Acta Anaesth. Bel., 2024, 75 | Suppl. 1: 39-46

Masterthesis / Original study

The effect of dobutamine on hepatic blood flow during goal-directed therapy: preliminary results

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Abstract

Background: **The influence of dobutamine on the liver blood flow during major abdominal surgery is not fully understood. The primary goal is to study the effect of dobutamine on the blood flow in the portal vein (PVF), the hepatic artery blood flow (HAF) and the hepatic blood flow (HBF).**
Methods: **Patients who were scheduled for pancreaticoduodenectomy were selected for inclusion and an informed consent was taken. Flow measurements are made with ultrasound transit time flow probes. Hemodynamic data was measured using the PulsioFlexTM. These hemodynamic data were measured at designated times: after resection (T1), after 10 minute infusion of 2 µg.kg-1.min-1 dobutamine (T3) and after 10 minutes of 5 µg.kg-1. min-1 dobutamine infusion (T4). In this study the first 15 included patients were analyzed. Primary endpoint was to determine the change in hepatic artery blood flow index (HAFi), portal vein flow index (PVFi) and hepatic blood flow index (HBFi). Secondary endpoints were to study the changes in the measured hemodynamic data. A total of 26 patients were selected, with inclusion of 15 patients for further analysis. Statistical analysis was made using ANOVA for repeated measurements.**
Results: **A total of 15 patients were included for statistical analysis. A significant increase in HBFi at T4, compared to baseline, was seen due to a dose-dependant increase in PVFi. In the hepatic artery, a steady decline of HAFi was measured. For secondary outcomes, a rise in mean cardiac index (CI) and a decrease in mean systemic vascular resistance index (SVRI) was seen.**
Discussion and Conclusions: **In this study, an increase in HBF was measured through an increase in PVF. Because the hepatic artery buffer system, the HAF decreased. This might suggest that dobutamine is capable of modulating the HBF during major abdominal surgery. For secondary outcomes, a rise in CI at low dose dobutamine infusion, but not increasing further at higher infusion rate, was seen.**

Keywords: **Dobutamine, hepatic blood flow, liver circulation.**

Introduction

The intricate balance of perfusion pressure and organ blood flow plays a pivotal role in maintaining vital organ blood supply and ensuring optimal physiological function. In some clinical settings increasing the cardiac output might be a possible therapeutic option to optimize this balance in oxygen delivery and oxygen consumption. The goal of this study was to analyze the effect of dobutamine on liver blood flow and perfusion.

Dobutamine is a synthetic catecholamine. It primarily acts as a β1- and β2-adrenergic receptor agonist, activating the Gs protein-coupled receptor, thereby increasing intracellular cAMP due to the activation of adenylate cyclase. The increased cAMP acts as a mediator with a downstream increase in intracellular Ca2+. Stimulation of the β1-receptor in the myocardium causes increased inotropy and increased heart rate. Activation

Approved by the ethical committee of the University Hospital of Ghent (BC-08919, Prof. Dr. Deron, 06/04/2021). EudraCT: 2020–005412-21. A written consent was obtained for each participant for this study. Subjects were included from 09/2021 until 7/2023.

of the β2-receptor causes the smooth vascular musculature to relax, with resulting vasodilatation and a decrease in systemic vascular resistance (SVR)[1,2]. These pharmacodynamic effects give dobutamine a favorable profile as a short-term treatment for cardiogenic shock, inodilatory support during the weaning of extra-corporeal circulation in cardiac surgery or as a diagnostic agent for patients with suspected coronary disease. While the possible cardiovascular benefits of dobutamine have been extensively studied, its influence on organ-specific blood flow, particularly hepatic blood flow (HBF), remains a subject of further study. There have been several studies involving animal models, human subjects during partial hepatectomy or patients in septic shock. But research during major abdominal surgery is lacking[3-6].

