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Original study

A comparative analysis of the effect of norepinephrine and dobutamine on hepatic blood flow

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Abstract

Background: **Goal-directed hemodynamic therapy (GDHT) is applied to optimize cardiac output and perfusion in patients undergoing major abdominal surgery. Dobutamine (DOBU) and norepinephrine (NOR) are commonly used agents with distinct systemic profiles, yet their comparative effects on hepatic blood flow (HBF) remain underexplored.**
Objectives: **To compare the effects of DOBU and NOR on hepatic and systemic hemodynamics during major abdominal surgery.**
Design and Setting: **Prospective observational study conducted in a tertiary academic center on patients undergoing elective pancreaticoduodenectomy.**
Methods: **Two observational cohorts were analyzed. One group received titrated doses of NOR to achieve a targeted increase in mean arterial pressure (MAP), while the other received incremental doses of DOBU. Hemodynamic parameters—including portal vein flow (PVF), hepatic artery flow (HAF), and total HBF—were measured using intraoperative transit-time flow measurement. Measurements were obtained at baseline and following two predefined dose escalations.**
Main Outcome Measures: **Changes in indexed PVF, HAF, and HBF, as well as cardiac index (CI), heart rate (HR), and MAP.**
Results: **DOBU significantly increased CI and HR, with a corresponding rise in PVF and total HBF, but reduced HAF at higher doses. NOR induced a dose-dependent increase in MAP but significantly reduced total HBF due to decreased HAF, without notable changes in CI or PVF.**
Conclusions: **DOBU enhances total HBF primarily via increased cardiac output but at the cost of tachycardia. NOR maintains MAP effectively but may compromise HBF due to vasoconstrictive effects. These findings support a tailored vasoactive strategy in perioperative management, especially in patients at risk for hepatic dysfunction.**

Keywords: **Dobutamine, Norepinephrine, Hemodynamics, Liver Circulation, Adrenergic Agents.**

Introduction

Adequate organ perfusion is essential to ensure tissue oxygenation and homeostasis during major surgery. Goal-directed hemodynamic therapy (GDHT) aims to optimize flow-related parameters such as cardiac output (CO) and stroke volume through individualized fluid and vasoactive drug administration, and has been associated with improved postoperative outcomes in high-risk patients undergoing major abdominal surgery[1–3].

Dobutamine (DOBU) and norepinephrine (NOR) are widely used vasoactive agents in GDHT protocols due to their predictable systemic hemodynamic effects. DOBU is a synthetic catecholamine that acts predominantly on β1-adrenergic receptors, enhancing myocardial contractility and increasing cardiac output; β2 stimulation induces mild vasodilation[4]. NOR, on the other hand, is a potent α-adrenergic agonist that increases systemic vascular resistance and MAP, with limited β1-mediated inotropic activity[5].

The liver plays a central role in metabolic, synthetic, and immunological functions. It receives approximately 25% of cardiac output through a dual inflow system: 75% via the portal vein and

25% via the hepatic artery[6,7]. Despite the portal vein providing the majority of blood volume, the hepatic artery accounts for up to half of the liver's oxygen supply due to higher oxygen content and pulsatile flow[6]. The hepatic arterial buffer response (HABR) compensates for fluctuations in portal flow by modulating hepatic artery flow, maintaining relatively constant total hepatic blood flow (HBF)[8].

Systemic hemodynamic changes and vasoactive drugs can disrupt this balance. NOR-induced vasoconstriction may reduce hepatic arterial inflow and impair venous drainage, potentially decreasing HBF[5,9]. Conversely, DOBU can enhance HBF by increasing CO and splanchnic blood flow, though this effect is modulated by dose, receptor distribution, and sympathetic tone[4,9].

Despite their frequent use in perioperative care, few clinical studies have directly compared the effects of DOBU and NOR on liver blood flow. A previous study by van Limmen et al has already reported the isolated effects of norepinephrine on hepatic blood flow in patients undergoing pancreaticoduodenectomy[10].

This study aims to compare their effects on portal vein flow (PVF), hepatic artery flow (HAF), and total HBF in patients undergoing pancreaticoduodenectomy, as well as their impact on systemic hemodynamic parameters including MAP, cardiac index (CI), and heart rate (HR). Understanding these effects is crucial for a more physiologically tailored approach to perioperative hemodynamic management.

