Vasopressin for prevention of blood loss during liver surgery

Physiological and clinical studies

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"It is a little startling to think that the amino acids when put together in a certain way, in a particular architecture, can lead to such an array of compounds exhibiting such a variety of physiological and pharmacological properties".

Vincent du Vigneaud, 1901-1978, awarded the Nobel Prize in Chemistry in 1955, for his work on biochemically important sulphur compounds, especially for the first synthesis of the polypeptide hormones oxytocin and vasopressin. Citation from "A Biographical Memoir" by Klaus Hoffman.

In loving memory of Olle Wisén

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ABSTRACT

Background: Hepatic resection is a major surgical procedure, with risk of substantial blood loss and need for blood transfusion. Blood loss and red blood cell transfusion are associated with postoperative morbidity and mortality, including time to recurrence of cancer. Various strategies are used to reduce blood loss, such as mechanical vascular occlusion and low central venous pressure anesthesia. Vasopressin is a non-adrenergic vasoconstrictor with prominent effects on the splanchnic circulation, used in treatment of vasoplegia in septic shock, but not previously evaluated in hepatic resection.

Aim: The aim of this thesis was to describe the effects of vasopressin on hepato-splanchnic hemodynamics, blood loss, transfusion requirements and postoperative outcomes during liver resection.

Methods: In Paper I, the effects of vasopressin and nitroglycerin on portal and hepatic venous pressure and portal and hepatic venous blood flow, were evaluated in an experimental study on 13 patients. In Paper II, the change of biomarker levels compared to baseline were described in 18 patients scheduled for hepatic resection, and the feasibility of a larger trial was assessed. Paper III described the protocol for a randomized, placebo-controlled double-blinded trial, comparing effects of vasopressin and placebo on blood loss, transfusion requirements and postoperative outcomes in hepatic resection. The trial included 270 patients, and the results are presented in Paper IV.

Results: Vasopressin did not affect the portal pressure but reduced the portal blood flow by 47% (SD 19%). Addition of nitroglycerin reduced the portal blood flow further, by 55% (SD 13%) and the hepatic venous blood flow by 30% (SD 13%). The portal pressure was reduced below baseline, but at the cost of hemodynamic instability. In Paper II, creatinine, troponin and lactate increased after hepatic resection, but there was no difference in biomarker levels between the vasopressin and placebo groups in Paper IV.

In Paper IV, blood loss at the end of surgery was median 450 ml (min 5; max 26500) in the argipressin group vs median 500 ml (min 10; max 10 000) in the placebo group, RR 0.90 (95% CI: 0.70-1.17). The number of patients who required blood transfusion during the study period was 43 (36.8%) in the vasopressin group and 52 (41.3%) in the placebo group, OR 0.84 (95% CI 0.48-1.49). There were less complications in the vasopressin group at 30 days after surgery, primarily due to less postoperative infections.

Conclusion: Vasopressin reduces portal and hepatic blood flow, but this effect does not translate to reduced blood loss or transfusion requirements after hepatic resection performed with low central venous pressure anesthesia and use of Pringle maneuver. The vasopressin-group had less complications at 30 days after surgery.

Keywords: hepatic resection, blood loss, transfusion, vasopressin, acute kidney injury

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SAMMANFATTNING PÅ SVENSKA

Blodförlust och blodtransfusion under cancerkirurgi är kopplat till ökad risk för postoperativa komplikationer, inklusive kortare tid till återfall i cancer. Vasopressin är ett kärlsammandragande läkemedel som påverkar blodflödet i mag-tarmkanalen, och därmed till levern. Syftet med denna avhandling var att undersöka effekterna av vasopressin på leverns blodcirkulation, och därefter studera om dessa effekter kan bidra till minskad blodförlust och behov av blodtransfusion under leverkirurgi.

I delarbete I undersöktes vasopressins effekter på blodtryck och blodflöde i portavenen och i levervenerna, i en fysiologisk studie på 13 patienter. I delarbete II observerade vi förändring av hemodynamiska mätvärden och laboratoriemarkörer för organpåverkan under leverkirurgi hos 18 patienter, och utvärderade studieprotokollet för en klinisk prövning. Delarbete III beskriver protokollet för en randomiserad, placebo-kontrollerad, dubbel-blindad studie som undersöker vasopressins effekt på blodförlust, njurskada och komplikationer under leverkirurgi. Denna prövning omfattade 270 patienter, och resultaten presenteras i delarbete IV.

Resultaten från delarbete I visar att vasopressin sänker blodflödet till levern, både som enda läkemedel och i kombination med nitroglycerin. Portavenstrycket påverkades inte av enbart vasopressin i denna patientgrupp med normalt utgångstryck i portavenen. I delabete II noterades påverkade biomarkörer för njurskada och hjärtskada, och parametrar för studieprotokollet till delarbete IV valdes ut. I delarbete IV sågs ingen skillnad mellan grupperna avseende blodförlust eller behov av blodtransfusion. De sekundära utfallsmåtten tyder på att vasopressin-behandling inte innebär ökad risk för akut njursvikt eller påverkan på organskademarkörer, och vasopressin-gruppen hade färre komplikationer vid uppföljning 30 dagar efter operationen jämfört med placebo-gruppen.

Sammanfattningsvis minskar vasopressin blodflödet genom levern, men detta bidrar inte till minskad blodförlust under leverkirurgi. De patienter som fick vasopressin under sin operation hade färre komplikationer vid uppföljning efter 30 dagar.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Wisén E, Svennerholm K, Sand Bown L, Houltz E, Rizell M, Lundin S, Ricksten SE. **Vasopressin and nitroglycerin decrease portal and hepatic venous pressure and hepato-splanchnic blood flow**. *Acta Anaesthesiol Scand*. 2018 Sep;62(8):1161.

II. Wisén E, Almazrooa A, Sand Bown L, Rizell M, Ricksten SE, Kvarnström A, Svennerholm K. **Myocardial, renal and intestinal injury in liver resection surgery—A prospective observational pilot study**. *Acta Anaesthesiol Scand*. 2021; 65: 886–894.

III. Wisén E, Kvarnström A, Sand-Bown L, Rizell M, Pivodic A, Ricksten SE, Svennerholm K. **Argipressin for prevention of blood loss during liver resection: a study protocol for a randomised, placebo-controlled, double-blinded trial (ARG-01)**. *BMJ Open*. 2023 Aug 24;13(8):e073270.

IV. Wisén E, Pivodic A, Skagervik A, Rizell M, Sand Bown L, Ricksten SE, Svennerholm K. **Argipressin for prevention of blood loss in hepatic resection: a randomized clinical trial.** *Manuscript, submitted.*

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ABBREVIATIONS

AE	Adverse Event
AKI	Acute Kidney Injury
CI	Cardiac Index
CO	Cardiac Output
CO_2	Carbon Dioxide
CRLM	Colorectal Liver Metastases
CRP	C-reactive Protein
CRRT	Continuous Renal Replacement Therapy
CVP	Central Venous Pressure
HABR	Hepatic Artery Buffer Response
HCC	Hepatocellular Carcinoma
hs-cTnI	High sensitive cardiac Troponin I
hs-cTnT	High sensitive cardiac Troponin T
HVP	Hepatic Venous Pressure
I-FABP	Intestinal Fatty Acid Binding Protein
ITBVI	Intrathoracic Blood Volume Index
KDIGO	Kidney Disease Improving Global Outcomes
LCVP	Low Central Venous Pressure
MAP	Mean Arterial Pressure
MINS	Myocardial Injury in Non-cardiac Surgery
mITT	Modified Intention to Treat
NO	Nitric Oxide
PHLF	Post-Hepatectomy Liver Failure
PPV	Pulse Pressure Variation
PVP	Portal Venous Pressure
RBC	Red Blood Cell
SAE	Serious Adverse Event
SFSS	Small for Size Syndrome
SIRS	Systemic Inflammatory Response Syndrome
SVR	Systemic Vascular Resistance
SVRI	Systemic Vascular Resistance Index
SVV	Stroke Volume Variation
SweLiv	Swedish National Quality Registry for Liver Cancer
TRIM	Transfusion Related Immunomodulation

DEFINITIONS IN SHORT

HABR	Hepatic Artery Buffer Response. Compensatory regulation of hepatic arterial blood flow in response to decreased or increased portal blood flow.
Pringle Maneuver	Occlusion of blood inflow to the liver, by mechanical occlusion of the portal vein and the hepatic artery, also known as hepatic pedicle clamping or portal triad clamping.
Vasopressin	Also known as arginin-vasopressin or AVP, is an endogenous hormone exerting effect on V1, V2 and V3 receptors. Argipressin is the synthetic vasopressin-analogue replicating the endogenous hormone with respect to receptor affinity, and is the active substance used in Paper I and IV.

1 INTRODUCTION

1.1 BACKGROUND

Liver surgery has been performed since the late 19th century and was initially afflicted with a high risk of blood loss and mortality. The concept of hepatic anatomical segments was introduced by Couinaud in 1957, and since then surgical techniques and anesthesiologic and perioperative care has continued to improve (1, 2). The first laparoscopic hepatic resection was performed in 1991, followed by robotic surgery in 1998, and both laparoscopic and robot hepatic surgery has become increasingly common (3).

In the western world, the main indication for hepatic resection, or hepatectomy, is colorectal cancer liver metastases (CRLM). Colorectal cancer was the third most common cancer diagnosis in 2022, and the second cause of cancer related death worldwide, followed by liver cancer (4). According to data from the Swedish National Board of Health and Welfare (Socialstyrelsen), the Swedish incidence of colorectal cancer is approximately 80 per 100 000 inhabitants each year for men and 72 per 100 000 for women (5). Out of these, 25-30% develop liver metastases, of which approximately one in four is amenable for curative surgery (6). Besides CLRM, the most common indications for hepatic resection include hepatocellular carcinoma (HCC), cholangiocarcinoma and gallbladder cancer. Approximately 600 hepatic resections are performed in Sweden each year (7).

Globally, the overall mortality after hepatic resection was 3.8 % in 2019 (8). In Sweden, the mortality at 90 days after surgery was 1.7% for CLRM, and >4% for primary cancers during the period of 2012-2023 (7). Postoperative complications are classified according to Clavien-Dindo (Table 1) (9). Major complications, defined as Clavien-Dindo grade ≥3, were reported in 8-24% of patients within 30 days of hepatic resection in Swedish cohorts. Of these, surgical and medical complications comprised approximately 10% each, and approximately 9% were infectious complications (7, 10). The overall 5-year survival after surgery for CLRM is 45-50%, and post-hepatectomy liver failure (PHLF) has been identified as the main cause of mortality, alone or in combination with multi organ failure (7, 10, 11).

Table 1. The Clavien-Dindo classification.

Grade	Definition
1	Any deviation from the normal postoperative course, treated with antiemetics, antipyretics, analgesics, diuretics, electrolytes or physiotherapy, and wounds treated bedside.
2	Complication requiring treatment with drugs other than for grade 1, as well as blood transfusions and total parenteral nutrition.
3	Complication requiring surgical, endoscopic or radiological intervention.
3a	Intervention not requiring general anesthesia.
3b	Intervention under general anesthesia.
4	Life-threatening complication, requiring intermediate or intensive care.
4a	Single organ dysfunction (including dialysis)
4b	Multiple organ dysfunction
5	Death

The Clavien-Dindo classification of surgical complications (9).

1.2 BLOOD LOSS AND OUTCOME

Blood loss during hepatic resection varies in different reports but can amount to more than 1000 mL depending on size and type of resection (12-15). Depending on transfusion thresholds, 10-25% of patients are expected to receive a red blood cell (RBC) transfusion in relation to hepatic resection, the risk increasing in presence of hepatic cirrhosis and portal hypertension (12, 16-19). In observational studies, blood loss and blood transfusions are associated with worse perioperative outcome, including survival and tumor recurrence, after cancer surgery including hepatic resection for CRLM and HCC. The association is independent of other risk factors, such as comorbidity or size of resection (18, 20-22).

The mechanism behind this effect remains unclear, but the concept of transfusion related immunomodulation suggests that the perioperative stress and immunosuppressive burden from transfusion of blood products creates a favorable environment for tumor progression (23). The risk of recurrence in colorectal cancer appears to be increased with transfusion during surgery, compared to pre- or postoperative, as well as with the number of transfused units, and possibly with older blood compared to blood that spent less time in storage (23, 24).

1.3 LIVER ANATOMY AND PHYSIOLOGY

The liver has several important functions such as synthesis of proteins and coagulation factors, filtration of portal venous blood, clearance of drugs and toxins and bile production and transport. It also has a highly compliant vascular bed, serving as a blood reservoir (25). The liver receives 20-25% of the cardiac output (CO), approximately 800-1200 mL/min, of which the portal vein supplies 75-80%, and the hepatic artery the remaining part (26). The blood is filtered through the hepatocytes and the space of Disse, where the filtrate is collected in the bile canaliculi and the blood is drained into the hepatic venous system, eventually emptying in the vena cava inferior. The portal venous pressure (PVP) is normally 6-12 mmHg, slightly higher than the central venous pressure (CVP). Portal hypertension is defined as a portal pressure gradient (difference between the pressure in the portal vein and the inferior vena cava) >5mmHg, and considered clinically significant if ≥10 mmHg (27, 28).