The liver is a central hub for synthesis, drug clearance, as well as nutrient- and blood storage. To function it relies on a finely regulated blood supply. In normal physiologic conditions the liver receives approximately 25% of the cardiac output. The hepatic circulation is a complex network of vessels, mainly involving the portal vein (70-80% hepatic blood supply) and hepatic artery (20-30% hepatic blood supply). This dual blood supply system provides the liver with the necessary substrates for its diverse array of functions. The liver has the ability to regulate its own blood supply, often separated in an intrinsic- and extrinsic system.

The intrinsic regulation consists of three important mechanisms: the metabolic regulatory system, the myogenic autoregulation and the hepatic arterial buffer response (HABR).

The metabolic regulatory system and myogenic autoregulation are weak regulatory mechanisms in the liver. The main intrinsic regulation occurs with the hepatic arterial buffer response. This describes the interplay between the portal vein and hepatic artery. The underlying mechanism is thought to be regulated by adenosine concentration in the space of Mall. When the portal vein flow (PVF) decreases an accumulation of adenosine will occur. This gives a reactive vasodilatation of the hepatic artery and thus an increase in hepatic arterial blood flow (HAF). The reverse process is also true, when a higher PVF results in decreased levels of adenosine and a decrease in HAF[7,9-11]. The increase in adenosine also activates the hepatorenal reflex, resulting in a decreased urinary output and thereby increasing intravascular volume. The PVF is dependent on the outflow of the splanchnic organs. These are subjected to their own intrinsic and extrinsic regulation. This extrinsic regulation can be divided into the sympathetic nervous system and humoral regulation.

The sympathetic nervous system for the liver originates at T7-T10, meet at the coeliac plexus and further merge with parasympathetic innervation coming from the vagus nerves to form the anterior and posterior hepatic plexus. Stimulation of the hepatic plexus leads to a constriction of the hepatic artery and the portal vein in animal models[12-15].

The humoral regulation is a complex set of interconnected pathways which can be separated into the renin-angiotensin-aldosterone system, the catecholamine system and the vasopressin system.

There have already been extensive studies on adrenoreceptor distribution in the splanchnic vasculature. The predominant receptors are the α1-receptors in the pre-portal arteries, hepatic artery and pre- and post-hepatic veins. Activation of these receptors leads to vaso- and venoconstriction with rise in resistance in the total splanchnic vasculature and a decreased venous capacitance. The β2-adrenoreceptors are primarily located in the hepatic veins and the presplanchnic- and hepatic artery. Activation causes a dilatation and increase in blood flow[13,16].

The expected primary action of dobutamine will be the activation of this last receptor, combined with its effects through increasing the cardiac output and decrease in systemic vascular resistance could lead to an increase in total hepatic blood flow, but the effect on the liver's own regulatory mechanisms during surgery is yet to be studied. The aim of this study to understand the effect of dobutamine on hepatic blood flow (HBF) during major abdominal surgery.

Methods

Study Design

This pilot prospective single-center cohort study was approved by the ethical committee of the University Hospital of Ghent (BC-08919, Prof. Dr. Deron, 06/04/2021). Study protocol is comparable with previous studies on hepatic blood flow in our institution[17,18].

Patients who will undergo a Whipple's procedure, are identified by their appearance on the operating theatre program. They are included during the pre-operative anesthesiology consultation where a written informed consent is taken from all participants. Inclusion and exclusion criteria are shown in Table I. A power analysis was made based on previous study results[18]. A hypothesis was made that a change of 15% in HBF was expected. For a β of 0.2, this resulted in a

Table I. — Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
ASA I – II – III	Allergy to dobutamine
Adult ≥ 18 years ≤ 80 years	Severe heart failure (EF < 25%) or renal insufficiency (Serum creatinine > 2mg/dL)
Able to comprehend, sign and date the written informed consent document to participate in the clinical trial	Hemodynamic unstable patients
Patient is scheduled for pancreaticoduodenectomy	Sepsis
	Atrial fibrillation or sinus tachycardia > 100 bpm on pre-operative electrocardiogram
	BMI > 40
	Severe coagulopathy (INR > 2) or thrombocytopenia (< 80 x 10^3 /µL)
	End stage liver disease or portal hypertension
	Pregnancy or breastfeeding women

needed inclusion of 28 patients for analysis, with 12 patients to accommodate expected dropout, for a total of 40 needed for inclusion. In this article, the first 15 subjects fully included will be analyzed.