Methods

Design and patients

Data from two prospective observational studies conducted at Ghent University Hospital, each evaluating the hemodynamic effects of a single vasoactive agent—NOR or DOBU—during elective pancreaticoduodenectomy were pooled for comparative analysis. Both studies were approved by the institutional ethics committee and registered prior to patient inclusion.

For the NOR study, approval was granted by the Ethics Committee of Ghent University Hospital (chairman Prof. Dr. Renaat Peleman) under EC number 2019/0395. The study was registered with EudraCT (2018-004139-66, 25/03/2019) and ClinicalTrials.gov (NCT03965117, 28/05/2019). For the DOBU study, ethical approval was granted on 6 April 2021 under EC number BC-08919, and the study was registered with EudraCT (2020-005412-21, 01/02/2021) and ClinicalTrials.gov (NCT04893655, 30/04/2021). An additional approval was obtained to allow comparative analysis of data from the two studies. This amendment was approved under reference number BC-08919 E03, and ethical clearance for this secondary analysis was granted on May 23, 2023.

Eligible participants in both studies were adults aged 18–80 years of either gender, classified as ASA physical status I–III, and scheduled for elective pancreaticoduodenectomy. Written informed consent was obtained prior to participation. Shared exclusion criteria included: allergy to the study medication, serum creatinine > 2 mg/dL, left ventricular ejection fraction < 25%, hemodynamic instability, atrial fibrillation, sepsis, body mass index > 40 kg/m², INR > 2, platelet count < 80 × 10^3/μL, end-stage liver disease, and pregnancy or breastfeeding. The DOBU study additionally excluded patients with sinus tachycardia (HR > 100 bpm).

After pancreatic resection and achievement of hemodynamic stability, hepatic blood flow (HBF) was assessed intraoperatively using perivascular transit-time flow measurement (TTFM; Medi-Stim AS, Oslo, Norway), with probes placed on the hepatic artery (for measurement of HAF) and portal vein (for measurement of PVF). Total HBF was derived from the sum of PVF and HAF. Simultaneously, systemic hemodynamic parameters including cardiac index (CI), heart rate (HR) and mean arterial pressure (MAP) were recorded.

In the NOR group, flow measurements were obtained at three predefined timepoints: baseline after resection (T1), after titration of NOR to achieve a 10–20% MAP increase (T2), and after further titration to achieve a 20–30% MAP increase (T3). In the DOBU group, measurements were also taken at baseline (T1), and after administration of DOBU at 2.5 μg/kg/min (T2) and 5 μg/kg/min (T3), with a minimum of 5 minutes of hemodynamic stabilization before each timepoint.

Somatostatin was administered intraoperatively in a subset of patients in both groups based on surgical indication.

The primary aim of this study was to compare the effects of DOBU and NOR at two different dosages on PVF, HAF and HBF. The secondary aim was to compare the effect of both agents on CI, MAP and HR.

Anesthesia and monitoring

Our hospital's standard Pancreatic Surgery Protocol was used in both studies. After insertion of an epidural catheter for postoperative analgesia, general anesthesia was induced and maintained with a target-controlled infusion of propofol (Schnider model), initiated at an effect-site concentration

of 5.0 mcg/ml. Bispectral Index (BIS; BISTM, Covidien, MA, USA) was maintained between 40–60. Intraoperative analgesia was provided using a target-controlled infusion of remifentanil (Minto model), starting at 5 ng/ml and adjusted according to HR and blood pressure. Rocuronium was used for neuromuscular blockade. Hemodynamic monitoring included a radial arterial line, a central venous catheter in the right internal jugular vein, and a femoral PiCCO catheter (Maquet, Getinge Group, Germany) for cardiac output monitoring via transpulmonary thermodilution.

