differ postoperatively between the cohorts. There were no significant differences in perioperative diuresis or in serum creatinine between the cohorts. One patient from 2010 and five patients from 2012 had an increase in serum creatinine > 26 mmol/L after 48 hours (n.s.), thus meeting the criteria for AKI.[45] Serum creatinine in these patients normalised before discharge (Table 7).
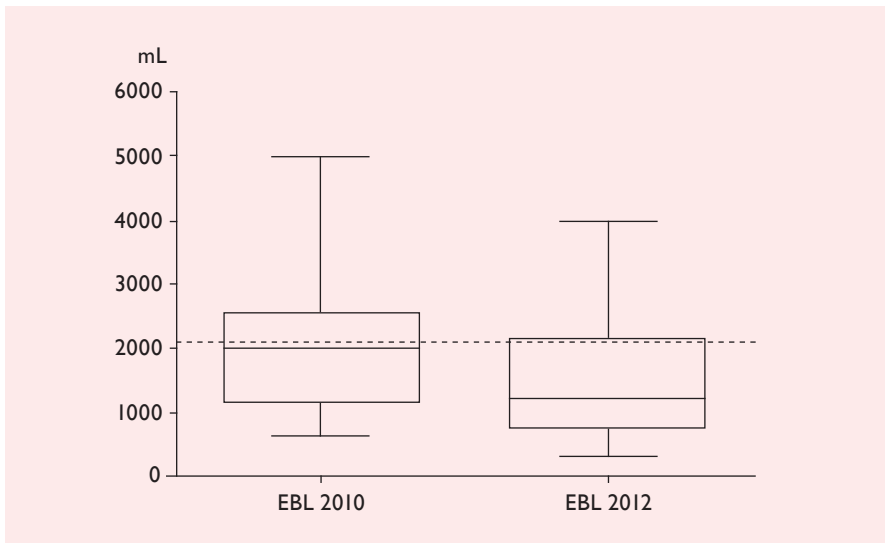
Figure 16. Estimated blood loss (EBL) in liver resection surgery 2010 and 2012, outliers excluded. Bold lines represent medians, boxes interquartile ranges. Mean blood loss 2010, when outliers are excluded, was 2114 mL. This is indicated by the dotted line.
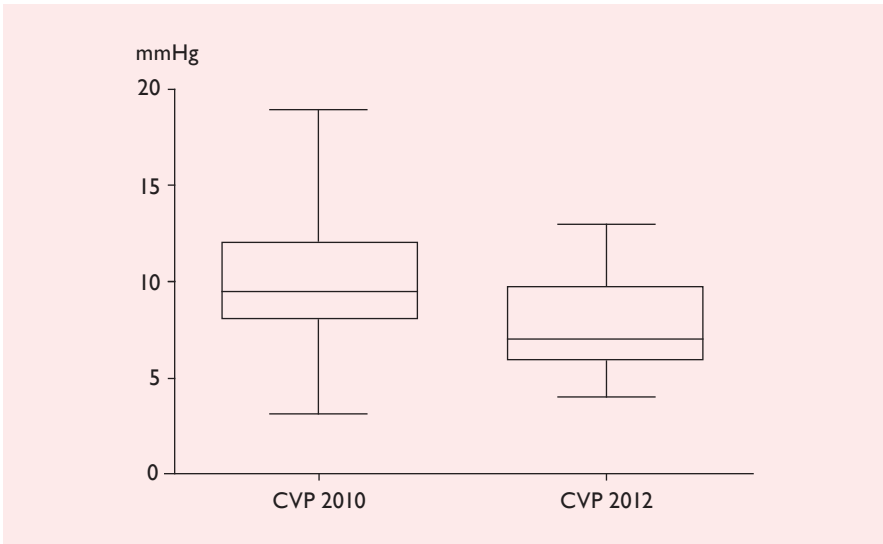
Figure 17. Median intra-operative values of CVP during liver resections in 2010 and 2012, respective, boxes show interquartile ranges (p = 0.0034).

Figure 18. Differences in vasoactive medication and use of epidural anaesthesia/analgesia between control group (year 2010, dark bar) and the goal-directed therapy group (year 2012, light bar).

Table 6.
Patient Characteristic and Intraoperative data in Study IV.