All patients received standardized anesthesia care, according to the existing departmental protocol. Anesthesia was induced and maintained using target controlled infusion (TCI) propofol (Schnider model) and remifentanil (Minto model). For intubation and relaxation, rocuronium was used. Additional bolus was administered before every measurement. Hemodynamic measurements (i.e. systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, central venous pressure, heart frequency, cardiac index, pulse pressure variation and dp/dtmax) were recorded using PulsioFlexTM with an ultrasound guided placed PiCCO catheter in the femoral artery. All patients received goal-directed therapy guided by the PulsioFlexTM using the Oldenburg algorithm.

The Oldenburg algorithm (shown in Figure 1) starts with measurement of the cardiac index (CI). If CI is below 2,0 L/min/m², an assessment was made if the pulse pressure variation (PPV) was greater than 12%. If so, a 200 ml intravenous crystalloid fluid bolus was given. If the PPV was less than 12%, a dobutamine infusion was started. If the CI was adequate, the mean arterial pressure (MAP) was assessed. If this was below 60 mmHg, a phenylephrine or ephedrine bolus was given while a possible other cause for hypotension was determined. If no other treatable cause was found, a noradrenaline infusion was started and titrated to desired effect. After each intervention the algorithm was reassessed.

Each participant received 3 ml/kg/h balanced crystalloid as maintenance fluid during the surgery, additional intravenous fluid was administered according to the Oldenburg algorithm.

Measurements of the hepatic blood flow were done using ultrasound transit time flow measurements (TTFM). HBF was measured in the hepatic artery (HAF) and portal vein (PVF), which is the sum of both PVF and HAF.

HBF and hemodynamic data were measured at designated times: first after resection (T1), this acted as baseline measurements followed by start of an infusion of dobutamine at a rate of 2 µg.kg-1.

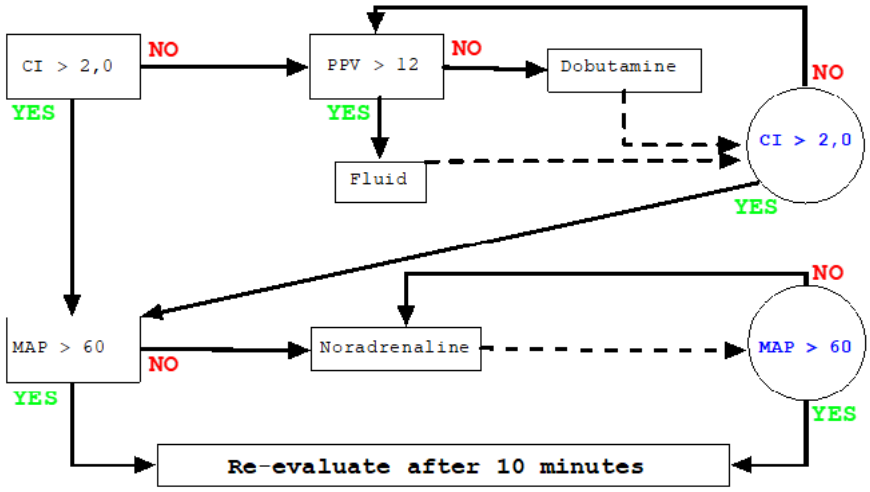

Fig. 1 — Oldenburg algorithm. Cardiac Index (CI), pulse pressure variation (PPV), mean arterial pressure (MAP).

min-1 (T2). After 10 minutes of infusion (T3), the infusion rate was increased to 5 µg.kg-1.min-1. After 10 minutes (T4), the last measurements were made and the dobutamine was discontinued. During the measurement of the HBF and the collection of the hemodynamic data, no boli phenylephdrine or ephedrine were given. A schematic overview of the different timestamps is shown at the end of this study (Figure 2).