Goal-directed hemodynamic therapy

All patients received a continuous baseline infusion of balanced crystalloid solution (Plasmalyte A; Baxter S.A., Lessines, Belgium), administered at 3 mL/kg/h. In case of intraoperative hypotension (defined as MAP < 60 mmHg) with a pulse pressure variation (PVV) of >12%, a fluid bolus of 200 mL crystalloids (Plasmalyte A) was administered. If hypotension occurred in the context of surgical bleeding, 200 mL of a plasma expander—either gelatin (Geloplasma; Fresenius Kabi, Schelle, Belgium) or 5% human albumin (Alburex 5%; CSL Behring, Mechelen, Belgium)—was given. To compensate for the delayed effect of fluid administration, additional vasopressor support was provided depending on heart rate (HR): when HR was <60 beats per minute, an ephedrine bolus of 6 to 9 mg was administered; when HR was ≥60 bpm, a phenylephrine bolus of 100 µg was used to augment blood pressure.

Measurements

In each study, the surgeon performed three flow measurements at predefined time points when the study medication was initiated. PVF and HAF were measured using TTFM. Both PVF and HAF were indexed to body surface area (BSA) using the Dubois formula and respectively named PVFi and HAFi respectively[11]. The total HBFi was calculated as the sum of HAFi and PVFi.

Hemodynamic variables were measured using PulsioflexTM (Maguet, Getinge Group, Germany). A PiCCO catheter was inserted into the femoral artery, and pulse contour analysis was calibrated via thermodilution. Prior to initiating experimental measurements, calibration of the pulse contour was repeated.

Statistical analysis

Statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria). Baseline demographic and intraoperative characteristics were summarized using means and standard deviations for continuous variables and frequencies for categorical variables. Group comparisons were performed using the Student's t-test for continuous variables and the Chi-square test for categorical variables. Normality was assessed using visual inspection of histograms and Q-Q plots.

To evaluate the effect of increasing medication dosages over time (T1, T2, and T3), a linear mixed-effects model was fitted to each indexed hepatic hemodynamic variable (HAF, PVF and HBF) as well as each systemic hemodynamic variable (CI, HR and MAP). Medication dose at each time point (T1, T2 and T3) and the type of study medication (DOBU vs. NOR) were included as fixed effects, with a random intercept for each subject to account for interindividual variability. Statistical significance was defined as $p < 0.05$.

A post-hoc power analysis was performed to assess whether the study was adequately powered to detect the observed difference in HBFi at T3.

Results

A total of 44 patients were included in the analysis, of whom 16 from the DOBU study and 28 from the NOR study. Baseline demographic and intraoperative characteristics of both groups are summarized in Table I. While most parameters were comparable between groups, baseline MAP and HR were significantly higher in the DOBU group, whereas total remifentanil administration was significantly greater in the NOR group.

Effect on systemic hemodynamics

Data are summarized in Table II. DOBU produced a significant dose-dependent rise in CI and HR. Compared to baseline, there was an estimated increase in CI of 0.40 L/min/m2 at T2 ($p < 0.05$) and 0.52 L/min/m2 at T3 ($p < 0.05$). The estimated increase in HR was 16 bpm at T2 ($p < 0.05$) and 38 bpm at T3 ($p < 0.05$). With DOBU, there was also a significant increase of 5 mmHg in MAP at T2 ($p < 0.05$), but not at T3. NOR, on the other hand, significantly increased MAP in a dose-dependent manner. Compared to baseline, there is an estimated increase of 11 mmHg at T2 ($p < 0.05$) and 20 mmHg at T3 ($p < 0.05$). There is no significant change in CI or HR at increasing dosages of NOR.

At both T2 and T3, DOBU had a significantly greater effect than NOR on CI, HR and MAP. The estimated difference in CI was 0.41 L/min/m² (95% CI [0.20, 0.62]; $p < 0.05$) at T2 and 0.49 L/min/m² (95% CI [0.28, 0.70]; $p < 0.05$) at T3, favoring DOBU. Similarly, DOBU led to

Table I. — Baseline demographic and intraoperative characteristics.