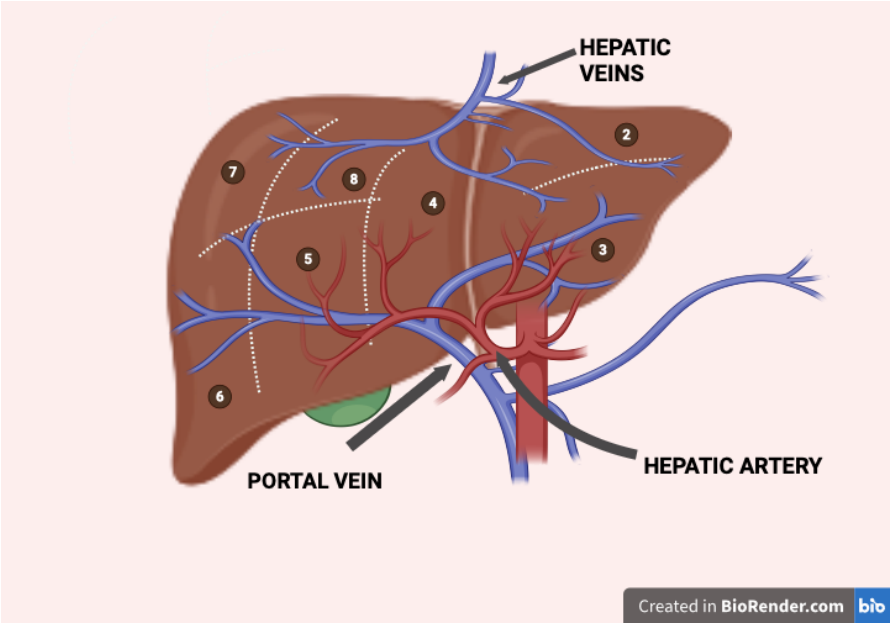

Figure 1. *The hepatic segments and hepatic blood supply. Segment 1 is located adjacent to, and behind, segment 4, and thus hidden in this view. Image created in http://BioRender.com*

The anatomical parts of the liver are defined as the right and left lobe, further divided into eight segments according to the portal venous vasculature (Figure 1) (29). The liver is unique in its ability to regenerate, and 70-80% of a normal

liver may be removed without permanent effects on liver function (30). If too much liver parenchyma is removed, there is a risk of PHLF. Definitions of PHLF include elevated INR and bilirubin on postoperative day 5, with cut off levels depending on laboratory methods and the criteria used (11, 31).

1.3.1 HEPATIC ARTERY BUFFER RESPONSE

The blood flow through the portal vein is passive and depends on blood flow in the mesenteric circulation, determined by systemic arterial pressure. If portal blood flow is reduced, the flow in the hepatic artery increases reciprocally, and vice versa if the portal flow increases, a phenomenon called the hepatic artery buffer response (HABR). However, if the flow in the hepatic artery decreases, it is not compensated by an increase in portal venous flow (32, 33).

After extensive hepatic resection, or in liver transplantation of a relatively small donor liver, the portal blood flow may be high in relation to a small liver remnant. In accordance with the HABR, blood flow in the hepatic artery decreases, and reduces the delivery of oxygenated blood to the liver. This may cause hypo-perfused areas and thrombosis, contributing to development of the "small for size syndrome" (SFSS) (34, 35). To mitigate the risk of SFSS, the portal blood flow can be reduced by surgical means, such as splenectomy or portocaval shunt, or pharmacologically, where terlipressin and somatostatin have been tested in pilot trials (36-38).

1.4 SURGICAL ASPECTS

Both in open and laparoscopic hepatic resection, the surgical procedure comprises three stages. During the dissection phase, access to the liver is gained and resectability of lesions is confirmed. The subsequent resection phase includes the hepatic parenchyma resection, after which hemostasis is ensured, and the abdomen is closed. Liver surgery is particularly challenging due to the lack of mechanisms for vasoconstriction in the hepatic sinusoids, contributing to increased risk of blood loss (2).

Hemi-hepatectomies or resection of more than two segments are considered major resections and are often performed with open surgery. Laparoscopic resections are performed in increasing number and are associated with less

postoperative complications and shorter hospital stay compared to open surgery, with comparable oncological outcomes (39, 40).

Several strategies are used as alternatives to surgery, or to improve the conditions before surgical procedures. To increase the volume of the future liver remnant, preoperative selective embolization of the portal vein induces atrophy of the ipsilateral liver lobe, while inducing hypertrophy of the contralateral lobe (41). Lately, addition of hepatic venous embolization has been suggested to improve results of embolization further (42). Radiofrequency ablation is an alternative to surgical removal of liver tumors, used alone or in combination with surgery, where the tumor is destroyed by use of radiofrequency waves in combination with heating of the lesion (43).

1.4.1 VASCULAR OCCLUSION

To mitigate blood loss during hepatic resection, and provide a clear operating field for the surgeon, mechanical vascular occlusion may be applied. The Pringle maneuver entails complete occlusion of both the inflow from the portal vein and from the hepatic artery (Figure 2). The portal and hepatic arterial branches may also be clamped selectively (44, 45). Occlusion is typically limited to 10-15 minutes intervals to reduce the risk of ischemia and reperfusion injuries, but up to 25 minutes has been considered safe when compared to shorter intervals (46).

Outflow occlusion either by selective clamping of the hepatic veins or total occlusion of the vena cava is less common due to technical challenges, increased operating times and risk of circulatory instability and postoperative complications (47).

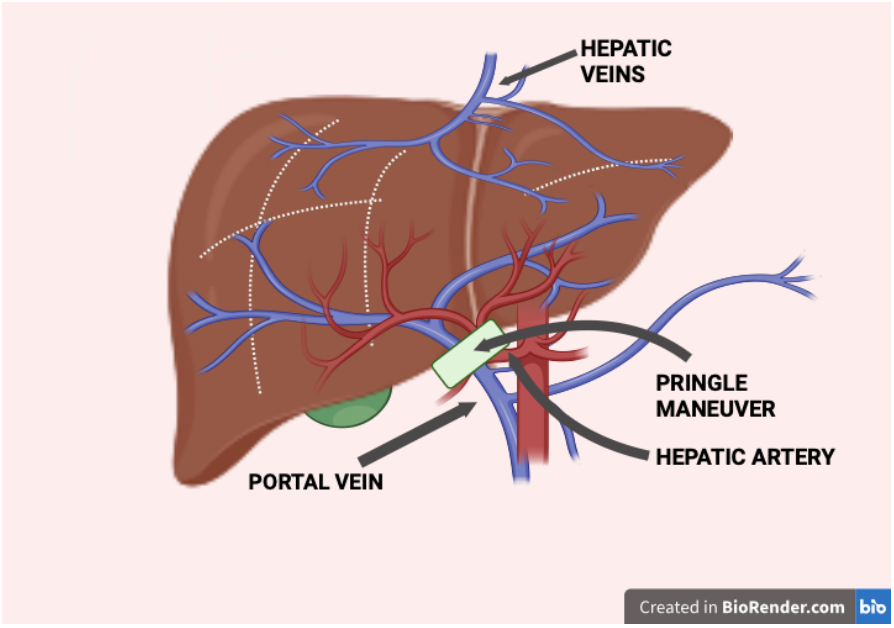

Figure 2. *The figure illustrates application of mechanical occlusion of the portal vein and the hepatic artery, the Pringle Maneuver, in light green. Image created in http://BioRender.com*

Occlusion of the portal vein not only impairs blood flow to the liver, but also obstructs the mesenteric venous outflow. This leads to accumulation of lactate and release of intestinal damages markers (48-50). At reperfusion, circulatory instability and acidosis may occur.

Evidence regarding the benefit of vascular occlusion in hepatic resection is conflicting. Continuous vascular occlusion reduced blood loss compared to no vascular occlusion in a systematic review from 2015 (51). However, the Pringle maneuver has been shown to affect tissue oxygenation and liver metabolism and is associated with increased risk of short-term complications compared to matched controls (49, 52). The ischemia and reperfusion injury associated with occlusion techniques may promote the growth of micro-metastasis, and lead to worse long-term oncological outcomes after hepatic resection for both CRLM and HCC according to a recent meta-analysis (53). However, other studies on hepatic resection does not show a negative impact on survival and recurrence rates with use of Pringle maneuver (54, 55).

1.5 ANESTHESIA FOR HEPATIC RESECTION

Anesthesia for hepatic resection can be challenging. Physical manipulation of the liver and vascular occlusion methods may cause circulatory disturbances and require continuous communication between surgery and anesthesia teams. Among other measures, the Enhanced Recovery After Surgery (ERAS) program for hepatic resection recommends use of multimodal pain treatment, goal directed fluid therapy with low CVP, and early mobilization (56).

1.5.1 REDUCTION OF BLOOD LOSS

The low CVP (LCVP) technique is the most established anesthetic method for reduction of blood loss in hepatic resection. Acute normovolemic hemodilution has been described: blood is drawn and replaced with albumin or crystalloids, and then retransfused after the resection phase. This method is reported to reduce blood loss but is not included in current treatment recommendations (56-58). Systemic use of tranexamic acid has been evaluated in a recent randomized controlled trial and is not recommended in hepatic resection (12).

1.5.1.1 LOW CVP-TECHNIQUE

Pringle maneuver controls bleeding from the portal venous and hepatic arterial vascular beds, but not from the hepatic veins. This venous "back-bleeding" is dependent on the hepatic venous pressure (HVP), which correlates to CVP in the horizontal position (59). In 1998, Johnson et al. showed a strong correlation between CVP and blood loss during hepatic resection, as well as improved postoperative outcomes when CVP was maintained ≤5 mmHg (60). These findings were confirmed in succeeding studies and shifted the strategy for anesthetic management of hepatic resection from preemptive fluid transfusion to a fluid restrictive approach (61-63).

In short, the LCVP technique aims for CVP ≤5 mmHg during the resection phase by restrictive use of maintenance fluid before and under the resection phase, and restoration to euvolemia when resection is completed. Other means to decrease CVP include vasodilatation by epidural analgesia or intravenous nitroglycerin, furosemide for regulation of volume status and low positive end expiratory pressure (PEEP). Systematic reviews and meta-analysis show that the LCVP technique reduces blood loss both in open and laparoscopic hepatic resection (64-66).

The LCVP technique is associated with a reduction of mean arterial pressure (MAP), and vasopressors (i.e. norepinephrine) are used to maintain adequate perfusion pressure (65). Concerns regarding fluid restriction and impact on kidney function have been refuted, also in laparoscopic surgery where the increased abdominal pressure may further compromise renal perfusion (63-65, 67). Low venous pressure and open resection surfaces increase the risk of air embolism. The risk is low, but with increasing number of laparoscopic procedures with carbon dioxide (CO_2) insufflation of the abdomen, and open procedures with a CVP close to zero, the risk of air or CO_2 embolus should not be neglected (65, 68). In summary, the balance between restrictive intravenous fluid therapy and the risk of hypoperfusion and relative hypovolemia is delicate.

1.6 VASOACTIVE DRUGS

During major surgery, vasopressors are used to counteract the vasodilatation from anesthesia and maintain adequate blood pressure. All vasopressors have the potential to induce hypoperfusion if used to excess. The catecholamines exert their effect on adrenergic alfa- beta- and dopaminergic receptors, located in vascular smooth muscle and in the heart, increasing contractility and heart rate as well as vasoconstriction, depending on receptor affinity. The catecholamine effects may be unreliable during acidotic conditions, and increase cardiac oxygen demand (69). Vasopressors exerting their effect on non-adrenergic receptors include vasopressin and angiotensin-II. A multimodal approach to vasoplegia has been suggested, both perioperatively and in sepsis, to reduce side effects of high doses of adrenergic vasopressors (70, 71).

1.6.1 VASODILATORS

Nitroglycerin exerts its effect by release of nitric oxide (NO), leading to vasodilatation primarily in the venous vascular beds. During hepatic resection, nitroglycerin infusion reduces PVP, but also MAP and CO, in patients both with and without portal hypertension (59, 72). Milrinone is primarily used in cardiac failure, as it increases cardiac contractility by phosphodiesterase inhibition as well as dilates both the systemic and pulmonary vascular beds. In

a small randomized trial on living liver donors, milrinone improved the visual assessment of the surgical field and reduced perioperative blood loss (73).

1.6.2 VASOPRESSIN

Vasopressin, also referred to as arginin-vasopressin, argipressin or AVP, is an endogenous peptide released from the posterior pituitary in response to increased plasma osmolality and arterial hypotension (74). Vasopressin exerts a multitude of effects via V1, V2 and V3-receptors, of which the most prominent are described in Figure 3. It is short-acting, with a half-life in the circulation of 5-35 minutes (75, 76).

The V1 receptors are located in vascular smooth muscle, and induces a prominent vasoconstrictive effect in general, and in the splanchnic circulation, leading to reduced portal blood flow (77-79). Under normal conditions, vasopressin plays a minor role in blood pressure regulation, but when the sympathetic and renin-angiotensin systems are compromised, as in sepsis, hypovolemic shock or during general or epidural anesthesia, the role of vasopressin becomes distinctly more important, shifting blood flow to vital organs (80, 81).

The V2 receptors are located in the collecting ducts of the kidney, mediating the anti-diuretic effects of vasopressin. The V1 receptors are also involved in renal function, by constriction of the glomerular efferent arterioles, rather than the afferent arterioles (79, 82). This may increase the glomerular filtration rate, but at a cost of higher oxygen consumption (83).

Vasopressin has several pro-coagulant effects. V1 receptors on platelets promote platelet aggregation, and V2 receptors on the vascular endothelium promotes release of von Willebrand Factor and Factor VIII (84). Vasopressin also cross-reacts with the oxytocin-receptors and modulates immune cells and the release of inflammatory mediators such as cytokines and prostaglandins (85-87).