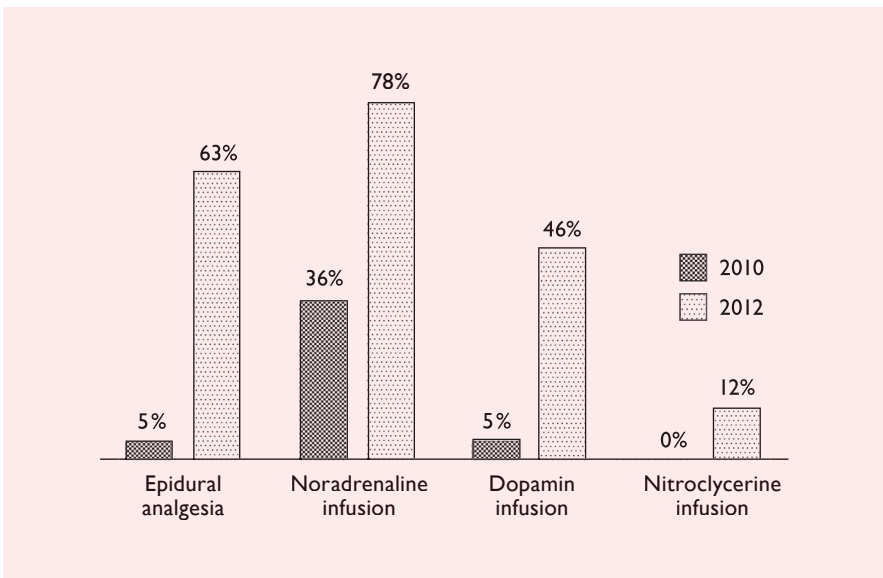|	Control (n = 39)	GDT (n = 41)	p-value
Age, years	60 [54-71]	64 [57-71]	NS
Minor resections	27	24	NS
Larger resections	12	17	NS
ASA	2 [1-2]	2 [2-2]	NS
Gender (male/female)	27/12	24/17	NS
Haemoglobin preop (g/dL)	11.5	11.8	NS
Creatinine preop (µmol/L)	77 ± 18	73 ± 18	NS
Bleeding (mL)	2320 [1400-3000]	1406 [800-2450]	0.008
Transfusions (units)	2 [0-4]	0 [0-2]	0.082
Colloids (mL)	1500 [1500-2000]	1000 [725-1500]	<0.001
Crystalloids (mL)	1800 [1500-2100]	1600 [1300-2225]	NS
Duration of anaesthesia, min	435 [328-503]	439 [339-518]	NS
Duration of surgery, min	313 [240-378]	326 [232-392]	NS
Noradrenaline infusion, n (%)	14 (36%)	32 (78%)	<0.001
Dopamine infusion, n (%)	2 (5%)	19 (46%)	<0.001
Nitroglycerine infusion, n (%)	0 (0%)	5 (12%)	<0.05
EDA activated, n (%)	2 (5%)	26 (63%)	<0.001
Urine output (mL)	655 ± 399	728 ± 410	NS
Urine output (mL/kg/h)	1.2 ± 0.6	1.4 ± 0.8	NS
Lactate baseline (mmol/L)	1.3 ± 0.6	1.3 ± 0.5	NS
Lactate maximal (mmol/L)	3.0 ± 1.4	3.5 ± 1.4	NS

Data are presented as median and interquartile range [IQR], as mean and standard deviation, ±SD, or as numbers (percentage). GDT, goal directed therapy; ASA, American Society of Anesthesiologists physical classification score; EDA, epidural analgesia/anaesthesia; NS, not significant.

Table 7.
Postoperative data from patients in Study IV.

	Control (n = 39)	GDT (n = 41)	p-value
Transfusions (units)	0 [0-1]	0 [0-0]	NS
Colloids (mL)	750 [500-1100]	500 [400-1000]	NS
Crystalloids (mL)	2200 [700-2600]	2600 [2000-3250]	0.02
Noradrenalin infusion, n (%)	4 (10%)	7 (17%)	NS
Dopamine infusion, n (%)	1 (3%)	2 (5%)	NS
Time in PACU*, hours	20 [18-22]	20 [18-22]	NS
Length of hospital stay, days	8 [7-11]	8 [7-9]	NS
Haemoglobin baseline (g/dL)	10.7 ± 1.2	10.6 ± 1.2	NS
Haemoglobin lowest (g/dL)	9.7 ± 1.1	9.8 ± 1.3	NS
Urine output/24 h (mL)	1681 ± 704	1868 ± 879	NS
Urine output (mL/kg/h)	1.1 ± 0,5	1.15 ±0.35	NS
Lactate maximal at PACU (mmol/L)	3.3 ± 1.4	3.5 ± 2.0	NS
Creatinine increase within 48 h (µmol/L)	3 ± 11	9 ±21	NS
Creatinine increase > 26 µmol/L, n (%)	1 (3%)	5 (12%)	NS
Postoperative infection, n	9 (23%)	8 (20%)	NS

Data are presented as median and interquartile range [IQR], as mean and standard deviation, ±SD, or as number (percentage). GDT, goal directed therapy; PACU, post-anesthesia care unit.

Discussion

Methodological considerations

Ethical issues

Patients were informed about the risks related to invasive monitoring. The interventions performed in Studies I–III prolonged total operation time by 1½-2 hours due to the time taken for surgical placement of the hepatic and portal venous catheters and performance of the experimental protocol. We did not experience any complications related to catheter insertion or the experimental procedure.

Intra-operative changes of body position

In previous studies examining the effects of changes in patient position on intra-operative haemorrhage, either 5–15° head-up[9,29] or 15° head-down[5,10] tilt has been suggested. In our study, we chose a head-up tilt of 10° rather than 15° in order to limit haemodynamic consequences in the form of inadequate cerebral perfusion. Likewise, a 10° instead of 15° head-down tilt was chosen to avoid possible adverse effects on cerebral circulation (congestion) with the head-down position.[46]

Venous pressure recordings

In the first two studies we investigated the effect of alterations in both patient position and the degree of positive end-expiratory pressure on venous pressures. The rationale behind patient tilt is that blood in the venous capacitance vessels is redistributed from the liver due to the gravitational effect, either into the lower part of the body and the legs (head-up) or into the thoracic cavity, the lungs and the heart (head-down). The liver on the other hand, is close to the pressure indifference point, i.e. the axis around which the operating table moves during tilting.