Primary and secondary outcomes

The primary outcome of this study is to further analyze the relationship between dobutamine and the HBF and its components: HAF and PVF.

Further, as a secondary outcome, the effects of dobutamine on the measured hemodynamic data will be analyzed and discussed.

Data analysis

As previously mentioned in this article, the influence of dobutamine on the hemodynamic data and HBF in the first 15 included patients was analyzed and discussed. HBF was calculated by the sum of its main components. Both the PVF and the HAF were indexed based on body surface area (BSA) for better comparison between subjects. BSA was derived following the Du Bois method, with the following formula:

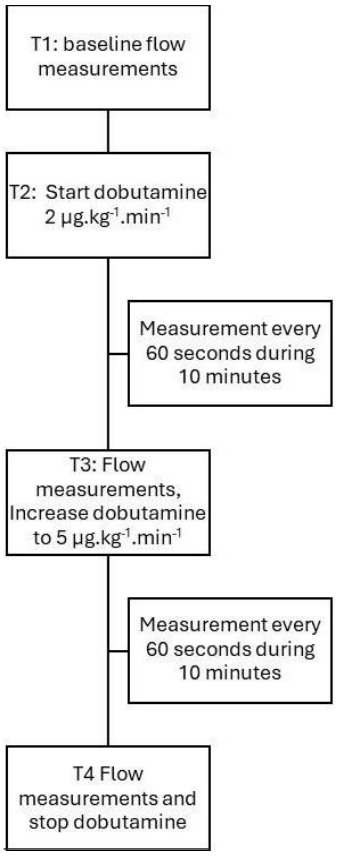

Fig. 2 — Measurement flowchart describing the timing of measurement and dobutamine dosing.

$$BSA = 0.007184 \times Height^{0.725} \times Weight^{0.425}.$$

The portal vein flow index (PVFi) and the hepatic artery flow index (HAFi) were calculated using the following formula:

$$PVFi = PVF/BSA \text{ and } HAFi = HAF/BSA.$$

The same formula was used to calculate CI and stroke volume index (SVI).

For data analysis IBM SPSS Statistics (version 29) was used. Before further statistical analysis the Shapiro-Wilk test was used to confirm that the measured blood flow and hemodynamic measurements are normally distributed. If so, ANOVA with repeated measurements was chosen as statistical test with a post hoc Bonferroni adjustment for significance. The data at the designated time T1, T3 and T4 will be compared. Data from T2 was not analyzed as this was the start of dobutamine infusion and a difference with baseline (T1) was not expected. A cutoff value of $p < 0,05$ will be considered as a significant statistical outcome.

Results

Subject inclusion flowchart

A total of 26 patients were included in this study so far. There were 11 drop-outs before measurements could be made (Figure 3). One patient withdrew from the study before start of surgery. The most frequent factor for drop-out was the inability to safely place a PiCCO catheter, mostly due to visualized arterial plaques in the femoral artery with ultrasound. A placement of an arterial line there could lead to plaque release and/or thrombosis with an ischemic event in the lower extremity. Second most common cause was the interruption of the surgery due to unexpected inoperability of the lesion. The last 2 factors for drop-out were equipment failure for measurements (ultrasound probes or PiCCO catheter) and the intra-operative need for vascular reconstruction. In total 15 patients were included for data analysis.

Demographics

The mean age of the participants was 62 years with most being categorized ASA 2, no ASA 1 patients were included in this study. There was an almost equal inclusion of male and female subjects, most of them being former smokers. Around 20% of patients used betablockers. The choice to start somatostatin perioperatively, which was administered during 40% of the Whipple procedures, was made by the surgeon.