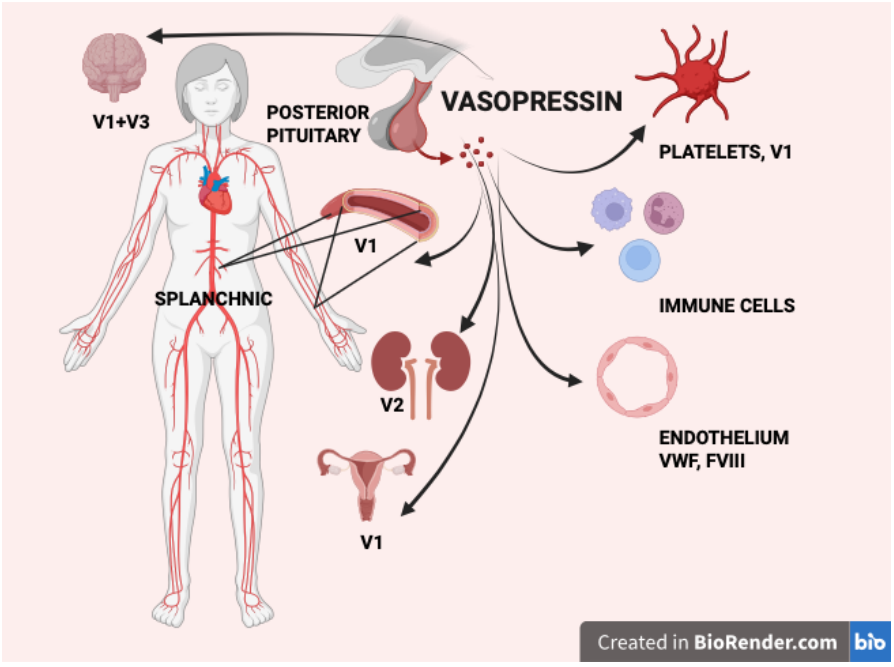

Figure 3. *Distribution of vasopressin receptors. VWF: Von Willebrand Factor, FVIII: Factor VIII. Image created in https://BioRender.com*

Several synthetic vasopressin-analogues are available for medical use, with different relative receptor affinities defining the properties of each analogue. Argipressin is the synthetic analogue most closely replicating endogenous vasopressin, with a V1:V2 affinity of 1:1. The plasma half-life of argipressin is short, <10 minutes in most preparations, and it is usually administered as a continuous intravenous infusion. Terlipressin has a stronger affinity for V1-receptors, 2.2:1, and a longer metabolic elimination time of 4-6 hours and is often administered as intermittent injections. Indications for use of terlipressin includes bleeding esophageal varices and hepatorenal syndrome (HRS), while argipressin is suggested as second line vasopressor in sepsis (71, 88, 89).

Selipressin is a highly selective V1-receptor agonist, inducing vasoconstriction and suggested as an alternative to vasopressin in sepsis treatment (90). Desmopressin is a pharmacological agent with effect on the non-vascular vasopressin receptors, available for treatment of various platelet- and coagulation disorders and central diabetes insipidus (84, 91).

1.6.3 VASOPRESSIN IN VASODILATORY STATES

In health, circulating levels of endogenous vasopressin are low, 1-4 pg/mL, increasing to 10-20 pg/mL in response to hypovolemia. In septic shock, levels initially increase to 100-200 pg/mL and then decline rapidly, to stay inappropriately low in relation to blood pressure for several days (81). Vasopressin has been evaluated for treatment of vasoplegia in sepsis in two large, randomized trials; VASST and VANISH. In VASST, vasopressin did not reduce mortality compared to norepinephrine, except for the subgroup with less severe septic shock (92). The subsequent VANISH trial compared treatment with vasopressin to norepinephrine as the initial vasopressor, alone and in combination with corticosteroids. Vasopressin did not reduce the number of kidney-failure free days, but showed a reduced need for renal replacement therapy in the vasopressin group (93). The Surviving Sepsis Campaign recommends vasopressin as second line vasopressor in sepsis (71).

Cardiac surgery is associated with vasoplegia after cardiopulmonary bypass. A small physiological study of vasopressin effects in cardiac surgery patients indicates that renal perfusion is impaired by vasopressin, while glomerular filtration rate increases (83). However, the large, randomized VANCS trial, comparing vasopressin and norepinephrine for treatment of vasoplegia after cardiac surgery, found less complications including acute kidney injury (AKI) in the vasopressin group compared to the norepinephrine group (94).

Liver failure is characterized by several clinical features. In portal hypertension there is an overproduction of vasodilatory molecules, leading to peripheral vasodilatation, decentralization of blood volume and increased CO (95, 96). Increased resistance in the cirrhotic liver causes collateral flow to develop, leading to development of varicose veins in the ventricle and esophagus, as well as splenomegaly and ascites (97). Terlipressin reduces the PVP and splanchnic blood flow, thereby redistributing the blood volume from the splanchnic to the central circulation (98). This redistribution may increase renal perfusion pressure and glomerular filtration rate by effects on renal vasculature. In liver transplantation, terlipressin has been shown to reduce PVP and the incidence of AKI (99, 100). A recent meta-analysis suggests that continuous infusion of terlipressin reduces perioperative blood loss, but not transfusion requirements, in a mixed cohort of liver transplantation and hepatic resection patients (101).

1.6.4 VASOPRESSIN IN HEMORRHAGIC SHOCK

In experimental animal models of hemorrhagic shock, vasopressin increases survival, both compared to fluid resuscitation alone and to placebo (102, 103). In humans, addition of vasopressin to fluid resuscitation alone reduced fluid requirements, including RBC transfusion, in trauma patients in a randomized controlled trial from 2010. Vasopressin was also associated with reduced mortality (104). These findings were confirmed in a recent, large randomized controlled trial on trauma patients, where Sims et al. reported reduced transfusion requirements with vasopressin treatment compared to placebo, without increased incidence of adverse events (105).

1.6.5 VASOPRESSIN IN HEPATIC RESECTION

A limited number of trials have investigated the perioperative effects of terlipressin in hepatic resection, and none investigate vasopressin. Only two trials report effects on blood loss and transfusion requirements (101). In a randomised, controlled trial, Abbas et al. showed decreased blood loss in the terlipressin group compared to the placebo group in major hepatic resections (1892 mL vs 1351 mL). However, ASA class III patients were excluded from the trial, and fluid replacement strategy was considerably more liberal than the ERAS recommendations (13). These limitations also apply to the study by Mahdy et al. who investigated the effect of terlipressin on PVP in a randomized trial on patients undergoing either hepatic resection or Whipple procedure. Evaluation of secondary outcomes revealed reduced blood loss and transfusion requirements in the terlipressin group (14). The CVP was >5mm Hg in both studies, and the use of Pringle maneuver was either not allowed or not commented on.

Regarding postoperative outcomes in hepatic resection, Kohler et al. performed a randomized controlled trial comparing terlipressin to placebo. There was no difference regarding the primary outcome, a composite endpoint of surgical complications, but terlipressin did improve renal function compared to placebo (106). The effects of terlipressin in patients with PVP >12 mmHg after hepatic resection were investigated by Li et al., and less hepatic failure and need for abdominal drainage was noted in the terlipressin group (37). In summary, available trials either focus on postoperative effects of terlipressin after hepatic resection or are performed under circumstances that differ from current recommendations.

1.7 ORGAN DAMAGE

1.7.1 ACUTE KIDNEY INJURY

Acute kidney injury is a complication to major surgery, and is in turn associated with other postoperative complications, including increased length of stay in hospital and mortality (107, 108). The current definition of AKI according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria is oliguria (<0.5 mL/kg for >6 hours), and an increase in serum creatinine >26.5 μmol/L within 48 hours, or an increase with 1.5 times the baseline value within seven days. The definition further includes three grades of severity according to level of increase in creatinine (109).

In the recent multi-center study EPIS-AKI, including >10 000 patients undergoing major surgery, the incidence of AKI was 18.4% (110). Previously reported incidence has varied between 3 and 35%, depending on AKI classification and type of surgery (108, 111-113). In hepatic resection, the incidence of AKI is estimated to 10-21%, with major resections carrying the higher risk. Other risk factors include preoperative hypertension and chronic kidney disease, intraoperative hemodynamic instability, blood loss and RBC transfusion, hypovolemia as well as fluid overload, and use of vasopressors (110, 111, 114, 115).

The current definition of AKI uses creatinine as a marker of manifest kidney injury, while novel biomarkers such as the tubular cell cycle arrest marker TIMP-2/IGFBP-7 (NephroCheck®), are being evaluated for early detection of renal stress, before actual kidney injury occurs (111, 116, 117). Ideally, early detection of AKI risk enables initiation of treatment bundles and prevention of manifest AKI.

1.7.2 MYOCARDIAL INJURY

Myocardial Injury in Non-cardiac Surgery (MINS) is defined as prognostically relevant cardiac injury due to ischemia, identified by increase in high- sensitive cardiac troponin T (hs-cTnT) or troponin I (hs-cTnI) above the 99th percentile, within 30 days of non-cardiac surgery (118). Different prognostic thresholds are suggested depending on the troponin assay used, and in case an elevated troponin is present already at baseline. Most MINS occur within the first days after surgery, and in contrast to the definition of acute myocardial infarction,

clinical symptoms or electrocardiographic changes are not required for diagnosis (118, 119). The VISION study investigated patients undergoing inpatient non-cardiac surgery and revealed that 8% of patients fulfilled MINS criteria. Only 16% of these patients experienced clinical cardiac symptoms. MINS was associated with increased 30-day mortality, regardless of presence of clinical ischemic symptoms (119). The importance of perioperative screening of cardiac biomarkers as important predictors of mortality and complications in major non-cardiac surgery has been emphasized in several publications (118-121).

1.7.3 INTESTINAL HYPOPERFUSION

Intestinal ischemia is an uncommon but severe complication to vasopressor use in vasodilatory shock, according to a pharmacovigilance analysis based on the Word Health Organization database (122). Specific data on incidence of mesenteric ischemia in hepatic resection is lacking.

Biomarkers for detection of intestinal injury are being evaluated, where good diagnostic accuracy is described for Intestinal Fatty Acid Binding Protein (I-FABP), a marker of early enterocyte cell death. Low levels of I-FABP are present in the circulation, indicating normal enterocyte cell turnover (123). Levels rise after episodes of intestinal ischemia, and I-FABP is released in hepatic resection, both with and without use of Pringle maneuver (48, 124). However, use of I-FABP in clinical practice is limited by the processing time of the analysis method. D-lactate is the stereoisomer of L-lactate, produced by bacteria in the gastrointestinal tract, and present in the circulation only in case of compromised mucosal integrity (123).

In retrospective studies, lactate has proven to be an unspecific marker of general hypoperfusion and does not have a high specificity for intestinal ischemia (123). Lactate is metabolized in the liver, and several factors such as impaired lactate metabolism and use of Pringle maneuver may influence lactate levels during liver surgery (49, 50). However, elevated lactate is associated with postoperative renal dysfunction, length of stay in hospital and mortality at 90 days in hepatic resection (125).

2 AIM

The overall aim of this thesis was to describe the effects of vasopressin on hepato-splanchnic hemodynamics, blood loss, transfusion requirements and postoperative outcomes during liver resection.

2.1 SPECIFIC AIMS

- To evaluate the effects of vasopressin, alone and in combination with nitroglycerin, on PVP, HVP and portal and hepatic venous blood flow (Paper I).

- To describe the change of biomarker levels compared to baseline after hepatic resection (Paper II).

- To assess if vasopressin infusion during hepatic resection reduces blood loss at the end of surgery compared to placebo (Paper IV).

- To assess if vasopressin infusion during hepatic resection reduces transfusion requirements on the day of surgery and during the study period, compared to placebo (Paper IV).

- To explore effects of vasopressin infusion during hepatic resection on biomarker levels, incidence of AKI and postoperative complications after hepatic resection (Paper IV).

3 PATIENTS AND METHODS

3.1 PATIENTS

In Paper I, II and IV, oral and written study information was provided at the preoperative consultation or at admission to hospital, and patients provided both oral and written consent.

Paper I included 13 adult patients undergoing elective open hepatic resection at Sahlgrenska University Hospital, classified as American Society of Anesthesiology (ASA) class I-II. Exclusion criteria were use of ≥2 anti-hypertensive medications, BMI >30 kg/m^2, and expected surgical difficulties with catheterization of the portal or hepatic veins.

Paper II included 18 adult patients undergoing elective open hepatic resection at Sahlgrenska University Hospital, ASA class I-III. Exclusion criteria were infection, treatment with corticosteroids, preoperative renal failure (eGFR<30 mL/min/1.73m^2), coagulation disorder, minor hepatic resection (wedge resection) or other surgical or medical conditions rendering the patient unsuitable for participation.

Paper IV included 270 consecutive adult patients, ASA class I-III, scheduled for laparoscopic or open hepatic resection at Sahlgrenska University Hospital. Exclusion criteria included inability to assimilate the study information and give consent, simultaneous surgery for other tumor or minor resection (superficial tumor <2 cm), terminal renal failure (eGFR <15 mL/min/1.73m^2), pregnancy, allergy to Empressin®, inclusion in another interventional trial or previous randomization in the present trial, hyponatremia, active infection or other surgical or medical reason rendering the patient unsuitable for participation.

3.2 METHODS

3.2.1 ANESTHESIA

The patients in Paper I, II and IV were all treated according to the anesthesia standard operating procedure for hepatic resection at Sahlgrenska University

Hospital. This included induction with fentanyl, propofol and rocuronium, and maintenance of anesthesia with sevoflurane and fentanyl. For open surgery, an epidural catheter was placed and activated with bupivacaine, fentanyl, and adrenaline. Standard monitoring included electrocardiogram, pulse oximetry, end-tidal CO_2 and invasive arterial blood pressure. Cardiac output monitoring by thermodilution (Picco®) or non-invasive CO monitoring (FlowTrac®) was used if indicated.