The use of a fluid-filled central venous catheter, commonly situated in the superior caval vein, to measure central venous pressure with simultaneous patient tilt can be problematic. Pressure measured by a central venous catheter corresponds to the level of a transducer that is placed at the level of the right atrium. When the relationship between the transducer and the level of the right atrium changes, such as during patient tilt, the transducer level must be repositioned. If the catheter tip is situated in the superior caval vein, the vertical distance between the catheter tip and hepatic veins changes upon patient tilt. This changes the relationship between CVP and hepatic venous pressure in a way that may be difficult to predict. The uncertainty regarding the effects of intra-operative patient tilt on hepatic venous pressure is reflected in the

literature, as different authors recommend either head-up,[9,47] head-down[5,11] or alternatively no tilt[28] to minimize bleeding during hepatic surgery.

In order to overcome the measurement problems with hydrostatic catheters described above, we decided to use non-fluid filled, tip-manometer catheters. These catheters have a sensor placed directly in the tip (Figure 5). After calibration, the tip-manometer catheter can be surgically placed in the relevant vessel and is thereafter insensitive to hydrostatic changes in the transducer in relation to patient position. To prevent drift during the experimental procedure the tip-manometers were zeroed by immersion in a body temperature saline solution before and after the pressure measurements. Despite this, drift could occur when changing from saline solution to blood.

For measurements of CVP in Studies I–III, the transducer was carefully positioned at the right atrial level using a laser spirit level. However it is not possible to ensure that an identical zero pressure level is achieved on each occasion and in Studies I and II it would have been an advantage to be able to measure CVP with both tip-manometer and conventional fluid-filled catheters for comparison. In Study IV, recording was done twice an hour by the anaesthetic staff. The performance of correct measurements of CVP in the clinical situation is challenging,[16,48] as it depends on an adequate position of the pressure transducer.

Portal and hepato-splanchnic blood flow

The transhepatic venous blood flow was evaluated in Study III. Ideally this would have been performed by direct ultrasound-based flow measurements of the relevant vessels: the portal vein and the hepatic artery. This technique proved to be difficult in our intra-operative setting and was therefore abandoned. We therefore chose to apply a concept that did not allow us to measure absolute flows in these vessels, but rather flow changes in the portal and hepatic veins. This analysis was accomplished by measurement of arterial oxygen saturation as well as oxygen saturation in portal and hepatic venous blood. Using the Fick principle, changes in portal and hepato-splanchnic blood flow could be calculated. In order for these calculations to be valid, one must assume that the studied agent, vasopressin, does not affect intestinal or hepatic oxygen consumption. To our knowledge, there is no data to suggest that this is the case in the in vivo.

Steady state vasopressin concentration

To ensure that steady state was reached during the vasopressin infusion in Study III, one could argue that we should ideally have had a longer measurement period than 15 minutes. This might have increased the likelihood that the hepatic arterial buffer response (HABR) was fully established. However, the plasma half-life of vasopressin is only 1–2 minutes[33,49] (fast phase) and steady state should therefore be established

at 3–5 times this interval. Accordingly we have assumed that steady state was indeed reached at each measurement period. The infusion time used is similar to that used by Wagener et al in their study.[33]

Estimated blood loss (EBL)

The magnitude of blood loss for patients in Study IV was obtained from the anaesthetic records, where the anaesthetic and scrub nurses estimate total blood loss at the end of each case. There will almost always be some degree of inaccuracy in these estimates, but the determinations were made in the same way for both cohorts.

Statistical considerations

The collection of data during surgery in Studies I–III was technically demanding and prolonged the operation time, with a large operating team involved. This explains our small sample size in these studies and may increase the risk of type 2 errors. Nevertheless the studies were adequately powered according to the analysis performed prior to starting our investigation.

Time constraints limited us from having a control group, instead the patients served as their own controls. For the same reason, in Study III, a control measurement after discontinuation of vasopressin would have been desirable. Instead two control measurements were performed, at steady state, before administration of vasopressin in order to assess any changes with time in the absence of any intervention. In Study III if a significant overall ANOVA was present, the analysis was continued with paired t-tests between baseline (mean of C1 and C2) and vasopressin infusion values. Due to multiple comparisons in Study I and II, the Hochberg approach was used to avoid error due to multiple testing.[44,50] In Study IV, we examined changes in the perioperative course in two cohorts of patients before and after the introduction of the GDT/LCVP technique. The study was retrospective, and considering that changes were made in the context of a "bundle", it is difficult to determine the significance of individual interventions. The interventions were not stepwise protocolled; rather this was left to the discretion of the individual anaesthetist with the aim of achieving our stated cardiovascular goals.

Figure 19. Data collection during the study protocol.

Study design

The aim in Studies I and II was to assess the effect of some of the interventions used in the LCVP management concept on central, portal and hepatic venous pressure. In Study III we investigated the effect of vasopressin on hepatic pressures and flow (figure 19). Our assumption in all three studies was that a decrease in hepatic venous pressure would in turn lead to lower blood loss. In Study IV we evaluated the consequences of introducing GDT/LCVP on the peri-operative course by comparing two cohorts of patients before and after the introduction of goal directed bundled care, in terms of blood loss and postoperative renal function.