	DOBU (n = 14)	NOR (n = 28)	p-value
Demographics			
Age (years)	62.8 (11.0)	62.8 (11.0)	0.179
Sex (Male / Female)	9 / 7	14 / 14	0.932
Length (cm)	171.7 (9.9)	170.0 (8.2)	0.576
Weight (kg)	69.5 (11.2)	72.5 (13.0)	0.430
BMI (kg/m^2)	23.5 (2.7)	25.0 (3.8)	0.142
Preoperative status			
MAP (mmHg)	103.2 (9.8)	93.7 (10.3)	0.005*
HR (bpm)	81.1 (9.7)	74.6 (10.8)	0.047*
ASA (I / II / III)	0 / 11 / 5	2 / 19 / 7	0.525
Smoker (Yes / Former / No)	1 / 9 / 6	8 / 9 / 11	0.140
Intraoperative data			
Duration of surgery (min)	597.4 (105.6)	597.4 (105.6)	0.337
Total amount of crystalloids (ml)	4402.7 (1375.4)	4163.6 (1569.3)	0.540
Total amount of colloids (ml)	110.3 (236.6)	189.7 (285.8)	0.255
Estimated blood loss (ml)	404.1 (230.9)	347.6 (217.9)	0.342
Urinary output (ml)	601.2 (323.8)	781.2 (439.2)	0.082
Medication			
Amount of propofol (mg)	3462.4 (895.1)	3866.0 (985.0)	0.108
Amount of remifentanil (mcg)	3754.8 (1227.9)	4522.9 (1423.1)	0.032*
Use of somatostatin (Yes / No)	6 / 10	20 / 8	0.060

* Indicates statistically significant difference between groups; Data are expressed in mean (SD).
BMI Body Mass Index, MAP Mean Arterial blood Pressure, HR Heart Rate, ASA American Society of Anesthesiologist physical status.

Table II. — Estimated effects of increasing doses of DOBU and NOR on systemic hemodynamics, compared to baseline.

	Group	T1	T2		T3	
			β	95% CI	β	95% CI
CI (L/min/m2)	DOBU	3.00	+0.40*	[0.23, 0.56]	+0.52*	[0.36, 0.69]
	NOR	3.12	-0.01	[-0.28, 0.25]	0.03	[-0.23, 0.30]
MAP (mmHg)	DOBU	73	+5*	[2, 8]	+0	[-3, 3]
	NOR	73	+11*	[7, 16]	+20*	[15, 24]
HR (bpm)	DOBU	79	+16*	[11, 21]	+38*	[33, 43]
	NOR	78	-3	[-11, 5]	-3	[-11, 5]

* Indicates statistically significant change compared to T1 ($p < 0.05$).
CI: cardiac index; MAP: mean arterial blood pressure; HR: heart rate; DOBU: dobutamine; NOR: norepinephrine

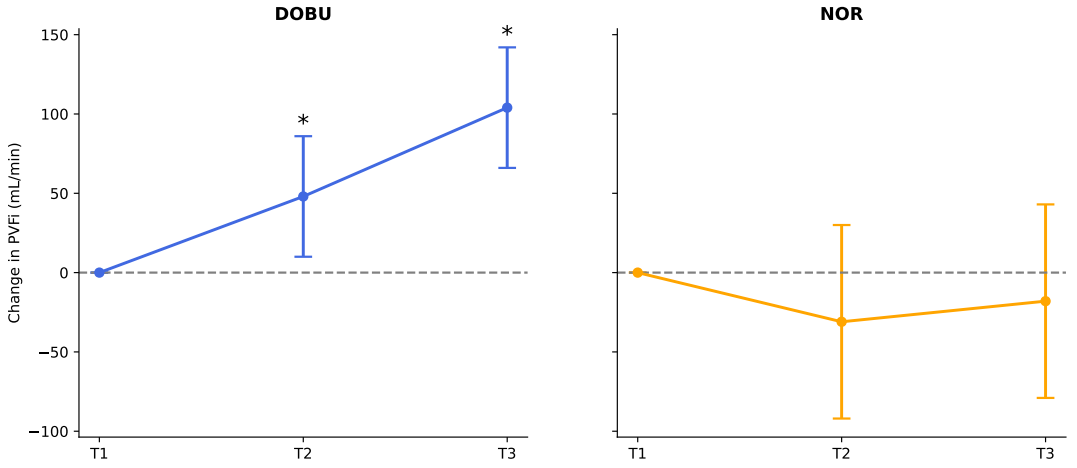
significantly higher HR values compared to NOR, with an estimated difference of 19 bpm (95% CI [12, 25]; $p < 0.05$) at T2 and 41 bpm (95% CI [35, 47]; $p < 0.05$) at T3. In contrast, NOR produced significantly greater increases in MAP than DOBU, with differences of 7 mmHg (95% CI [3, 10]; $p < 0.05$) at T2 and 20 mmHg (95% CI [16, 24]; $p < 0.05$) at T3.