Low CVP technique was applied, with a target CVP ≤5mmHg (or a reduction of CVP with 1/3 from baseline) during the resection phase. To this end, maintenance fluid therapy was restricted to 1.5 mL/kg/h of crystalloid, and the epidural was activated if available. Low PEEP, diuretics, and nitroglycerin were added if needed to achieve the target CVP. In parallel with measures to achieve LCVP, norepinephrine was used to maintain a MAP of 65-70 mmHg, and a cardiac index (CI) >2.5 L/min/m^2 was recommended. Transfusion of RBC was suggested at hemoglobin <80 g/L for otherwise healthy patients.

3.2.2 MEASUREMENT OF PORTAL AND HEPATIC VENOUS PRESSURE

In Paper I, PVP and HVP were measured by surgical insertion of one-lumen central venous catheters (Arrow® 16G), into the portal and the hepatic veins under direct visual control. The catheters were connected to pressure transducers, zeroed and positioned at the right atrial level. Pressures were sampled by an analog-digital converter at a rate of 20 Hz and transferred to the software program AcqKnowledge® (Biopac) for offline analysis. In Paper II, PVP was measured via a 23G needle, inserted by the surgeon into the portal vein, and connected to a pressure transducer in the standard monitoring system.

3.2.3 CALCULATION OF BLOOD FLOW CHANGES

The change in portal and hepatic venous blood flow relative to baseline was calculated using the formula described in Figure 4, derived from Fick's principle. In short, the oxygen saturation in blood before and after passing through an organ is compared, reflecting the oxygen extraction and hence blood flow through the organ. Fick's principle is most often used to compare oxygen saturation in arterial and mixed venous blood to assess the total body oxygen extraction, reflecting the cardiac output, but it may also be applied in other situations and for single organs.

In Paper I, blood samples for oxygen saturation measurements were obtained from arterial, portal venous, and hepatic venous blood. The change in splanchnic blood flow draining into the portal vein (ΔQpv), and the change in hepatic venous blood flow (Qhv) compared to baseline, was calculated at two measurement points: after infusion of vasopressin (post-V), and after infusion of vasopressin and nitroglycerin in combination (post-V+N) (Figure 4).

$$\Delta Qpv\ (\%) = \frac{Qpv^{(post\text{-}V)}}{Qpv^{(pre\text{-}V)}} = \frac{(SaO_2{}^{(pre\text{-}V)} - SpvO_2{}^{(pre\text{-}V)})}{(SaO_2{}^{(post\text{-}V)} - SpvO_2{}^{(post\ V)})} \times 100$$

Figure 4. *Formula for calculation of change in portal venous blood flow relative to baseline. ΔQpv= change of portal venous blood flow compared to baseline (%), pre-V: before infusion of vasopressin, post-V: after infusion of vasopressin, SaO_2: arterial oxygen saturation, $SpvO_2$: portal venous oxygen saturation. Adapted from Paper I with permission from John Wiley & Sons Ltd.*

3.2.4 STUDY PROCEDURE PAPER I

Paper I was an experimental non-randomized study, aiming to determine the effect of vasopressin, alone and in combination with nitroglycerin, on PVP, HVP and portal and hepatic venous blood flow. At each measurement point, CI was obtained by thermodilution, and systemic vascular resistance index (SVRI), intrathoracic blood volume index (ITBVI) and stroke volume index (SVI) were obtained from Picco® readings. Recordings of PVP, HVP, MAP and CVP were performed, and samples for arterial and venous blood gas analysis were obtained.

After dissection of the liver area, the surgical procedure was paused and catheters were inserted into the portal and hepatic veins. Two baseline measurements of pressure recordings were performed to confirm a steady state (measurement points control; C, and baseline; BL). Infusion of vasopressin was started at a rate of 9.6 U/h for 5 min (to ensure adequate plasma concentration) and continued at a rate of 4.8 U/h for another 15 min. Another set of measurements were performed (measurement point vasopressin; V). Infusion of nitroglycerin (glycerylnitrate 1 mg/mL) was added and dosed

individually to achieve a target MAP of 60 mmHg. After a period of 5 min with consistent MAP, the last set of measurements were made (measurement point vasopressin + nitroglycerin; V+N). Each patient served as its own control regarding PVP, HVP and calculated change of blood flow (Figure 5).

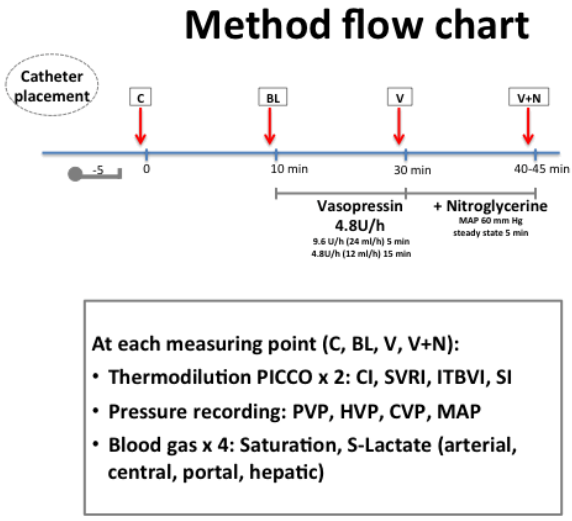

Figure 5. *Study procedures in Paper I. C: control, BL: baseline, V: vasopressin 4.8 U/h, V + N: vasopressin 4.8 U/h + nitroglycerin to a MAP of 60 mmHg. CI: cardiac index, SVRI: systemic vascular resistance index, ITBVI: intrathoracic blood volume index, SI: stroke volume index, PVP: portal venous pressure, HVP: hepatic venous pressure, CVP: central venous pressure, MAP: mean arterial pressure. Reproduced from Paper I with permission from John Wiley & Sons Ltd.*

3.2.4.1 OUTCOMES PAPER I

The primary outcomes in Paper I were the absolute change in PVP and HVP, as well as relative change in portal and hepatic venous blood flow, compared to baseline. Secondary outcomes were change from baseline in systemic hemodynamics at measurement point V and V+N, and portal and hepatic lactate levels at measurement point V and V+N compared to baseline.

3.2.5 STUDY PROCEDURE PAPER II

Paper II was a prospective observational pilot study, aiming to describe changes in hemodynamics and in biomarkers of organ dysfunction during hepatic resection. Hemodynamic measurements (CO, CI, SVRI and PVP) were performed at baseline (after induction of anesthesia), and before and after resection. Blood samples were obtained at baseline, before and after resection and postoperative day (POD) 1, 2 and 5. Biomarker analysis included creatinine, urea, amylase, D-lactate, hs-cTnT and I-FABP, as well as blood gas analysis of arterial and portal venous blood, a panel of inflammatory markers and urine samples for analysis of N-acetyl-β-D-glucosaminidase (NAG). Blood loss was assessed at the end of surgery, including weighing of used gauze throughout the surgical procedure (Figure 6).

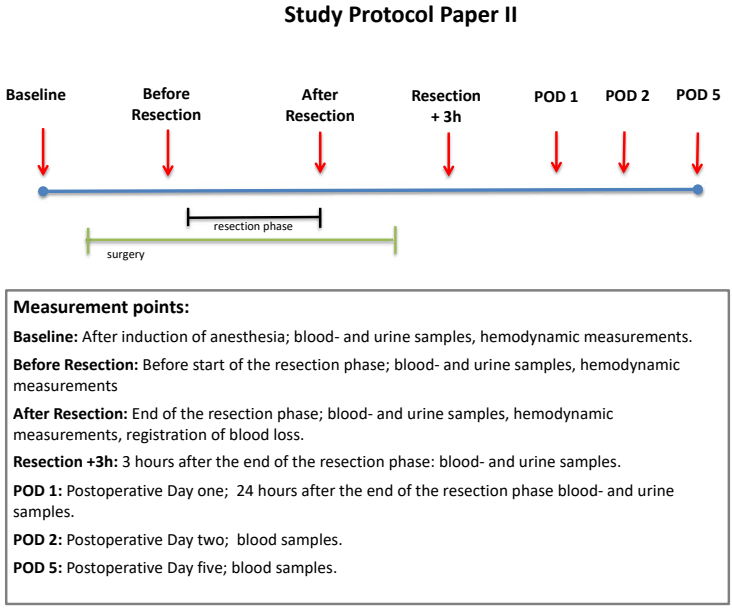

Figure 6. *Study procedures performed at measurement points in Paper II. POD: postoperative day. Reproduced from Paper II with permission from John Wiley & Sons Ltd.*

3.2.5.1 OUTCOMES PAPER II

In Paper II, the primary outcome was the change of biomarkers, in particular creatinine, hs-cTnT and lactate, compared to baseline as well as hemodynamic changes during the hepatic resection.

3.2.6 STUDY PROCEDURE PAPER IV

The design of this single-center, randomized, placebo-controlled double-blinded trial is described in detail in Paper III. The timing of study activities is described in Figure 7. The study period was defined as the time of inclusion until the expected day of discharge, i.e. POD 2 for laparoscopic surgery and POD 5 for open surgery. Complications were reported by the surgical team in the Swedish National Quality Registry for Liver Cancer (SweLiv) at POD 30. Adverse events (AEs) were collected during the study period and followed until resolution. Adverse events occurring after POD 2 or 5 respectively were not registered, since they were not considered related to the perioperative effect of vasopressin. An external monitor (Gothia Forum) oversaw the study procedures and data collection.

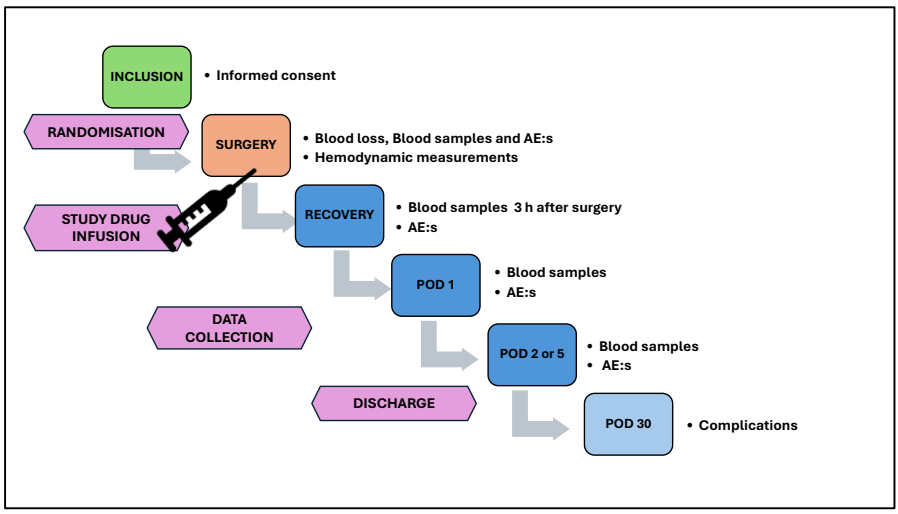

Figure 7. *Study activities in Paper IV, from inclusion to expected day of discharge, and at postoperative follow up 30 days after surgery. POD: postoperative day, AE: adverse events.*

Several additional sub-studies, apart from Paper IV, are planned within this trial. Analysis of I-FABP, inflammatory markers and coagulation tests, as well as assessment of pain scores and opioid consumption, will be reported separately and are not part of the present thesis.

3.2.6.1 RANDOMIZATION AND BLINDING

Patients were randomized on the day of surgery by use of an electronic randomization tool, to receive active treatment (argipressin) or placebo

(normal saline). The randomization was performed by an unblinded assisting nurse not participating in clinical care, who also prepared the study drug and delivered it to the attending anesthesia team. Hence participants, study staff, and the anesthesia and surgery teams were blinded to allocation. The active drug and placebo were both colorless, transparent solutions, and delivered in identical syringes. The allocation groups were stratified according to planned type of resection (open or minimally invasive, defined as laparoscopic or robot assisted) and size of resection ("small" defined as ≤2 segments, "large" defined as ≥3 segments or hemihepatectomy).

3.2.6.2 INTERVENTION

Active treatment consisted of argipressin (Empressin®) 0.8 U/mL, administered by intravenous infusion at 0.056 mL/kg/h, corresponding to 0.045 U/kg/h, resulting in 3.6 U/h for a patient weight of 80 kg. A weight-based schedule for infusion rate in mL/h was available for the anesthesia team. Normal saline, infused at the same rate, was used as placebo. The study drug was started as soon as a central venous catheter was placed and continued at a constant rate until closing of the abdomen, when it was tapered off. Norepinephrine and other vasoactive medications were used at the discretion of the treating anesthesiologist, to achieve target MAP and CVP. Choice of surgical technique, application of Pringle maneuver and local hemostatic agents was left at the discretion of the surgeon.

3.2.6.3 OUTCOMES

The primary outcome was blood loss at the end of surgery (mL), measured according to a standardized protocol. Secondary outcomes were proportion of patients receiving RBC transfusion during the study period (%), and the volume of RBC transfusion on the day of surgery and during the study period (mL). Additional, exploratory secondary outcomes included time with applied Pringle maneuver (min), achievement of CVP target (%), total dose of norepinephrine used during surgery (μg), urinary output on the day of surgery (mL), AKI (%) and change of biomarker levels including creatinine, hs-cTnI and lactate. Postoperative exploratory secondary outcomes included time to discharge, radicality of resection and complications at POD 30 according to the Clavien-Dindo classification (9).

3.3 STATISTICAL METHODS

3.3.1 STATISTICAL ANALYSIS PAPER I AND II

For Paper I, power calculations were performed both for a reduction of PVP with 25% (2-3 mmHg) and for a relative reduction of portal venous flow by 20% compared to baseline. The power calculations resulted in a planned inclusion of 13 patients. Due to the observational nature of Paper II, no power calculation was performed. Logistic as well as economic restraints regarding analysis of the inflammatory markers contributed to the limited sample size.