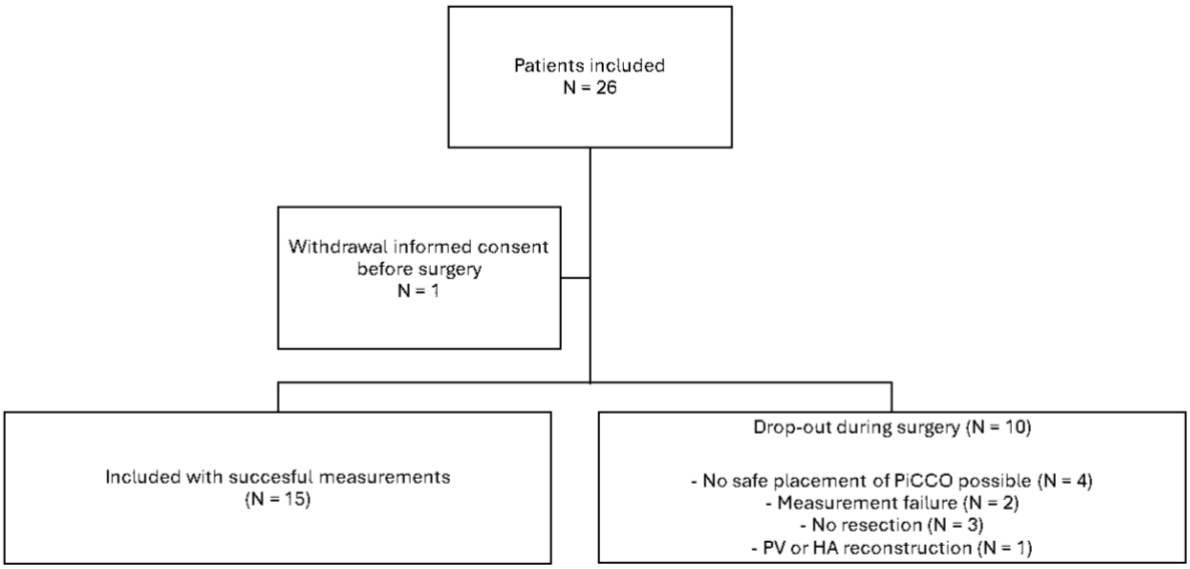

Fig. 3 — Inclusion flowchart of the study showing the selection and drop-out.

Table II. — Demographic characteristics of subjects included for analysis. Standard deviation or SD.

Category	Total (n = 15)
Mean age in years (SD)	62 (11)
Mean length in cm (SD)	163 (25)
Weight in kg (SD)	74 (28)
Male gender (%)	8 (53)
Smoker Active / Former / Never	1 / 9 / 5
ASA 1 / 2 / 3	0 / 10 / 5
Betablocker use (%)	3 (20)
Somatostatin use (%)	6 (40)
ACE-Inhibitor use (%)	3 (20)

Data analysis

In Table III, a steady increase in total HBFi was seen with increasing dobutamine infusion rate. At T4, a mean increase of 15,3% flow was measured compared to baseline, which is statistically significant compared to T3 and baseline. When this increase was compared to the measured CI, no difference in percentual blood flow going to the liver was noted.

When examining PVFi, a significant increase in blood flow even at lower doses of dobutamine was seen, which increased further with higher infusion rates. At T3, a mean increase of 13,7% was measured, compared to an increase of 31,6% in flow at T4 compared to baseline. When this again was compared to the CI, a significant increase at T4 going up to almost 13% of the total CI was noted.

For the HAFi, a different trend was observed. At T3, a slight decline in flow was measured, which decreased further at T4, with a total decline of 21,6% compared with no dobutamine. Not only does the HAFi decrease, but also the percentage of total CI going through the hepatic artery.

Table IV shows the measured hemodynamic data with the PulsioFlex. In this data a dose dependent rise in systolic blood pressure and heart rate was measured, with only a slight rise in MAP at T3 compared to baseline. No significant changes could be seen in diastolic blood pressure. The CI also rised to 3,4 L.min-1.m-2 in T3, but didn't increase further in T4. No significant changes in CVP were measured.

The vasodilatory properties of dobutamine could also be seen in the significant dose dependent drop in SVRI at higher dobutamine infusion, dropping almost 14% in T4. A steady increase in PPV and SVV was also measured, also most notably at T4. Further, a dose dependent decrease in SVI was measured, but also with an increase of dP/dtmax.