Effect on hepatic blood flow

Table III provides a summary of the data. DOBU significantly increased PVFi in a dose-dependent manner. Compared to baseline, there was an estimated increase in PVFi of 48 mL/min at T2 ($p < 0.05$) and 104 mL/min at T3 ($p < 0.05$) (Figure 1). HAFi, however, showed a significant decrease of 33 mL/min/m² at T3 ($p < 0.05$) but no significant change at T2 (Figure 2). This results in a significant increase of 71 mL/min in HBFi at T3 ($p < 0.05$). There is no significant change at T2 (Figure 3).

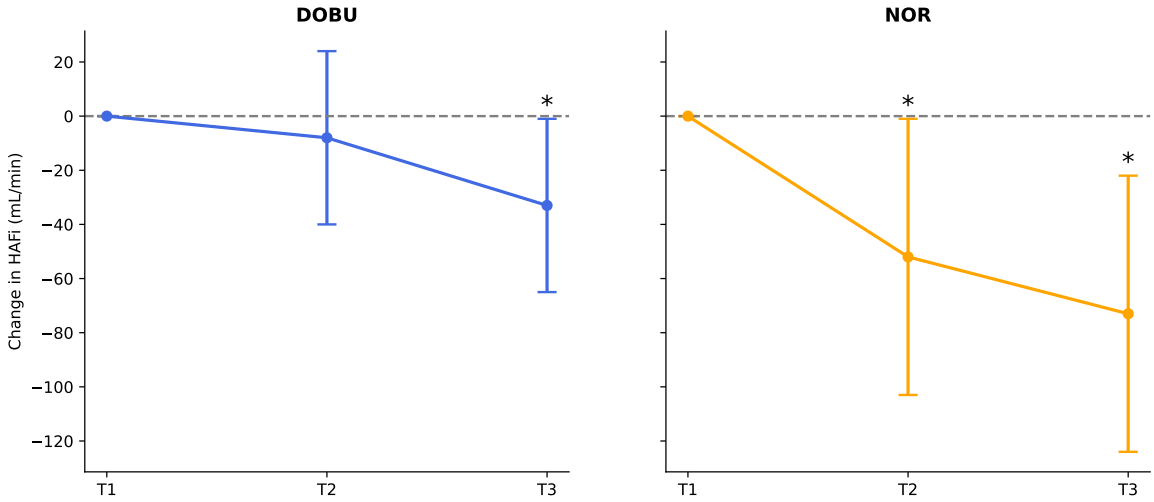
NOR, in contrast, significantly decreased total HBFi in a dose-dependent manner. Compared to baseline, there was an estimated reduction of 83 mL/min at T2 ($p < 0.05$) and 91 mL/min at T3 ($p < 0.05$) (Figure 3). This reduction was driven by a significant decline in HAFi, with an estimated decrease of 52 mL/min at T2 ($p < 0.05$) and 73 mL/min/m² at T3 ($p < 0.05$) (Figure 2), while PVFi remained unchanged (Figure 1).

At both T2 and T3, DOBU had a significantly greater effect than NOR on PVFi, HAFi, and total HBFi. The estimated difference in PVFi was 79 mL/min (95% CI [32, 127]; $p < 0.05$) at T2 and 74 mL/min (95% CI [74, 170]; $p < 0.05$) at T3, favoring DOBU. Similarly, the reduction in HAFi was significantly less pronounced with DOBU compared to NOR, with an estimated difference of 44 mL/min (95% CI [4, 84]; $p < 0.05$) at T2 and 40 mL/min (95% CI [0, 80]; $p = 0.05$) at T3. Consequently, DOBU resulted in significantly