Significance tests were performed at the 5% significance level. In Paper I, measurement points were compared to baseline by use of two-way analysis of variance for repeated measures (ANOVA), followed by paired t-tests when significant. In Paper II, data was considered non-normally distributed, and Friedman's test was used, followed by Wilcoxon signed rank test if significant. Spearman rank correlation was used for evaluation of association between variables. All analyses were performed in Statistical Package for the Social Sciences (SPSS, version 23 or 25).

3.3.2 STATISTICAL ANALYSIS PAPER IV

The statistical analysis plan for Paper IV was published and described in detail in Paper III (supplemental file 4). The power calculation was based on blood loss data from hepatic resections at Sahlgrenska University Hospital. To show a 35% reduction of mean blood loss in the treatment arm compared to the placebo arm (962 mL vs 625 mL), with a power of 80% and a 5% significance level, 118 patients in each arm were needed. To compensate for an estimated drop-out rate of 5%, a total of 248 evaluable patients were planned for inclusion.

Based on data from Paper II, approximately 10% of the patients were expected to have spread malignant disease, discovered at surgery. These patients were excluded after randomization. Since they received a small amount of study drug, they remained in the safety population but were not part of the evaluable, modified intention to treat population (mITT).

The primary outcome (blood loss at the end of surgery) was compared between groups, using a generalized linear model with lognormal distribution. The

analysis was adjusted for randomization strata of laparoscopic, open small, and open large surgical procedures. Following confirmation of the primary analysis, the main secondary outcomes (proportion of patients receiving RBC transfusion, and volume of RBC transfusion) were included in a fixed sequential testing in the mentioned order.

All other secondary outcomes were exploratory, and hence not subject to adjustment for multiplicity. The effect of treatment on the primary endpoint was tested in the following subgroups: surgical technique (open or laparoscopic), extent of surgery (small or large), extent of surgery within open surgery (small or large), indication for surgery, hepatic cirrhosis and age. Analysis was performed using SAS software V. 9.4.

3.4 ETHICAL CONSIDERATIONS

3.4.1 APPROVALS AND REGISTRATIONS

Paper I and II were approved by the regional Ethical Review Board in Gothenburg (Dnr 879-13, amendment T819-16, and Dnr 740-18). Paper II was registered at Biobank Sweden (Dnr SU2018-05405, sample ID 447). Paper IV was approved by the Swedish Ethical Review Authority (Dnr 2021-03557), the Swedish Medical Products Agency (Dnr 5.1-2021-90115, EudraCT 2021-001806-2), and registered at Biobank Sweden (Dnr SU 2021-05601, sample ID 0795). Paper IV was registered in the Clinical Trials Information System (CTIS) at implementation (EU CT 2024-514332-25-00). All trials were registered at ClinicalTrials.gov. Personal data was handled according to the General Data Protection Regulation (GDPR) and databases were registered with the Data Protection Officer at Region Västra Götaland.

3.4.2 ETHICAL CONSIDERATIONS

In Paper I, the experimental procedure and measurements were performed during a pause in surgery. In relation to the overall length of surgery and the impact of the surgical procedure itself, risks associated with prolonged anesthesia and insertion of venous catheters were considered minimal.

The observational design of Paper II did not put the participant at physical risk from intervention. Attending clinicians were responsible for clinical follow up of study laboratory results.

In Paper IV, emphasis was put on potential risks with vasopressor use, i.e. excessive vasoconstriction and subsequent hypoperfusion of end organs such as the heart and kidneys. Due consideration was given to the argipressin dose, and treatment was given relative to body weight to avoid over- and underdosing. Signs of hypoperfusion were closely monitored.

The amount of blood required for blood sample analysis was considered negligible in relation to surgery and expected blood loss in all of the studies.

4 RESULTS

4.1 PAPER I: PHYSIOLOGICAL EFFECTS

In Paper I, 24 patients consented to participate during the period September 2016 to March 2017. Eight patients were considered ineligible due to catheterization difficulties during surgery. Two patients were not possible to assess due to logistic reasons, and one patient was excluded due to recent heart failure (unknown at inclusion), leaving 13 patients for analysis. Baseline characteristics are described in Table 2.

Table 2. Demographic data Paper I.

Baseline characteristics Paper I	**n=13**
Age, mean, y	58.3
Female sex, n (%)	2 (15.4)
ASA class, n (%)	
I	5 (38.5)
II	8 (61.5)
Medical history, n (%)	
Hypertension	3 (23.1)
Ischemic heart disease	1 (7.7)
Diabetes Mellitus type I	1 (7.7)
Diagnosis, n. (%)	
Colorectal liver metastasis	8 (61.5)
Intrahepatic / perihilar cholangiocarcinoma	2 (15.4)
Other metastasis	2 (15.4)
Other diagnosis (benign)	1 (7.7)

Baseline characteristics of participants in Paper I.

4.1.1 PORTAL AND HEPATIC BLOOD PRESSURE MEASUREMENTS

Infusion of vasopressin raised the HVP and CVP compared to baseline, while PVP remained unchanged. When infusion of nitroglycerin was added, both PVP, HVP and CVP were reduced to values below baseline (Figure 8).

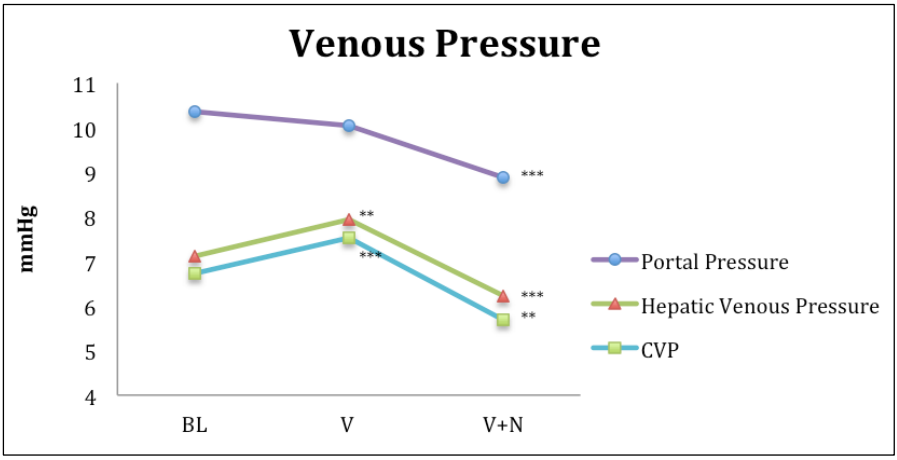

Figure 8. *Portal, hepatic, and central venous pressures (mmHg). BL: Baseline, V: Vasopressin infusion 4.8U/h, V+N: Vasopressin infusion 4.8 U/h + nitroglycerin infusion to MAP 60 mmHg, CVP: central venous pressure. Asterisks indicate significant difference vs baseline: **=p<0.01, ***=p<0.001. Reproduced from Paper I with permission from John Wiley & Sons Ltd.*

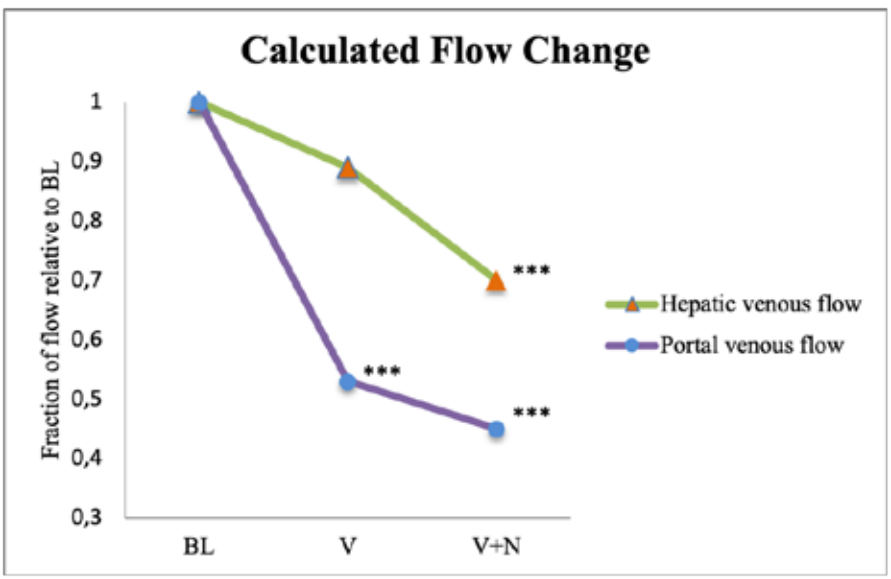

Figure 9. *Calculated changes in portal and hepatic venous blood flow, relative to baseline (%). BL: baseline, V: vasopressin infusion 4.8U/h, V+N: Vasopressin infusion 4.8 U/h + nitroglycerin infusion to MAP 60 mmHg. Asterisks indicate significant difference vs baseline: ***=p<0.001. Reproduced from Paper I with permission from John Wiley & Sons Ltd.*

4.1.2 CALCULATED CHANGES IN BLOOD FLOW

Infusion of vasopressin induced a calculated reduction of portal blood flow by 47% (SD 19%) compared to baseline, while the hepatic blood flow was not reduced. Addition of nitroglycerin reduced the portal blood flow further, by 55% (SD 13%), and hepatic blood flow by 30% (SD 13%), compared to baseline (Figure 9).

4.1.3 HEMODYNAMIC MEASUREMENTS

Infusion of vasopressin increased the MAP, while infusion of nitroglycerin reduced the MAP to 60 mmHg, in accordance with the study protocol. Cardiac index was reduced significantly after infusion of nitroglycerin (Table 3).

Table 3. Hemodynamic measurements Paper I.

	Baseline	Vasopressin 4.8 U/h	Vasopressin 4.8 U/h + Nitroglycerin[a]	p-value
MAP (mmHg)	70 (7.7)	77 (6.3)**	60 (3.5)**	<0.01
CI (l/min/m^2)	3.2 (0.7)	3.2 (0.7)	2.7 (0.5)***	<0.01
SVRI (Dyn*s*cm^{-5}/m^2)	1619 (378)	1801 (378)*	1653 (276)	<0.01
ITBVI (mL/m^2)	863 (307)	947 (472)	884 (383)	0.12
SVI (mL/m^2)	37.2 (4.9)	38.9 (6.4)*	30.7 (4.4)***	<0.01
HR (beats/min)	86 (13)	83 (13)**	88 (13)	<0.01

*Results of hemodynamic measurements during surgery in Paper I. Values are presented as mean (SD), p-value obtained by ANOVA, followed by t-test. Asterisks indicate significant difference vs baseline: *=p<0.05, **=p<0.01, ***=p<0.001. MAP: mean arterial pressure, CI: cardiac index, SVRI: systemic vascular resistance index, ITBVI: intrathoracic blood volume index, SVI: stroke volume index, HR: heart rate.*

[a] Nitroglycerin to MAP 60 mmHg. Reproduced from Paper I with permission from John Wiley & Sons Ltd.

4.2 PAPER II: FEATURES OF HEPATIC RESECTION

Of 39 patients screened for participation between November 2018 and April 2019, 20 were eligible for inclusion. Two patients were excluded due to spread disease discovered at surgery, leaving 18 patients for assessment. Cannulation of the portal vein was possible in 12 patients. Baseline characteristics are described in Table 4.

Table 4. Demographic data Paper II.

Baseline characteristics	**n=18**
Age, median (Q1:Q3), y	74 (67; 76)
Sex, n (%)	
Female	6 (33.3)
ASA class, n (%)	
I	1 (5.6)
II	14 (77.8)
III	3 (16.7)
Medical history, n (%)	
Hypertension	9 (50.0)
Diabetes Mellitus type II	5 (27.8)
Ischemic heart disease	4 (22.2)
Cardiac failure	2 (1.7)
Preoperative eGFR (mL/min/1.73m^2), median (Q1;Q3)	70 (60; 86)
Diagnosis, n (%)	
Colorectal metastasis	8 (44.4)
Hepatocellular carcinoma	3 (16.7)
Intrahepatic cholangiocarcinoma	4 (22.2)
Gallbladder cancer	2 (11.1)
Metastasis, malignant melanoma	1 (5.5)

Baseline characteristics of the study participants in Paper II. Adapted from Paper II with permission from John Wiley & Sons Ltd.

Mean blood loss was 1308 (SD 770 mL), and the weighing of used gauze did not add to the reliability of the blood loss estimations (unpublished data). All gauze was wet and wrung out before use and wrung out again before weighing.

4.2.1 LABORATORY RESULTS

Creatinine values peaked at 3 hours after resection but did not differ from baseline at POD 5 (Paper II). Acute kidney injury occurred in 5 patients (28%), but only one still fulfilled the KDIGO criteria for AKI at POD 5. Neither serum urea nor NAG in urine were affected. Median hs-cTnT increased over time but was within the normal range and was correlated to creatinine values (r 0.62). Five patients had elevated hs-cTnT already at baseline, and 5 patients fulfilled the MINS criteria after surgery. Arterial as well as portal venous lactate (n=12) increased over time (Table 5). I-FABP levels at 3 hours after resection did not correlate to use of PM (r -0.31). The inflammatory markers were used for design of the study protocol for Paper IV (unpublished data).

Table 5. Biomarkers Paper II.