Discussion

This study showed that even a low dose dobutamine infusion can alter the blood flow balance in the liver.

When looking at the results of HBF, several observations emerge. A notable trend is the dose-dependent increase in total HBF without significant increase in received percentual flow of CI. Which is to be expected and probably aligns with most organs after a dobutamine-induced increase of CI. Interestingly, this increase solely occurs through the portal vein. There, a dose-dependent increase in PVF was noted, even at low doses of dobutamine infusion. This is in contrast to the steady decline of the HAF. As discussed in the introduction, the primary mechanism of dobutamine is through the activation of the β1,2-adrenoreceptor, which is mainly located in the pre-portal arteries in the splanchnic circulation and the hepatic artery and veins. Thus, a possible hypothesis is, due to the

Table III. — Hepatic blood flow measurement (SD).

Measurement	T1	T3	T4
Total HBFi (ml.min-1 .m-2)	489,9 (138,6)	529,1 (137,8)	564,8 (131,7) *#
Relative HBFi (% of CI)	16,6 (4,8)	15,7 (4,1)	16,2 (3,8)
PVFi (ml.min-1 .m-2)	340,5 (87,3)	387,2 (121,4) *	448,1 (127,9) *#
Relative PVFi (% of CI)	11,5 (3,2)	11,5 (3,4)	12,9 (3,6) *#
HAFi (ml.min-1 .m-2)	149,2 (100,8)	141,9 (96,7)	116,9 (85,2) *#
Relative HAFi (% of CI)	5 (3,4)	4,3 (2,8) *	3,4 (2,4) *#
T1: Baseline measurements T3: Dobutamine 2 µg.kg-1.min-1 T4: Dobutamine 5 µg.kg-1.min-1 . * Statistical significance (p<0,05) compared to T1. # Statistical significance (p<0,05) compared to T3.			

Table IV. — Hemodynamic measurements (standard deviation, SD).

Measurement	T1	T3	T4
MAP (mmHg)	72 (11)	78 (10) *	73 (8) #
SBP (mmHg)	108 (15)	127 (14) *	133 (11) *
DBP (mmHg)	51 (8)	53 (8)	50 (6) #
Cardiac Index ($L.min^{-1}.m^{-2}$)	3,0 (0,5)	3,4 (0,5) *	3,5 (0,6) *
HR (bpm)	79 (8)	94 (12) *	116 (16) *#
CVP(mmHg)	8 (3)	8 (2)	7 (3)
SVRI ($dyn.sec.cm^{-5}.m^{-2}$)	1706 (398)	1685 (327)	1468 (294) #
dP/dtmax ($mmHg.sec^{-1}$)	1176 (197)	1631 (276) *	2015 (299) *#
SVI ($ml.m^{-2}$)	38,3 (5,0)	36,3 (6,2)	30,9 (7,1) *#
PPV (%)	8 (4)	10,3 (6)	16,3 (7) *#
SVV (%)	13 (6)	16,3 (7)	24,1 (9) *#
T1: Baseline T3: Dobutamine 2 µg.kg-1.min-1 T4: Dobutamine 5 µg.kg-1.min-1. * Statistically significant (p<0,05) in comparison to T1. # Statistically significant (p<0,05) in comparison to T3.			

effect of the dobutamine infusion, that an increase in CI and splanchnic vasodilation in those vessels was created, which all lead to an increase in PVF. Only at an infusion rate of 5 µg.kg-1.min-1 a significant increase of percentage of flow in the portal vein relative to the cardiac index was seen. This increased PVF probably causes an increase of adenosine washout in the space of Mall, activating the HABR with a consequent vasoconstriction of the hepatic artery and a decrease in HAF. This mechanism counteracts the expected arterial vasodilation caused by β2-receptor activation by dobutamine. In animal studies, it is shown that there is a limit to the amount of vasoconstriction or vasodilatation the hepatic artery can achieve in response to changes in PVF. The limits of this effect were not shown in this study as a steady decline up to 21% in HAF was measured, with no signs of reaching the limits of its vasoconstrictive abilities[19,20].