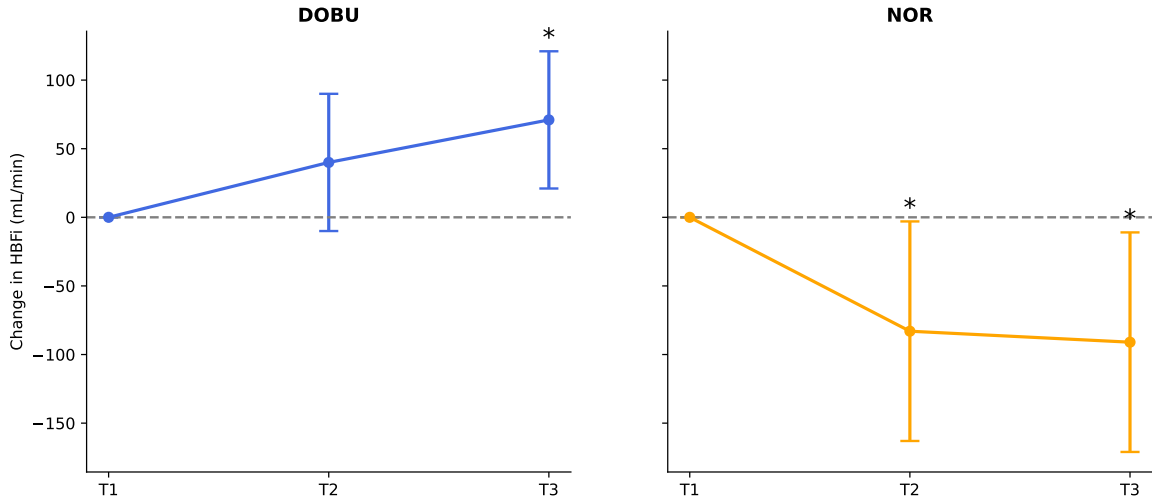
* Indicates a statistically significant difference ($p < 0.05$) compared to T1

Fig. 1 — Relative change of PVFi with increasing doses of DOBU and NOR.



* Indicates a statistically significant difference ($p < 0.05$) compared to T1

Fig. 2 — Relative change of HAFi with increasing doses of DOBU and NOR.



* Indicates a statistically significant difference ($p < 0.05$) compared to T1

Fig. 3 — Relative change of HBFi with increasing doses of DOBU and NOR.

Table III. — Estimated effects of increasing doses of DOBU and NOR on hepatic hemodynamics, compared to baseline.

	Group	T1	T2		T3	
			β	95% CI	β	95% CI
PVF_i (mL/min)	DOBU	351	+48*	[10, 86]	+104*	[66, 142]
	NOR	333	-31	[-92, 30]	-18	[-79, 43]
HAF_i (mL/min)	DOBU	148	-8	[-40, 24]	-33*	[-65, -1]
	NOR	215	-52*	[-103, -1]	-73*	[-124, -22]
HBF_i (mL/min)	DOBU	499	+40	[-10, 89]	+71*	[21, 120]
	NOR	215	-83*	[-163, -4]	-91*	[-170, -11]

* Indicates statistically significant change compared to T1 ($p < 0.05$)
PVFi: indexed portal vein flow; HAFi: indexed hepatic artery flow; HBFi: indexed hepatic blood flow; DOBU: dobutamine; NOR: norepinephrine.

higher HBFi than NOR at both timepoints, with differences of 123 mL/min (95% CI [61, 185]; $p < 0.05$) at T2 and 162 mL/min (95% CI [100, 224]; $p < 0.05$) at T3.

Based on observed group means at T3 (DOBU: 570 ± 129 mL/min; NOR: 458 ± 144 mL/min), a post-hoc power analysis confirmed that the sample size was sufficient to detect the observed difference of 112 mL/min with >90% power (Cohen's d = 0.82, two-sided $\alpha = 0.05$).