General discussion

Liver resection is currently the treatment of choice for colo-rectal tumours with hepatic metastases where five-year survival is negligible in untreated patients, compared to 30–40% in those undergoing hepatic resection.[51] Liver resection is also used to treat primary hepato-biliary tumours, and in living donor transplants.[26] Blood loss during liver surgery has decreased markedly over recent decades, with improvements in anaesthetic and surgical techniques.[27] The potential for massive haemorrhage is, however, ever present, since the liver is a highly vascular organ.[26] Blood loss and subsequent blood transfusions have been identified as independent predictors of postoperative morbidity and mortality.[1,2,6,52]

The main sources of bleeding during liver surgery originate from the hepatic venous system. Lowering the pressure in the hepatic veins should therefore reduce the transmural driving pressure when these vessels are transected, thereby reducing blood loss. Central venous pressure has often been used as a surrogate for pressure in the hepatic venous system. Thus, the aim of the LCVP anaesthetic management in liver surgery is to reduce CVP, and by extension, hepatic venous pressures in order to achieve this goal. To reduce CVP, a number of interventions are recommended, such as fluid restriction,[5] diuretics,[53] vasodilation,[8,28] inotropes,[54] respiratory manipulations (low tidal volume, zero PEEP) and alterations in body position.[9,11,29] Venesection has also been suggested in some studies.[30,55] Few studies have previously examined the effect of these interventions in isolation, in terms of reducing blood loss in liver surgery. Rather, they have been studied in various combinations. Different surgical manoeuvres are also employed to manipulate vascular inflow (i.e. Pringlés manoeuvre) and outflow from the liver, with or without the low CVP technique.[4,13]

Interventions to reduce CVP and their effects on hepatic venous pressures

Patient position, PEEP and nitroglycerine

In this thesis we have evaluated the effect of several interventions, both alone and in combination. The effects of intra-operative changes in body position, PEEP and nitroglycerine on portal and hepatic venous pressure in relation to MAP and CO have been examined.

Patient tilt, either head-up or down, has been suggested by several authors but as discussed above it is difficult to predict whether these manoeuvres will decrease hepatic or portal venous pressures as these structures are in close proximity to the pressure and volume indifference point.[56] Opinions differ as to whether patient tilt should be employed, and if so, in which direction.

In Study I, we showed that while patient tilt (10° head-up or head-down) had marked effects on CVP and MAP, pressures in the hepatic vascular bed measured by tip-manometry, remained almost constant.[40] We concluded that standard monitoring of CVP, with fluid-filled catheters in the superior caval vein, is not useful to estimate pressure changes in the hepatic venous circulation during patient tilt. We also concluded that there is no rationale for head up tilt in open liver resection surgery. A head-up position, as recommended by Jones and Sonawalla,[9,29] combined with fluid restriction, peripheral venous vasodilatation and diuretics may increase the risk of decreased venous return leading to cardiovascular instability, as shown in our study, with markedly reduced blood pressure during head up tilt.

Melendez and co-workers have advocated 15° head down tilt in order to increase venous return and reduce the risk of venous air embolism when CVP is low.[5,16] In addition

to the improved haemodynamic stability in the head down position, these authors also suggest that head down position may contribute to an increased glomerular filtration rate due to an increase in plasma atrial natriuretic protein leading to improved renal function, as shown in animal studies.[5]

In Study I, despite an increase in CVP in the head down position, pressures in the hepatic vascular bed changed minimally. Combined with the fact that MAP also increases, we concluded that, from a haemodynamic point of view, head down tilt might be beneficial. However, the resulting increase in CVP will not reflect the actual pressures within the liver vascular bed.

In Study I we also evaluated the effect of PEEP on hepatic venous pressures. It has been suggested that PEEP increases the intra-thoracic pressure,[21] which in turn will be transmitted to the central and hepatic veins.[57-59] Zero PEEP is therefore sometimes recommended.[26,60] We showed that changes in PEEP from 5 to 10 cm H_2O did result in small but significant increases in central and hepatic venous pressures. The changes in HVP caused by changes in PEEP are very small (~ 1 mmHg), however, and considering the positive effects of PEEP in reducing atelectasis and improving gas exchange during general anaesthesia,[61] we believe that the benefits of using moderate PEEP override the potential risks. Previous studies also indicate that short-term application of PEEP up to 10 cm H_2O has limited effects on the splanchnic circulation.[62,63]

Nitroglycerine is a potent vasodilator and its use, either as an intravenous infusion[10,64] or sublingually,[17] has been advocated by several authors in order to achieve target CVP values or when other strategies have proven insufficient. Nitroglycerine has previously been shown to decrease portal venous pressure in patients with portal hypertension.[32,65] The major effect of nitroglycerine is venodilatation, leading to increased splanchnic and systemic venous/vascular capacitance, thus allowing the same blood volume to be accomodated in the venous capacitance vessels at a lower pressure.[21] In Study II, we showed that a nitroglycerine infusion led to parallel reductions in hepatic, portal and central venous pressures with the patient in the horizontal position (Figures 12 and 13). Consequently, it should be possible to use CVP to guide nitroglycerine dosage, as changes also reflect the hepatic venous pressures.[41] Nitroglycerine administration also resulted in a reduction in cardiac output as well as in mean arterial pressure (MAP). Head-down tilt during nitroglycerine infusion improved both MAP and CO without a substantial increase in hepatic venous pressure. This confirmed the results from Study I; that patient tilt causes dissociation between CVP and HVP, as CVP increased markedly while HVP increased only marginally. Consequently, CVP cannot be used as a surrogate for PVP and HVP in the head-down position.