These findings hint that dobutamine might be a potential pharmacological agent to modulate hepatic and splanchnic blood flow. Both surgery and anesthesia alter HBF. Many anesthetic agents reduce HBF by reduction of PVF. This is mainly caused by a decreased CI. As such, administration of dobutamine could hold relevance during major abdominal surgery in order to restore the post-induction reduction of HBF[21]. Several studies have shown that the HABR is still intact after liver transplantation, which could still be manipulated using dobutamine infusion[22,23]. Dobutamine increases PVF, and therefore also splanchnic flow. This must be studied further before such conclusions can be made[24,25].

The secondary outcome to analyze the influence of dobutamine on the measured hemodynamic data, which is already well understood and studied. In this study, a dose dependent rise of systolic blood pressure and heart rate was seen, with only a slight rise in MAP at lower dobutamine infusion. Although this results in an initial rise in CI with a dobutamine dose of 2 µg.kg-1.min-1, after an increase in dobutamine infusion a further increase

in CI wasn't measured. This is probably due to the measured dose-dependent decline in SVI caused by the increasing tachycardia. By increasing heart rate, the diastolic time is shortened which decreases the filling time for left ventricle, leading to a diminished end diastolic blood volume. The decrease in SVRI is also expected due to the arterial vasodilation caused by activation of the β2-adrenoreceptor. This effect is increased further with higher dobutamine infusion rates. Most likely this will also lead to venous blood pooling due to an increased venous capacitance, which might contribute to the decline of preload. This might explain the rise in PPV and SVV due to higher preload variance coming from positive pressure ventilation. The dP/dtmax is the maximum pressure change the left ventricle generates, usually at the end of the isovolumetric contraction. It is dependent on inotropy, end-diastolic volume and systemic diastolic resistance[26]. The measured fall in SVRI and SVI should give an expected decrease in dP/dtmax, but given the strong ionotropic properties of dobutamine, it still gives a net increase due to the increased contractility.

Through the used perioperative goal-directed therapy protocol on fluid management, inotropes and vasopressors, the variance in preload status between subjects was minimized. This could have a big impact on the measurements. With a baseline PPV of 8% and standard deviation of 4%, most patients were on the predetermined desired area in the Frank-Starling curve and preload status during this study. This makes it possible to compare the different subjects without too much variance in preload status. Baseline cardiac function may vary, but subjects with severe heart failure are not included based on the exclusion criteria.

Several study pitfalls and limitations should be disclosed. Firstly, this article only analyses preliminary results of the first 15 included patients for analysis. Therefore this article lacks the power needed to make a definitive conclusion, which will be possible when the study is concluded.

Secondly, HBF and CI are dependent on numerous factors. Pre-operative cardiovascular reserve between patients, preload status before the start of measurement, individual differences in ventilatory settings or anatomical variance in liver vasculature to name a few. In this study, differences in preload and ventilatory settings were minimized through a strict standardized goal-directed therapy before measurements were made. Lastly, as shown in the inclusion flowchart, there is a relatively high percentage of dropout which is mostly due to the unpredictable nature of high risk surgery such as a pancreaticoduodenectomy. To ensure a good quality of comparable measurements all patients with need for vascular reconstruction were excluded, as the acquired data might not be of use for comparison. To ensure a minimum of possible adverse events a cautious approach was held during the placement of the PiCCO catheter, resulting in a higher drop-out rate.

In conclusion, these preliminary findings indicate that dobutamine may serve as a promising tool for modulating HBF and, consequently, the splanchnic circulation. However, definitive conclusions must await the inclusion of all planned subjects. Nevertheless, these results suggest potential applications for dobutamine in major abdominal surgery and possibly beyond. Future studies on these effects might include patients with known hepatic failure and undergoing major surgery, although measurement of HBF might prove difficult.

Acknowledgements and potential conflicts of interest: We don't have any conflict of interest to disclose.

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doi.org/10.56126/76.S1.09