	After induction	After dissection	After resection	Resection + 3 h	POD 1	p-value
Creatinine (μmol/L)	76.5 (43; 134)	-	-	89 (50; 155)***	87.5 (46; 187)**	<0.01
hs-cTnT (ng/L)	9.9 (5;36.4)	9.7 (5; 40.2)	10.8 (5; 38.2)	12.7 (5; 27.9)	13.7 (6;208)***	<0.01
NAG (U/L)	7.4 (2.5-44.1)	5.5 (0.5-35.6)	6.5 (0.5-43.1)	6.0 (0.5-44.1)	3.7 (0.5-30.3)	0.62
Urea (mmol/L)	6.2 (3.6; 10.0)	-	-	6.0 (2.8; 9.2)	6.0 (2.5; 12.7)	0.17
Arterial Lactate (mmol/L)	1.1 (1.0; 1.4)	1.8 (1.3; 2.2)***	3.4 (2.7; 4.4)***	2.3 (1.7; 4.1)***	-	<0.01
Portal Lactate (mmol/L)	-	1.9 (1.4; 2.2)	3.6 (3.3; 4.2)**	-	-	<0.01
D-lactate (mmol/L)	<0.28	<0.28	<0.28	<0.28	<0.28	-
I-FABP (ng/L)	2360 (581; 4010)	2100* (380; 4480)	2035 (1330; 5920)	4105** (1170; 10 000)	766*** (209; 2380)	<0.01

*Results of biomarker analysis in Paper II, obtained during surgery and until postoperative day one. Values are presented as median (minimum; maximum). P-value calculated by use of Freidman's test, followed by Wilcoxon's rank test. Asterisks indicate significant difference vs baseline: *=p<0.05, **=p<0.01, ***=p<0.001, hs-cTnT: high sensitive cardiac Troponin T, NAG: urine N-acetyl-ß-D- glucosaminidase, I-FABP; intestinal fatty acid binding protein, POD 1: postoperative day 1. Reproduced from Paper II, with permission from John Wiley & Sons Ltd.*

Table 6. Hemodynamic measurements Paper II.

	Baseline	Before resection	During resection	After resection	p-value
HR (beats/min)	62 (56; 73)	71 (60; 80)**	74 (50; 120)***	69 (62; 83)**	<0.01
MAP (mmHg)	73 (66; 81)	75 (72; 82)	75 (55; 90)	70 (66; 78)	0.13
CVP (mmHg)	8 (7; 9)	7 (5; 9)	4.5 (3; 9)**	5.5 (5; 7)**	<0.01
CI (L/min/m^2)	2.5 (2.1; 3.1)	2.7 (2.2; 3.0)	2.5 (1.6; 4.1)	2.6 (2.0; 3.4)**	<0.01
SVRI (Dyn*s* cm^{-5}/m^2)	2190 (1680; 2435)	1997 (1712; 2892)	2299 (1430; 3200)	1940 (1501; 2200)*	0.03
PVP (mmHg)	-	12 (10.5; 14)	-	13 (10.5; 15.5)	0.13

*Hemodynamic measurements obtained during surgery in Paper II. Values are presented as median (Q1;Q3), p-value calculated by use of Friedman's test, followed by Wilcoxon's rank test. Asterisks indicate significant difference vs baseline: *=p<0.05, **=p<0.01, ***=p<0.001. HR: heartrate, MAP: mean femoral arterial pressure, CVP: central venous pressure, C:; cardiac index, SVRI: systemic vascular resistance index, PVP: portal venous pressure. Reproduced from Paper II with permission from John Wiley & Sons Ltd.*

4.2.2 HEMODYNAMIC MEASUREMENTS

Hemodynamic measurements showed that CVP was <5 mmHg during the resection phase of surgery, and MAP and CI were maintained within the standard operating procedure recommendations. The PVP was not increased after surgery (n=12), and notably, the measurements were technically difficult (Table 6).

4.3 PAPER IV: EFFECTS OF VASOPRESSIN IN HEPATIC RESECTION

From April 2022 until January 2025, 376 patients were screened for participation. A total of 106 were excluded; 50 patients declined participation, 20 were planned for a minimal resection, and 36 fulfilled other exclusion criteria. Of the remaining 270 patients, 133 patients were randomized to active treatment, and 137 patients to placebo.

Twenty-five patients were excluded after randomization: 22 were discovered to have spread disease at surgery, one had an ongoing bleeding on the day of surgery due to previous ablation treatment, one had a change of planned surgical procedure, and one received the wrong treatment at randomization, leaving 119 patients in the argipressin group, and 126 in the placebo group for the primary outcome analysis. The 30 day follow up was completed by 239 participants. Baseline characteristics are displayed in Table 7.

Table 7. Demographic data Paper IV.

Baseline characteristics	Argipressin n=119	Placebo n=126
Age, mean (SD), y	65.8 (12.9)	66.3 (11.8)
Sex, n (%)		
Female	44 (37.0)	51 (40.5)
Body mass index, mean (SD)[a]	26.4 (4.9)	26.3 (4.6)
ASA class, n (%)		
I (healthy, fit patient)	18 (15.1)	10 (7.9)
II (mild systemic disease)	67 (56.3)	76 (60.3)
III (severe systemic disease)	34 (28.6)	40 (31.7)
Clinical Frailty Scale, median (min; max)[b]	3 (1; 5)	3 (1; 6)
Medical history, n. (%)		
Ischemic heart disease	9 (7.6)	8 (6.3)
Cardiac failure	2 (1.7)	7 (5.6)
Hypertension	55 (46.2)	66 (52.4)
Diabetes Mellitus type II	30 (25.2)	26 (20.6)
Hepatic cirrhosis	8 (6.7)	8 (6.3)
Diagnosis, n (%)		
Colorectal metastasis	53 (45.7)	63 (50.0)
Hepatocellular carcinoma	21 (17.8)	14 (11.1)
Intrahepatic cholangiocarcinoma	10 (8.6)	8 (6.3)
Gallbladder cancer	9 (7.6)	17 (13.5)
Perihilar cholangiocarcinoma	8 (6.9)	8 (6.3)
Metastasis (not colorectal)	5 (4.3)	5 (4.0)
Other diagnosis (malignant)	1 (0.9)	2 (1.6)
Other diagnosis (benign)	11 (9.4)	9 (7.2)
Chemotherapy within the last 3 months, n (%)	38 (32.2)	44 (35.2)
Surgical details, n (%)		
Major resection (≥3 segments)	27 (22.7)	38 (30.2)
Minimally invasive surgery	32 (26.9)	31 (24.6)

Baseline characteristics of the participants in Paper IV. ASA: American Society of Anesthesiologists.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Clinical Frailty Scale Scores range from 1-9, with higher scores indicating greater frailty.

4.3.1 BLOOD LOSS AND TRANSFUSIONS

Blood loss at the end of surgery did not differ between the groups; median 450 mL (min 5, max 26500) in the argipressin group vs median 500 mL (min 10, max 10 000) in the placebo group, RR 0.90 (95% CI: 0.70-1.17) (Figure 10).

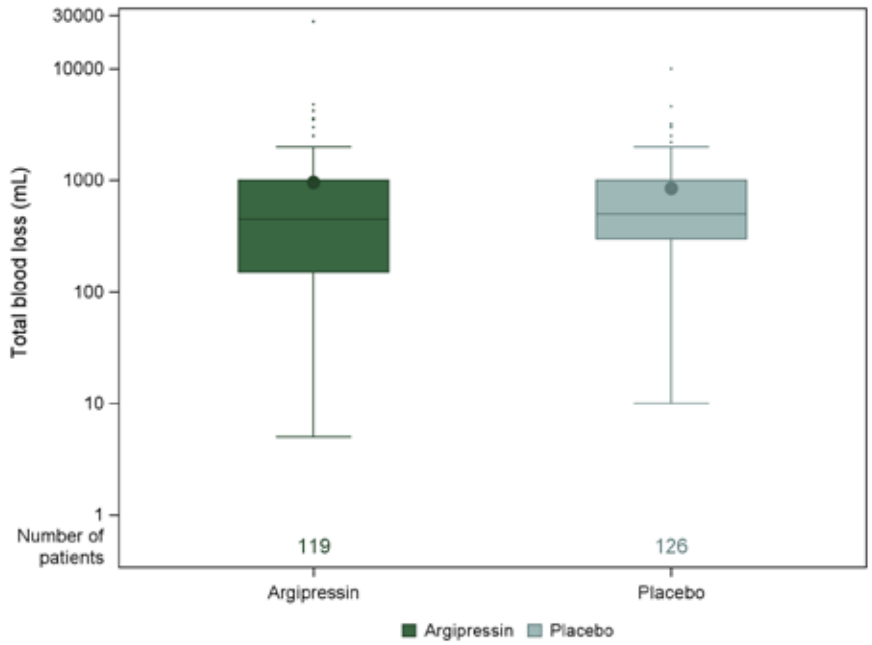

Figure 10. *Blood loss at the end of surgery, by treatment group (modified intention to treat population). The y-axis is log-transformed. The horizontal line within the box plot represents the median, the circle indicates the mean, the top and bottom of each box indicate the interquartile range, and whiskers indicate 1.5 times the interquartile range. Small dots indicate outliers.*

Neither proportion of patients transfused, nor transfused RBC and plasma volume, differed between the groups. Three patients in the treatment group received transfusion of platelets, vs five in the placebo group (Table 8). One patient in the argipressin group experienced an unexpected surgical blood loss of 26 500 mL. A post hoc sensitivity analysis was performed on the mITT population with blood loss ≤10 000 mL, with similar results as the original mITT analysis: median blood loss 450 mL in the argipressin group vs 500 mL in the placebo group, RR 0.87 (95% CI: 0.68-1.12). There was no evidence of interaction by type of surgery (minimally invasive vs open), extent of resection ("large" or "small"), indication for surgery, presence of hepatic cirrhosis, or age on the primary outcome (Paper IV).

Table 8. Blood loss and transfusions.

	Argipressin	Placebo	Treatment effect (95% CI)	p-value
Blood loss during surgery (mL), mean (SD), median (range)[a]	955 (2511) 450 (5; 26500) n=119	848 (1151) 500 (10; 10000) n=126	RR 0.90 (0.70 - 1.17)	0.44
RBC transfusion study period**,** n (%)[b]	43 (36.8)	52 (41.3)	OR 0.84 (0.48 - 1.49)	0.56
RBC transfusion day of surgery (mL) (patients who received transfusion), mean (SD), median (range)[a]	1002 (2338) 555 (200; 13160) n=30	757 (726) 518 (250; 3108) n=39	RR 0.95 (0.64 - 1.41)	0.80
RBC transfusion study period (mL), mean (SD), median (range)[a]	1097 (2164) 570 (250; 14020) n=43	864 (744) 582 (250; 4502) n=52	RR 0.96 (0.71 - 1.30)	0.79
Plasma transfusion study period (mL), mean (SD)[a]	1507 (2838) n=15	945.1 (920) n=19	RR 1.13 (0.60 - 2.12)	0.70
Platelet transfusion study period, n (%)	3 (2.5)	5 (4.0)	-	-

Blood loss during surgery and transfusion requirements during the day of surgery and during the study period. OR: odds ratio, RR: relative risk, HR: hazard ratio, RBC: red blood cell.

[a] Treatment effect expressed by RR (95% CI) from linear regression with lognormal distribution adjusted for randomization strata.

[b] Treatment effect expressed by OR (95% CI) from logistic regression adjusted for randomization strata.

4.3.2 PERIOPERATIVE DATA

No major differences were observed when comparing surgical and anesthesiologic parameters between the two groups. In both groups, CVP and MAP were maintained according to the standard operating procedure, and the time with applied Pringle maneuver did not differ between the groups (Table 9). Hemodynamic measurements were registered at baseline and every 30 minutes during the resection phase of surgery, and no differences between the groups were observed. Median time to discharge from hospital was seven days in the argipressin group, and eight days in the placebo group (HR 1.21, 95% CI: 0.93-1.58) (Paper IV).

Table 9. Perioperative variables Paper IV.

	Argipressin n=119	Placebo n=126	Treatment effect (95% CI)	p-value
Duration of surgery, mean (SD), min[a]	316 (150)	339 (145)	RR 0.94 (0.85 - 1.03)	0.18
Duration of Pringle maneuver, mean (SD), min[a]	34 (31)	35 (32)	RR 1.04 (0.86 - 1.26)	0.66
Conversion from minimally invasive to open surgery, n /n of planned minimally invasive surgery (%)[b]	8/41(19.5)	11/42(26.2)	-	0.64
Achievement of CVP goal, n (%)[c]	102 (86.4)	112 (89.6)	OR 0.75 (0.34 - 1.65)	0.48
Norepinephrine, mean (SD), µg[a]	2306 (1955)	3036 (2419)	RR 0.80 (0.62 - 1.04)	0.10
Urinary output, mean (SD), mL[d]	1810 (533)	1830 (592)	MD -22.65 (-171 - 125)	0.76
Digital hypoperfusion, n (%)	0 (0.0)	1 (0.8)	-	-
Volume of study drug (safety population), mean (SD), mL[e]	20.5 (11.4) n=133	22.1 (10.3) n=137	-	0.09

Perioperative surgical and anesthesiologic variables registered during surgery. OR: Odds Ratio, adjusted for randomization strata, RR: Relative Risk, adjusted for randomization strata.

[a] Treatment effect expressed by RR (95% CI) from linear regression with lognormal distribution.

[b] P-value calculated by Fischer's exact test.

[c] Treatment effect expressed by OR (95% CI) from logistic regression.

[d] Treatment effect expressed by mean difference (95% CI) from linear regression adjusted for randomization strata.

[e] Treatment effect expressed by p-value from unadjusted Mann-Whitney U test.

4.3.3 LABORATORY RESULTS

The perioperative laboratory results, including hs-cTnI, lactate and creatinine, did not differ between the groups. Hs-cTnI values above the upper limit were detected in 7/88 (8%) of the women and in 15/142 (11%) of the men (Table 10).

Table 10. Laboratory results Paper IV.