Nitroglycerine administration also altered changes in CO in response to patient tilt. In Study I, CO was unchanged after head-down tilt. After nitroglycerine administration in Study II however, CO increased when head-down tilt was applied. This was presumably in response to the preceding vasodilation and fall in CO caused by nitroglycerine. Nitroglycerine's rapid onset/offset make it suitable for lowering the HVP in liver resec-

tion surgery during the resection phase when the bleeding risk is high. According to Lautt, a reduction in portal pressure leads to a reduction in portal flow. This leads, in turn, to a redistribution of blood from the hepatic reservoir into the systemic circulation,[20] resulting in a decrease in liver volume. When transecting the liver parenchyma during surgery, two pressure gradients are created: one from CVP/HVP to incision and one from PVP to incision (Figure 20). Both these haemorrhaging pressures (the intrahepatic transmural distending pressures) will be reduced by nitroglycerine.
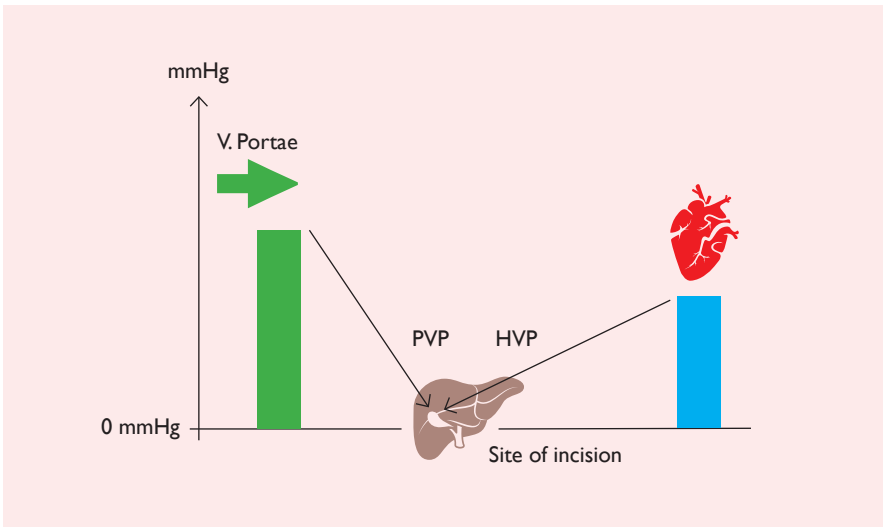

Figure 20. Surgical intervention changes the pressure drop from portal to central venous pressure by exposing the circulation to atmospheric pressure, thus creating two "haemorrhaging pressure heads".

In two of our patients nitroglycerine infusion resulted in marked hypotension without a pronounced effect on the venous pressures. These patients had double and triple antihypertensive therapy, which may have impaired the cardiovascular response to venodilation. These patients' underlying cardiovascular disease may also have altered the haemodynamic response to a decrease in venous return. The rapid offset time of nitroglycerine, however, allows for immediate discontinuation in case of negative central haemodynamic effects. Despite this, meticulous care with control of haemodynamics during liver resection is necessary, particularly in patients with coexisting cardiovascular conditions or renal dysfunction. Preoperative evaluation should aim to identify patients in whom intraoperative hypovolemia and active venodilatation may jeopardize the outcome.

Does a reduction in CVP lead to less blood loss?

A number of studies,[5,9,10,31] although not all,[53,66] have shown a reduction in bleeding with the LCVP anaesthetic technique. The rational role for CVP monitoring during liver resection has also been questioned.[67] Niemann et al did not demonstrate any difference in blood loss during right donor hepatectomy with or without CVP monitoring. Interestingly, however, all patients studied were subject to the LCVP technique.[67]

There is only one randomized prospective study comparing LCVP management to control: Wang randomized 50 patients planned for liver resection for hepatocellular carcinoma, to either an LCVP group or a control group. Lower total intraoperative blood loss (900 vs 2300 mL) was observed in the LCVP group compared to controls. There were no differences in postoperative complications, or hepatic and renal function between the groups. The LCVP group had a shorter length of hospital stay.[10]

CVP is not the only factor of importance in regard to intra-operative blood loss.[53,68] The liver has a high compliance, and an increase in blood volume can occur with little increase in vascular pressures.[68] An increase in hepatic blood volume may have a significant impact on the magnitude of bleeding.[20] Changes in vascular tone for other reasons may also be of importance.[69] Other factors such as coagulation status, the presence of cirrhosis or portal hypertension, and the skill of the surgeon are obviously also relevant.

Interpretation of CVP can be difficult because it is affected by many variables, e.g. intra-abdominal pressure, cardiac pump function, valvular disease, dysrhythmias, mechanical ventilation, volume status and vasodilation.[21] Intraoperative CVP measurement is also affected by other factors such as surgical retraction, liver manipulation and variations in patient position. Correct position of the transducer at the right atrial level is also important,[16] but difficult to achieve.[48]

Other interventions to reduce hepatic pressure and flow

Vasopressin, acting on V1 receptors in the hepato-splanchnic vascular bed, produces a potent vasoconstriction leading to decreased portal pressure and flow in patients with portal hypertension.[33] Vasopressin has also been shown to reduce blood loss in liver transplantation.[34] Although the effects of vasopressin on hepatic pressures in patients with portal hypertension have been described previously,[32] data are limited regarding the effects in patients with normal portal venous pressure. Vasopressin has a different mechanism of action to sympathomimetics, and the effects can differ between different vascular beds. It is not obvious therefore that the effect in patients with normal portal venous pressure would be the same as in those with portal hypertension.

In our study administration of low- to moderate doses of vasopressin in patients without previously known portal hypertension caused a marked reduction in portal venous (mesenteric) blood flow and a less pronounced decrease in hepato-splanchnic blood flow, a minor increase in hepatic and central venous pressures but no change in portal venous pressure. Cardiac output and stroke volume showed minor, but significant, increases and systemic vascular resistance (SVR) remained unchanged.

In Study III it is interesting to note that portal pressure did not decrease as an effect of the reduction in portal flow, compared to observations made in patients with portal hypertension. This is probably due to an autoregulatory increase in resistance in the hepatic vascular bed,[69] to maintain portal pressure and to preserve the hepatic venous pressure gradient, despite the reduction of portal flow. The reduced portal flow causes an adenosine-mediated increase in the hepatic artery blood flow (the HABR mechanism), leading to increased hepatic sinusoidal pressure that is then transmitted to the portal vein, and this may also explain the absence of change in the portal pressure.[20]

The absence of effect on portal venous pressure by vasopressin, in contrast to previous studies, could be explained by an increased stiffness of abdominal capacitance vessels, which offsets the decrease of intra-abdominal blood volume. Consequently there is no net effect on portal venous pressure, but a decrease in portal venous flow. Thus, it would seem that vasopressin may decrease portal venous pressures in patients with portal hypertension[33] but is less likely to do so in patients with normal portal pressures, as we found in Study III.

According to Lautt and co-workers, reduced portal blood flow reduces the intrahepatic distending pressure of the highly compliant hepatic capacitance vessels and results in a passive expulsion of blood from the liver into the central venous compartment, leading to a decrease in liver volume.[20] If so, one would expect the vasopressin-induced decrease in portal blood flow, as demonstrated in Study III, to be accompanied by a decrease in liver blood volume. It is known from plethysmographic measurements in animal studies that vasopressin decreases the hepatic blood volume by constriction of hepatic capacitance vessels.[70] However, intravascular pressures of venous compartments are dependent not only on the blood volume of the venous capacitance vessels, but also on their tone.

Although no data on the effect of vasopressin/terlipressin on intra-operative bleeding in liver resection surgery are available, terlipressin has been shown to decrease blood loss in liver transplantation in patients with portal hypertension.[35] This has been attributed to the fall in portal venous pressure seen with vasopressin due to pre-capillary mesenteric vasoconstriction and a pressure drop along the intestinal vascular bed with a consequent fall in portal venous pressure. The question then arises whether the intra-operative use of vasopressin may also decrease blood loss in patients without portal hypertension undergoing liver resection surgery. If the major driving force for intra-operative bleeding is the intrahepatic transmural distending pressure, vasopressin is less likely to decrease bleeding, as neither portal venous nor hepatic venous pressures decreased with vasopressin, as previously discussed. On the other hand, if the major determinant of bleeding in liver resection surgery is the volume of the intra-hepatic capacitance vessels and/or transhepatic blood flow, then vasopressin could potentially decrease bleeding. Raedler et al. showed that vasopressin, but not placebo, reduced bleeding and improved outcome after blunt liver trauma and uncontrolled haemorrhagic shock in a pig model.[37] Survival was also improved with vasopressin

therapy when compared to adrenaline and other vasopressors, suggesting a different mechanism of action.[38,71]

Westaby and co-workers evaluated the effects of vasopressin and nitroglycerine in patients with portal hypertension, alone and in combination. They found that while both vasopressin and nitroglycerine reduced the portal venous pressures in their own right, in combination, portal pressure fell disproportionally further.[32] Whether a combination of nitroglycerine and vasopressin can reduce both portal venous pressure and flow, and thereby further reduce bleeding during liver surgery, requires further investigation.

Vasopressin is used to increase SVR and improve MAP in cases of refractive vaso-plegia, whether due to sepsis or other causes.[72,73] In Study III no increase in SVR was observed. MAP increased slightly following an increase in cardiac output. In healthy volunteers MAP does not increase with vasopressin due to a reflex bradycardia.[74] In the present study, vasopressin did not induce a reflex fall in heart rate. This could be explained by the use of the inhaled anaesthetic sevoflurane, which is known to atten-uate the baroreceptor reflex.[75] In contrast to the response to vasopressin in healthy volunteers and post-cardiac surgical patients, cardiac output increased in the present study, most likely due to centralisation of the blood volume and an increase in CVP and preload. We interpret this observation as a vasopressin induced increase in thoracic blood volume leading to an increase in cardiac preload. This may, in turn, be caused by vasopressin-induced constriction of systemic venous capacitance vessels, including those of the abdominal compartment, leading to a centralisation of the blood volume, increasing preload, cardiac output, CVP and HVP. Bragadottir et al. demonstrated a similar increase in CVP.[76] These authors also showed that vasopressin increased left-sided filling pressures, further supporting the theory that vasopressin, at the dos-ages used in the present study, increases central blood volume.