Analysis	Visit	Argipressin	Placebo	Change from baseline, argipressin	Change from baseline, placebo	p-value
Creatinine (μmol/L)	Baseline	70.4 (18.4)	74.9 (26.2)			
	End of surgery	80.9 (21.7)	89.2 (29.9)	10.5 (10.2)	14.4 (12.9)	0.021
	POD 1	81.6 (26.8)	88.1 (40.5)	11.3 (17.4)	13.4 (21.2)	0.63
	POD 2	80.0 (39.7)	84.1 (52.1)	10.0 (33.4)	9.2 (31.5)	0.66
	POD 5	74.6 (34.2)	73.1 (29.0)	2.2 (30.0)	-1.9 (20.2)	0.71
hs-cTnI (ng/L)	Baseline	7.6 (25.1)	3.9 (3.0)			
	End of surgery	9.8 (18.4)	8.2 (12.7)	2.0 (20.2)	4.3 (12.6)	0.75
	POD 1	35.3 (175.8)	20.8 (92.6)	27.4 (175.9)	17.0 (93.1)	0.80
Lactate (mmol/L)	Baseline	1.4 (0.4)	1.3 (0.5)			
	End of surgery	3.1 (1.9)	2.9 (1.4)	1.7 (1.9)	1.6 (1.4)	0.95
	Surgery +3h	2.5 (1.9)	2.3 (1.3)	1.2 (1.8)	1.0 (1.3)	0.78
	POD 1	2.1 (1.4)	2.0 (1.2)	0.7 (1.4)	0.7 (1.1)	0.87
INR	Baseline	(0.2)	(0.1)			
	POD 1	1.4 (0.2)	1.4 (0.2)	0.3 (0.3)	0.4 (0.2)	0.21
	POD 2	1.4 (0.3)	1.4 (0.2)	0.3 (0.4)	0.3 (0.2)	0.71
	POD 5	1.3 (0.2)	1.3 (0.2)	0.2 (0.3)	0.2 (0.2)	0.97
Bilirubin (μmol/L)	Baseline	10.9 (7.9)	11.4 (9.1)			
	POD 1	24.2 (21.8)	22.8 (20.1)	13.0 (19.4)	11.5 (16.0)	0.76
	POD 2	21.5 (18.1)	22.0 (18.3)	10.5 (16.3)	11.2 (16.8)	0.68
	POD 5	23.1 (26.8)	20.8 (21.0)	12.2 (27.3)	9.4 (18.4)	0.86
CRP (mg/L)	Baseline	9.6 (19.5)	7.2 (16.1)			
	End of surgery	7.5 (14.0)	6.3 (14.6)	-2.1 (6.6)	-1.0 (3.3)	0.77
	POD 1	49.5 (29.4)	48.0 (28.1)	39.8 (30.4)	40.4 (26.0)	0.89
	POD 2	94.6 (43.9)	96.5 (47.1)	84.4 (44.7)	89.1 (46.6)	0.54
	POD 5	89.2 (46.9)	88.4 (50.0)	76.3 (55.1)	81.7 (50.2)	0.80
Hemoglobin (g/L)	Baseline	126.8 (15.8)	125.0 (15.2)			
	End of surgery	113.6 (16.7)	113.1 (15.0)	-13.1 (12.2)	-12.0 (13.1)	0.33
	POD 1	107.1 (15.8)	105.3 (13.4)	-19.9 (13.9)	-19.7 (14.8)	0.89
	POD 2	101.6 (14.4)	100.3 (11.9)	-25.7 (14.9)	-24.0 (15.8)	0.41
	POD 5	100.3 (12.8)	100.3 (12.6)	-24.4 (16.3)	-23.1 (17.9)	0.77

Results of laboratory analysis during the study period. Data are presented as mean (SD) and p-value for the change from baseline compared between the groups was obtained by unadjusted Mann-Whitney U test. hs-cTnI: high sensitive cardiac Troponin I, INR: international normalized ratio, CRP: C-reactive protein.

Table 11. Postoperative complications Paper IV.

	Argipressin n=119	Placebo n=126	Treatment effect
Acute Kidney Injury, n (%)	23 (19.3)	27 (21.4)	OR 0.89[a] (95% CI: 0.47-1.69)
Radicality of resection, n (%)			p= 0.28[b]
Whole tumour removed	77 (66.4)	70 (56.5)	-
Residual tumour present	17 (14.7)	25 (20.2)	-
Cannot be assessed	22 (19.0)	29 (23.4)	-
Highest Clavien grade, n (%)			p=0.028[c]
Major postoperative complication, n (%) (Clavien grade ≥3)	20 (17.2)	27 (21.8)	OR 0.76[a] (95% CI: 0.39 - 1.45)
Postoperative complications, Clavien grade			
Clavien 2 (Pharmacological treatment other than treatment with antiemetics, antipyretics, analgesics, diuretics, electrolytes, or physiotherapy)	25 (21.6)	45 (36.3)	-
Clavien 3a (Treatment requiring local anesthesia)	10 (8.4)	19 (15.1)	-
Clavien 3b (Treatment requiring general or epidural anesthesia)	4 (3.4)	6 (4.8)	-
Clavien 4a (Single organ dysfunction)	3 (2.5)	1 (0.8)	-
Clavien 4b (Multiorgan dysfunction)	1 (0.8)	0 (0.0)	-
Clavien 5 (death)	2 (1.7)	1 (0.8)	-
Postoperative complications, n (%)	45 (38.8)	72 (58.1)	OR 0.43[a] (95% CI: 0.25-0.74)
Liver failure	8 (6.7)	9 (7.1)	p=1.00
Renal failure	7 (5.9)	2 (1.6)	p=0.09
Bile leakage	11 (9.2)	9 (7.1)	p=0.64
Ascites	4 (3.4)	8 (6.3)	p=0.38
Bleeding	9 (7.6)	8 (6.3)	p=0.80
GI perforation/leakage	1 (0.8)	0 (0.0)	p=0.49
Other gastrointestinal complication	4 (3.4)	8 (6.3)	p=0.38
Infectious complication, any	30 (25.2)	49 (38.9)	p=0.028
Infectious complication - abdominal	6 (5.0)	14 (11.1)	p=0.10
Infectious complication - liver/cholangio	3 (2.5)	3 (2.4)	p=1.00
Infectious complication - other	24 (20.2)	34 (27.0)	p=0.23
Cardiovascular complication	6 (5.0)	7 (5.6)	p=1.00
Venous thromboembolic event	0 (0.0)	2 (1.6)	p=0.50
Complication requiring intensive care	4 (3.4)	2 (1.6)	p=0.44
Other complication	15 (12.6)	24 (19.0)	p=0.22

Complications registered at follow up at 30 days after surgery. If not otherwise stated, p-value is obtained from Fisher's exact test.

[a] Treatment effect expressed by Odds Ratio from logistic regression adjusted for randomization strata.

[b] Treatment effect expressed by p-value from Chi-square test.

[C] Treatment effect expressed by p-value from Mantel-Haenszel Chi-square trend test.

4.3.4 POSTOPERATIVE COMPLICATIONS

The incidence of postoperative complications registered at the 30-day follow up was lower in the argipressin group, primarily due to a lower rate of postoperative infections. Acute kidney injury was reported in 23 patients (19.3%) in the argipressin group and in 27 patients (21.4%) in the placebo group. The surgery was equally successful in both groups regarding radicality of resection (Table 11).

4.3.5 ADVERSE EVENTS

The rate of adverse events did not appear to differ between the groups, and the vast majority of AEs were related to the surgical procedure rather than the study intervention (Table 12).

Table 12. Adverse Events and Serious Adverse Events.

	Argipressin (n=133)	**Placebo (n=137)**	**Overall (n=270)**
AE, n (%)	75 (56.4)	86 (62.8)	161 (59.6)
Treatment-related AE	2 (1.5)	2 (1.5)	4 (1.5)
Procedure-related AE	69 (51.9)	83 (60.6)	152 (56.3)
SAE, n (%)	38 (28.6)	43 (31.4)	81 (30.0)
Treatment-related SAE	1 (0.8)	0 (0.0)	1 (0.4)
Procedure-related SAE	36 (27.1)	41 (29.9)	77 (28.5)
AE leading to discontinuation, n (%)	2 (1.5)	0 (0.0)	2 (0.7)
AE leading to death, n (%)	2 (1.5)	1 (0.7)	3 (1.1)

Adverse events and serious adverse events, registered during the study period. AE: adverse event, SAE: serious adverse event.

5 DISCUSSION

Despite efforts to improve both surgical and anesthesiologic care, blood loss and blood transfusions along with postoperative complications remain a reality in hepatic resection, as emphasized by the recent Helix multicenter trial (12). In the present thesis, the previously established and approved pharmacological agent vasopressin was evaluated as a potential treatment for reduction of blood loss in hepatic resection. Vasopressin is suggested as second line vasopressor treatment of vasoplegia in septic shock and has been shown to reduce complications after cardiac surgery as well as transfusion requirements in trauma (71, 94, 105).

The physiological effects of vasopressin on hepatic hemodynamics were evaluated in an experimental, non-randomized study, followed by an appraisal of hemodynamic and biomarker response during hepatic resection. To determine the effects of vasopressin on blood loss and transfusion requirements, as well as perioperative AKI and postoperative complications, a randomized, placebo-controlled, double-blinded trial was performed. The randomized study design minimized the risk of selection bias and the influence of possible confounders, and the study protocol, including the statistical analysis plan, was published before study completion.

5.1 PRESSURE AND BLOOD FLOW

Anesthesia and intensive care aim to support vital functions and maintain oxygenation by ensuring adequate blood flow to vital organs. For practical reasons, blood pressure is often measured as a surrogate for blood flow, even though both parameters are relevant for organ perfusion. The effects of vasopressin and nitroglycerin on PVP, HVP and blood flow through the liver in patients undergoing hepatic resection, was investigated at the start of this research project.

In Paper I, vasopressin reduced the portal blood flow almost by half, while the PVP remained unchanged. This finding is in accordance with results from physiological studies suggesting an autoregulatory mechanism to maintain PVP even during major changes in portal blood flow in the healthy liver (126).

However, in the cirrhotic liver, the effect of the vasopressin-analogue terlipressin on PVP is well established and is the basis for terlipressin treatment of bleeding esophageal varices and hepatorenal syndrome (88, 89). Terlipressin also reduces PVP in liver transplantation (77, 99). The patients in Paper I had normal PVP at baseline, which may explain the lack of vasopressin effect on PVP.

The portal blood flow is reduced by vasopressin, as shown in previous physiological studies, and terlipressin is shown to reduce portal blood flow in liver transplantation (96, 127). Lautt et al. showed that a reduction of portal blood flow reduces the intrahepatic distention pressure and causes expulsion of blood from the liver area, decreasing the liver volume (128). These findings evoked the theory that a reduction of portal and hepatic blood flow could function as a "physiologic Pringle" while preserving the oxygenation of the liver by the HABR effect, in contrast to mechanical occlusion methods where the portal and arterial blood supply to the liver is obstructed. Ideally, this redirection of blood away from the surgical field would contribute to a reduction of blood loss and minimize the need for Pringle maneuver, presuming that reduction of portal and hepatic blood flow rather than PVP is the major determinant of blood loss during hepatic resection. In combination with LCVP, the effect on blood loss would potentially be enhanced, compared to current treatment with norepinephrine as the first line vasopressor during hepatic resection.

Nitroglycerin is shown to influence hepatic hemodynamics by its vasodilatory properties, and could theoretically add benefits to vasopressin treatment by reduction of liver volume and distention pressure (59). However, the physiological effects on hepatic pressures and blood flow in Paper I were complicated by circulatory instability, with a marked reduction of CI when nitroglycerin was added to vasopressin. In current practice, a target MAP at least >65-70 mmHg is recommended, and the effect of nitroglycerin on hepatic blood flow with a higher target MAP than 60 mmHg was not evaluated in Paper I. These factors contributed to the choice of pursuing vasopressin alone, and not in combination with nitroglycerin, as the study drug in Paper IV.

5.2 BLOOD LOSS AND TRANSFUSIONS

Vasopressin did not reduce blood loss or transfusion requirements compared to placebo in Paper IV. Presumably, portal blood flow was reduced as shown in Paper I, even though not measured in Paper IV. The fact that Pringle maneuver was used at the discretion of the surgeon, and that this mechanical inflow occlusion potentially blunted a vasopressin-induced reduction of portal blood flow, likely contributed to the lack of effect on perioperative blood loss.

A randomized controlled trial by Sims et al., investigating the effects of vasopressin in traumatic injury, showed reduced transfusion requirements in the vasopressin group (105). A previous, smaller, randomized controlled trial also showed reduced need of RBC and fluid transfusion in trauma patients, after an infusion of vasopressin for 5 hours (104). The positive effect of vasopressin in trauma is likely multifactorial. Improved hemodynamics in shock by vasoconstrictive effects, water retention by stimulation of V2 receptors, as well as direct procoagulant effects may all contribute to improved outcomes. There was no increased risk of adverse events in the treatment groups in any of the studies, indicating that vasopressin is safe to use in relatively hypovolemic, vasoconstricted trauma victims (104, 105).

The results regarding blood loss and transfusion in Paper IV trial are in contrast to previous randomized controlled trials investigating terlipressin in hepatic resection (13, 14). Both Mahdy et al. and Abbas et al. employed a fluid liberal protocol with maintenance crystalloid 8 mL/kg/h, and did not apply LCVP anesthesia according to current recommendations (56). The study by Mahdy et al. included a mixed population of patients undergoing hepatic resection or Whipple procedure, where baseline PVP was >15 mmHg, and Pringle maneuver was not allowed (14). Abbas et al. reported a mean blood loss of approximately 1900 mL in the placebo group, twice as high as the blood loss reported in Paper IV. These differences may explain the marked reduction of blood loss in the mentioned trials. In Paper IV, where the LCVP technique was maintained and the Pringle maneuver applied, vasopressin treatment did not add further reduction of blood loss.