The almost 40% decrease in mesenteric blood flow demonstrated in Study III is of course potentially concerning when considering intestinal oxygenation. In patients with vasodilatory shock after cardiac surgery, vasopressin, at the same infusion rates as used in the present study, induces an intestinal and gastric mucosal vasoconstriction.[77] In Study III we did not observe any signs of splanchnic hypoperfusion, as reflected by the absence of changes in the arterial to portal vein lactate gradients during this short-term infusion of vasopressin. Wagener et al. found that vasopressin during liver transplantation, using approximately similar infusion rates as in our study, did not induce gastric mucosal acidosis, as assessed by gastric tonometry.[33]

Vasopressin-induced renal ischaemia is another significant concern. Renal vasocon-striction and impaired renal oxygenation have been shown to occur in postoperative cardiac surgery patients treated with vassopressin.[76] In Study III, however, postoper-ative creatinine values were not increased after the short-term vasopressin infusion. They were, in fact, lower seven days postoperatively compared to preoperatively ob-tained values. Mukhtar et al. examined the effects of terlipressin in patients undergoing liver transplantation and found lower serum levels of cystatin C and creatinine and a

lower incidence of acute postoperative kidney injury compared to a control group.[36,78] However, the safety of intra-operative vasopressin in terms of splanchnic and renal complications should be assessed in a larger study of patients undergoing liver resection surgery.

Risks with the LCVP anaesthetic technique

Air embolism

The risk of air embolism in liver surgery may increase when a direct communication between a source of air and the vasculature is created and a pressure gradient favouring the passage of air into the hepatic circulation is established, especially if the liver is cirrhotic or fibrotic and unable to collapse due to stiffness of the tissue. A low CVP may cause a negative pressure gradient at the surgical site.[16] Partial compression of the inferior vena cava could also contribute to a Venturi effect, causing air to be drawn from small hepatic veins into the IVC.[15] A head-down tilt to prevent the risk of air embolism has been recommended by some authors[5] but has been questioned by others.[79] Although clinically significant air emboli are rare during liver resection,[80] surgeons and anaesthetists should be aware of the signs, investigations and management of this life-threatening intra-operative complication.[81]

Renal Hypoperfusion

With the LCVP anaesthetic management, concerns have been raised regarding the risk of hypoperfusion of vital organs. This has limited the use of this technique at some centres.[14] Fluid restriction, with or without the use of diuretics, is usually included in the LCVP concept in order to achieve permissive hypovolemia. The minimum acceptable systolic blood pressure and diuresis are 90 mmHg and 25 mL/h, respectively. Despite these limits, the risk of hypoperfusion of vital organs, the kidneys in particular, may be increased and this has led to the technique being called into question.[17]

In other types of surgery, hypotension and hypoperfusion of the splanchnic and renal circulation, increase the risk for pre-renal acute renal failure.[82] Slankamenac et al. reported a 15% incidence of acute renal injury after liver surgery,[39] according to the RIFLE criteria (Risk, Injury, Failure, Loss of kidney function and End stage kidney disease).[83] They created a prediction score for postoperative renal failure including four factors: cardiovascular disease, diabetes mellitus, preoperatively elevated alanine aminotransferase (ALAT) and chronic renal failure.

In a randomized controlled prospective study Wang et al. did not find any difference in postoperative (seven days) renal function between the LCVP group and those with a normal CVP (6–8 mmHg) after liver resection surgery.[10] In a retrospective observational study of almost 500 liver resections Melendez et al. reported similar findings.[5] In liver transplantation surgery, reports of adverse effects on renal function

with the low CVP technique have shown mixed results.[47,84] In a recently published study by Correa-Gallego et al., 2116 patients were retrospectively assessed regarding renal function after LCVP-assisted hepatectomy.[17] Acute kidney injury (AKI) was seen in 17% of the patients and of these, <1% developed a clinically relevant AKI, 90 days postoperatively. These authors concluded that clinically relevant renal dysfunction was uncommon after LCVP hepatectomy. Interestingly, only 16% of the patients in the Correa-Gallego study had a normal estimated GFR preoperatively.[85] The question remains what the impact of a transient AKI has on long-term survival. An interesting finding is that vasopressin used in liver transplantation surgery in patients with portal hypertension has been shown to reduce the incidence of AKI.[36]

When implementing the LCVP anaesthetic technique at our hospital, special consideration was taken to preserve perfusion of vital organs including the kidney. A higher "lower limit" for minimum diuresis was set, 0.5 mL/kg/h instead of >25 mL/h, during the dissection and resection phases. Increases in crystalloid solution infusion were recommended if required, and blood loss was substituted by colloids to a haemoglobin level of 8 g/dL in patients without cardiopulmonary compromise. To avoid the risk of hypotension and hypoperfusion we introduced a compulsory monitoring and targeting of systemic flow and pressure to a cardiac index > 2.5 l/min/m^2 and a MAP > 65 mmHg (in patients without cardiac disease). Instead of a strict value of CVP $\leq$ 5 mmHg our aim was to achieve either a CVP $\leq$ 5 mmHg or a reduction of 1/3 of the initial CVP value. The rationale was to avoid an unnecessary stress on patients who may have had a higher CVP for other reasons. At the discretion of the anaesthetist, dopamine, noradrenaline, nitroglycerine and/or epidural analgesia were used in order to maintain the goals set and achieve appropriate volume resuscitation.

Effects of haemodynamic goal directed bundled therapy

In Study IV we retrospectively evaluated the effect of the changes in haemodynamic management in liver surgery in 2011, i.e. GDT/LCVP, on the perioperative course. We compared two cohorts of patients from 2010 and 2012, before and after the introduction of LCVP/GDT. Estimated blood loss (EBL) decreased by 40%, or almost one litre, after implementation of the new strategy, without an increase in postoperative renal dysfunction. Peroperative use of colloids was reduced by 500 mL (p<0.001).

The use of vasoactive agents increased (Figure 18). The effect of the different agents on the splanchnic vascular bed with regards to pressure, flow and volume has been studied previously; the combined effect is complex and demands meticulous monitoring of relevant variables. Dopamine was used to improve systemic perfusion and theoretically it could be useful in liver resection with LCVP anaesthesia, as it will counteract the lowering of the gradient for cardiac filling pressure (by positive inotropy and lowering CVP) and systemic hypoperfusion. Recently it has been shown that low doses of dopamine may increase renal oxygenation via a 40–50% increase in renal blood flow, with no changes in CVP[86] or portal venous pressure.[87] Dopamine potentially could

have a renal protective effect.[86] Low-dose dopamine in surgical patients has also been shown to increase portal venous blood flow,[87] as well as total splanchnic blood flow.[88] A small randomized controlled study, published by Ryu et al. showed that milrinone with its combined vasodilatory and inotropic effects, reduced blood loss with improved haemodynamic stability in liver resection compared to a control group.[54]

The use of noradrenaline increased in 2012. Experimental studies have shown that noradrenaline increases portal venous pressure but also causes a pronounced decrease in intra-hepatic blood volume, thus potentially decreasing the propensity for bleeding.[89] The net effect of noradrenaline, per se, on the risk of bleeding is therefore not immediately evident.

The use of an intra-operatively activated epidural markedly increased from 5% (2010) to 63% (2012) after introduction of the GDT/LCVP. Thoracic neuraxial blockade has been shown to decrease both hepatic venous and portal venous blood flow.[90,91] In addition, thoracic epidural anaesthesia/analgesia has been shown to cause a redistribution of blood from the intra-thoracic and splanchnic compartments to the lower extremities with a concomitant decrease in CVP.[92,93] The combined effect of the intra-operative vasodilatation and analgesia is then utilised. Concerns have been raised, however, about concomitant neuraxial analgesia in patients at risk of abnormal coagulation.[3]

Goal directed bundle therapy

The new management strategy introduced at our hospital successfully reduced blood loss. As it is a multimodal approach, it is difficult to quantify the significance of the individual interventions within the bundled haemodynamic GDT. Another example of "bundled care" is the "Enhanced Recovery after Surgery" (ERAS) concept. Likewise with ERAS, it is difficult to identify specific interventions that are decisive to the outcome.[94-96]

Our GDT approach was not stepwise protocolized; rather the choice of agents was at the discretion of the attending anaesthetist. The reduced blood loss can also be contributed to more meticulous surgery. When liver pressure is reduced, control of bleeding will be easier, leading to a virtuous circle. Instead of adapting the previously described methods of LCVP anaesthesia, we decided to incorporate a goal directed strategy to reduce the risk of developing postoperative renal failure. It is also important to identify patients at "high risk" in order to provide optimal organ protection strategies and individualise management.[39] We followed cardiac output continuously and believe that careful haemodynamic monitoring with goal directed resuscitation can reduce blood loss and complications in patients undergoing liver resection surgery. This is supported by a recently published study by Correa-Gallego et al., which showed that stroke volume variation guided GDT in LCVP-assisted hepatectomy led to the administration of less intra-operative fluids, which, in turn, was independently associated with decreased postoperative morbidity.[85]

Conclusions

- Head-up or head-down tilt resulted in marked changes in CVP but did not alter hepatic or portal venous pressures. CVP was not found to be representative of the pressures within the hepatic venous bed during changes in body position.

- Increasing PEEP from 5 to 10 cm H_2O resulted in a small increase in CVP, hepatic and portal venous pressures.

- Nitroglycerine infusion induced parallel reductions in CVP, hepatic and portal venous pressures in the horizontal body position. Although nitroglycerine caused a reduction in cardiac output and MAP, head-down tilt can be used to increase mean arterial pressure and cardiac output without a substantial increase in hepatic venous pressures. When body position is changed, however, CVP can no longer be used as a surrogate for hepatic venous pressure.

- Vasopressin did not lower portal venous pressure and resulted in a small increase in hepatic venous pressure, CVP, MAP and cardiac output due to a centralisation of blood volume. Vasopressin markedly reduced the portal blood flow and to a lesser extent the hepato-splanchnic blood flow.

- After introduction of goal directed therapy with low CVP management, median blood loss decreased by almost one litre without an increase in postoperative renal dysfunction.

Concluding remarks

In the studies included in this thesis we have examined some of the interventions that are potentially useful in the LCVP concept. The specific effects on hepatic venous pressures and flow, both individually and in combination, have been more fully elucidated.

The optimal anaesthetic technique to manipulate hepatic venous pressure and flow in order to minimise intra-operative bleeding, while simultaneously maintaining systemic haemodynamic stability and optimising risk profile (i.e, for renal injury), is not fully established. Whether the addition of vasopressin to the GDT/LCVP protocol could reduce blood loss even further, remains to be investigated.

We have shown with our work, however, that by combining a goal directed haemodynamic management strategy with LCVP in liver surgery that blood loss can be significantly reduced. Since 2012, blood loss during liver resection has reduced still further, and by applying the same principles during liver transplantation surgery blood loss, transfusion requirements and patient outcome (postoperative ICU stay, one year graft survival) have also been improved.

These changes have been made possible in large part by the positive collaboration we have had between anaesthetists/intensivists and surgeons, at our hospital.

With an individualised haemodynamic management strategy and by avoiding excessive volume loading, it is possible to improve short and long term outcomes for patients undergoing liver surgery. Whether a more aggressive approach with induced hypovolaemia[97] would result in further improvement should be evaluated with randomised, controlled prospective studies using precise protocol components.

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