Surgery is complex, and it is unlikely that any single strategy would affect outcomes as markedly as the paradigm shift initiated by introduction of the LCVP anesthesia technique. The surgery itself naturally has the most

significant impact on perioperative blood loss. The purpose of Paper IV was not to reduce surgical bleeding complications, but rather to contribute with improved surgical conditions and less potential risk for blood loss and transfusions for the patients following the expected course of treatment in hepatic resection.

5.3 BIOMARKERS OF VITAL ORGAN FUNCTION

Anesthesia and major surgery entail risk of complications, associated with the surgical procedure itself and its root cause, but also with anesthesia. The stress of surgery and anesthesia may manifest in injury to specific organs, such as the kidney and the heart, or in cerebral events such as stroke, as well as postoperative infections and respiratory complications. Hence, monitoring of organ function is important to optimize perioperative care. Biomarkers were explored in Paper II, and the choice of biomarkers was adjusted in the protocol for further exploration in Paper IV.

5.3.1 ACUTE KIDNEY INJURY

In Paper II, 28% of the patients had postoperative AKI, compared to 19.3% and 21.4% in the argipressin and placebo groups in Paper IV, respectively. This discrepancy may be explained by the small sample size in Paper II. The rate of AKI in Paper IV is in accordance with the recent EPIS-AKI multicenter trial, reporting an overall AKI rate of 18.4% in patients undergoing major surgery, including cardiac surgery procedures (110). A recent retrospective observational study by Worrall et al. included >13 000 patients and reported an incidence of AKI of 9.7%. Risk factors for AKI included intra-abdominal surgery, where the hepato-biliary surgery group had an AKI incidence of 15.1%. Most AKI occurred within the first 48 h after surgery, and AKI was still associated with postoperative complications and mortality (108).

The mechanism behind postoperative AKI development is multi-factorial. Reduced glomerular perfusion, microcirculatory and endothelial dysfunction with release of pro-inflammatory cytokines, inflammatory activation of pro-coagulant pathways leading to formation of micro-thrombi, tubular cell injury

and renal congestion have all been described (112). Additionally, blood loss and transfusions are associated with AKI in hepatic resection (107, 115).

Theoretically, several aspects of AKI development could be modulated by vasopressin. Vasopressin increases systemic perfusion pressure, restoring renal perfusion pressure to the autoregulatory range, but also specifically increases the glomerular perfusion pressure. Constriction of the efferent, but not the afferent, glomerular arteriole increases glomerular filtration, but this effect may come at the cost of increased oxygen demand (83). Vasopressin reduces cytokine release, and it has been suggested that V2 receptors are involved in the renal dysfunction in sepsis (85, 86). These effects may have contributed to the reduced need for continuous renal replacement therapy in the vasopressin group shown in the VANISH trial, comparing vasopressin and norepinephrine in combination with corticosteroids in sepsis (93).

The exploratory secondary outcomes AKI incidence and urinary output did not differ between the groups in Paper IV. Previous studies have not found an increased risk of AKI with application of LCVP anesthesia in hepatic resection, but vasopressin has not been evaluated previously in this aspect (63, 65, 67). The current definitions of AKI focus on creatinine, a marker of already manifest AKI. The development of novel biomarkers, indicating cell stress before manifest injury, is crucial to enable prevention of AKI by initiation of care bundles at an early stage.

5.3.2 MYOCARDIAL INJURY

In Paper II, 28% of the patients fulfilled MINS criteria, which is more than previous reports regarding major in-patient surgery (118, 119, 129, 130). This finding must be interpreted with caution considering the small sample size, and the correlation between hs-cTnT and serum-creatinine. The hs-cTnI analysis method used in Paper IV was not available when the MINS concept was defined, and cut off values for hs-cTnI in the MINS definition are extrapolated from previous definitions for hs-cTnT (values >the 99th percentile) (118). This may partly explain the lower incidence of elevated troponin levels (8% in women, 11 % in men) in Paper IV. This incidence is equal or lower than the incidence stated in previous reports in non-cardiac surgery (118, 119, 129, 130). The low incidence of elevated hs-cTnI in Paper IV, where no difference was shown between the argipressin and placebo group, indicates that the

vasoconstrictive effects of vasopressin in the fluid restrictive setting of hepatic resection, is safe regarding coronary perfusion. However, further studies are needed to confirm this exploratory finding.

5.3.3 LACTATE

Arterial lactate did not differ between the argipressin and the placebo group in Paper IV. None of the patients suffered from intestinal ischemia according to the registration of adverse events, and only one patient, in the placebo group, had signs of digital hypoperfusion (prolonged capillary refill time). Albeit being an unspecific marker, lactate levels are correlated to outcomes in hepatic resection (125). The risk of reduced microcirculation in the gut in relation to V1 agonists has been debated and could be a concern with use of vasopressin (131, 132). The intestines were under direct visualization during the surgical procedure in Paper IV, without signs of hypoperfusion during the course of the study. This, in combination with the low incidence of adverse events related to hypoperfusion, indicates that the study protocol in Paper IV did not affect intestinal perfusion to a major extent, even if further studies are warranted to confirm this observation.

5.4 PERIOPERATIVE CONSIDERATIONS

In Paper IV, the LCVP was successfully applied in both the argipressin and the placebo group, and hemodynamic measurements did not differ between the groups. As expected, the norepinephrine dose was numerically higher in the placebo group, but without reaching statistical significance. As summarized in recent publications, addition of non-adrenergic vasopressors to standard perioperative treatment of vasoplegia is associated with reduced morbidity, including atrial fibrillation, AKI as well as reduced length of stay in hospital (70, 133). Notably, the vasopressin dose in Paper IV was administered in a fixed dose, while in clinical practice the dose would have been adjusted according to the hemodynamic response.

The time with applied Pringle maneuver did not differ between the groups in Paper IV, contradicting the theory that redirection of blood away from the surgical field would improve the surgical conditions to the extent that the need of Pringle maneuver would be reduced. However, preferences vary between surgeons, where some use the Pringle maneuver preventively, blunting effects

of reduced hepatic blood flow. The individual surgeon's performance was not evaluated in relation to blood loss, but all surgeries were performed by a small, dedicated team of surgeons with long experience of hepatic surgery.

5.5 POSTOPERATIVE COMPLICATIONS

Despite continuous efforts to improve perioperative care, surgical procedures entail complications. In Paper IV, a lower incidence of complications, and postoperative infections in particular, was observed in the treatment group compared to the placebo group. This finding was despite the lack of difference in blood loss or transfusions which are known predictors of postoperative complications (20, 134, 135).

5.5.1 INFLAMMATORY RESPONSE

The immunological response to surgery and trauma in many ways resemble the response to sepsis, characterized by fever, tachycardia, hyperventilation and elevated or decreased white blood cells. Perioperative anesthesiologic care aims to reduce this stress response by a bundle of treatments, including adequate pain control with neuroaxial blocks if appropriate, metabolic control and prevention of hypothermia (136, 137).

Vasopressin has a multitude of effects on the immune system, including release of prostaglandins, modulation of cytokine levels and immune cells and interaction with the corticosteroid axis (85). In a cohort derived from the VASST trial, where vasopressin was compared to norepinephrine in sepsis, the vasopressin group had a reduced cytokine level compared to controls (86). A recent randomized controlled trial comparing terlipressin and norepinephrine in sepsis, found lower levels of CRP, interleukin 8 and tumor necrosis factor-α in the treatment group compared to controls (138).

The inflammatory response in open vs laparoscopic hepatic resection has been described, but the effects of vasopressin treatment on postoperative systemic inflammatory response syndrome (SIRS) in hepatic resection has not been evaluated (139). Levels of the vasopressin pre-pro hormone copeptin were evaluated in 41 patients with SIRS after abdominal surgery, indicating that the vasopressin response is well maintained after abdominal surgery, in contrast to the suggested vasopressin deficit in sepsis (81, 140). Notably, there was no

difference in change of CRP between the groups in Paper IV, despite the difference in postoperative infections.

5.6 METHODOLOGICAL CONSIDERATIONS

The papers included in this thesis have some limitations. In Paper I, measurements were performed before the actual liver resection. Hence, the effects of the hepatic resection itself and the consequences of use of Pringle maneuver were not assessed.

The relative blood flow changes in Paper I were calculated and not measured. Fick's principle assumes that all other factors, apart from the blood flow, are unchanged. In hepatic circulation, the HABR may increase the delivery of oxygenated arterial blood to the liver in response to reduced portal blood flow, increasing hepatic oxygenation and hepatic venous oxygen saturation. This could explain the less pronounced effect on calculated change of hepatic blood flow, compared to calculated change of portal blood flow, reported in Paper I. Direct flow measurement by doppler ultrasonography has been used previously, and could have been a way to confirm our calculated results (96). Furthermore, no control measurements were obtained after the experimental procedure, due to time constraints.

While the patients in Paper I served as their own controls, the study in Paper II lacked a control group. This limitation prevents conclusions regarding whether the noted hemodynamic and laboratory changes are representative for hepatic resection in particular, or for any type of major abdominal surgery. In addition, the baseline laboratory samples were taken after induction of anesthesia, not before, and it is possible that this influenced the laboratory results.

The single center design in Paper IV limits the external validity of the study. On the other hand, keeping data collection limited to one center had logistic benefits and ensured good adherence to protocol. Demographic and blood loss data were in accordance with the large multi-center Helix trial, indicating similar cohorts (12). No long term oncological follow up was performed in Paper IV, but is highly warranted, especially considering the lower rate of complications in the argipressin group, indicating that vasopressin effects may extend beyond the immediate perioperative time period.

Another limitation in Paper IV is the choice of blood loss as the primary outcome. A standardized protocol for blood loss assessment was used, and the same study nurse performed all measurements. Any measurement inaccuracy would be equally frequent in both groups due to the double-blinded randomized study design. Several formulas are available for quantification of blood loss, but transfusions are rarely included in the formulae, which made them unsuitable for this trial (141).

The dose of vasopressin was subject to careful consideration. Large randomized controlled trials in sepsis and trauma have used doses ranging from 0.01- 0.06 U/min (0.6-3.6 U/h) for up to 48 hours, compared to the shorter perioperative infusion used in the present study (92-94, 105). Based on these trials with long-term infusion of vasopressin, a dose in the higher interval was chosen to achieve the intended effect during the limited time of infusion, but with the dose related to weight to ensure comparable treatment for all patients.

5.7 CONCLUDING REMARKS

The findings in the present thesis regarding blood loss, AKI, troponin elevation and postoperative complications confirm that hepatic resection is still a high-risk procedure, motivating further studies in this area. The hypothesis that a reduction of portal and hepatic venous blood flow by vasopressin would reduce blood loss during surgery was not supported by the results from the randomized, controlled double-blinded trial in Paper IV, where no difference in blood loss or blood transfusion could be shown. Though the results were negative regarding the primary outcome, knowledge was gained regarding renal and cardiac outcomes in hepatic resection and the safety profile of vasopressin. There were less complications in the treatment group, and no evident difference in occurrence of adverse events.

Vasopressin has not been studied in hepatic resection with focus on blood loss and transfusion previously, indicating that this thesis will present novel information about an area of anesthesiologic care in hepatic resection not yet explored.

6 CONCLUSIONS

Infusion of vasopressin reduced portal and hepatic venous blood flow, but not PVP, in patients with normal baseline PVP. Addition of nitroglycerin reduced the portal and hepatic blood flow as well as PVP and HVP, at the price of hemodynamic instability.

Vasopressin does not reduce blood loss or transfusion requirements in hepatic resection performed under LCVP anesthesia with application of Pringle maneuver.

Creatinine, troponin and lactate levels increase after hepatic resection, but there was no increased risk of AKI or MINS with use of vasopressin compared to placebo.

Treatment with vasopressin during hepatic resection was associated with less postoperative complications compared to placebo. This effect was primarily due to a lower rate of postoperative infections.

The occurrence of adverse events was comparable between the treatment and placebo groups, indicating that vasopressin is safe to use in hepatic resection under LCVP anesthesia.

7 FUTURE PERSPECTIVES

In Paper IV, the overall transfusion rate was 38.8%, which is considerably higher than in the Helix trial (15.3%), despite similar mean blood loss (12). It would be worth evaluating in a future trial if a stricter transfusion protocol, or a bundle of care including pre-operative optimization, could reduce transfusion rates in hepatic resection in our setting.

Modulation of the inflammatory response to surgery could potentially improve postoperative immune competence and recovery (139). Inflammatory markers were analyzed as a sub-study to the trial in Paper IV, and hopefully the results will contribute to our knowledge regarding the immunomodulating properties of vasopressin.

The potential of vasopressin to influence mechanisms of perioperative AKI development in liver transplantation is promising. In addition to renal effects, vasopressin could restore SVRI and reduce portal flow to the transplanted liver, while preserving hepatic oxygenation by HABR. These effects have only been evaluated in part, and the results from the ongoing randomized controlled trial Low-dose Arginin-vasopressin Supplementation on Post-transplant Acute Kidney Injury After Liver Transplantation (AVENIR) (ClinicalTrials.gov ID NCT06344442) are eagerly anticipated (72, 96, 99).

In experimental studies on canine arteries, vasopressin is shown to have local vasodilatory properties by release of NO in selective vascular beds, and the systemic vasoconstrictive effect of vasopressin is not apparent in the human pulmonary artery in vitro (142, 143). Retrospective studies indicate favorable effect of vasopressin on persistent pulmonary hypertension in the newborn, and vasopressin is suggested as treatment in adults with cardiogenic shock and pulmonary hypertension (144-146). However, randomized controlled trials comparing vasopressin to standard treatment in pulmonary hypertension in adults are lacking, and would be an interesting field of future research.

The findings in this thesis indicate that use of vasopressin was safe in the tested doses, in the fluid restrictive context of LCVP anesthesia, opening the field for future studies on vasopressin in other types of abdominal surgery.

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