Discussion

This study provides a direct comparative analysis of how DOBU and NOR affect hepatic blood flow in humans. Using intraoperative transit-time flowmetry (TTFM) during pancreaticoduodenectomy – a surgical setting chosen for its relative hemodynamic stability and easy access to the hepatic vasculature – we were able to measure portal vein and hepatic artery flows directly, an approach rarely reported in human studies. The main findings confirm that these two vasoactive drugs have distinct effects on both systemic circulation and liver perfusion. In summary, DOBU significantly increased total HBF by augmenting portal venous inflow, whereas NOR caused a reduction in total HBF, primarily by constricting the hepatic arterial inflow. These divergent hepatic effects were observed even though both agents successfully achieved their primary systemic targets —DOBU increasing cardiac output and NOR elevating MAP.

DOBU's impact on systemic hemodynamics in our study was characterized by a dose-dependent increase in cardiac index and HR, with only modest changes in arterial pressure, consistent with its β-adrenergic agonist profile. NOR, in contrast, markedly increased mean arterial pressure with minimal change in cardiac output or heart rate, reflecting its predominant α1-adrenergic vasoconstrictive action. These systemic effects align with well-established pharmacology.

Regarding liver hemodynamics, DOBU and NOR exerted opposite effects on the dual hepatic blood supply. DOBU produced a significant increase in PVF, while HAF showed a mild decrease only at the highest dose. Consequently, total hepatic inflow was substantially increased under DOBU (especially at higher infusion rates). NOR, on the other hand, maintained portal flow relatively constant (no significant rise), but caused a significant reduction in hepatic artery flow, leading to an overall decrease in total liver perfusion. Perhaps the most noteworthy result is this divergence: DOBU improved total HBF, whereas NOR reduced it under the conditions studied. This observation is physiologically plausible. By boosting cardiac output and inducing some β2-mediated vasodilation in the mesenteric circulation, DOBU can drive more blood through the portal venous system and thus to the liver12. NOR's vasoconstrictive effect, in contrast, likely increases splanchnic vascular resistance, limiting flow through the hepatic artery.

Somatostatin administration was previously shown to lower baseline portal flow and modulate hepatic vascular responses[10]. In the present analysis, somatostatin was given in both cohorts, and although the study was not designed for stratified analysis, the proportion of patients receiving somatostatin was similar in both groups. While this reduces the risk of confounding due to group imbalance, somatostatin may still have influenced the hepatic hemodynamic response to both agents. As such, its presence should be considered a potential effect modifier when interpreting the observed drug-specific effects on hepatic blood flow.

Our findings align with previous clinical and preclinical studies examining splanchnic perfusion in patients treated with catecholamines. In an earlier human study during liver surgery (under enflurane anesthesia), Kainuma observed that dobutamine (3 μg/kg/min) increased PVF and total HBF without significantly changing HAF[12]. This mirrors our results and confirms that DOBU's augmentative effect on liver perfusion is largely via the portal vein. A comprehensive review by Asfar and colleagues[13] notes that DOBU

usually increases hepatosplanchnic blood flow in septic shock patients, especially in those with compromised baseline perfusion. The effects of DOBU on liver metabolic function, however, have been variable. For instance, even though DOBU can increase hepatic oxygen delivery, it does not always translate into improved liver oxygen uptake or function. Joly et al reported that in septic shock patients stabilized on fluids and NOR, a DOBU infusion (7.5 μg/kg/min) significantly raised cardiac index and improved gastric mucosal perfusion, but it did not significantly change indocyanine green clearance, a marker of hepatic blood flow and function[14]. All patients in that study had markedly reduced hepatocellular clearance at baseline, and the lack of improvement with DOBU suggests that factors like intrinsic cellular dysfunction may limit hepatic benefit in sepsis despite macrocirculatory improvements. Nonetheless, the general capacity of DOBU to enhance splanchnic perfusion is well documented. Creteur et al, for example, found that dobutamine could decrease the gastric mucosal PCO2 gap (implying better perfusion) in septic patients who had evidence of splanchnic oxygen debt[15].

In contrast, our results with NOR align with concerns that α-agonist vasopressors may compromise regional perfusion in the splanchnic bed. Animal models have shown adverse microcirculatory effects of NOR on abdominal organs. Krejci et al demonstrated in a porcine septic shock model that NOR (at doses raising MAP by ~20%) reduced superior mesenteric artery flow by ~26% and significantly decreased microvascular blood flow in the intestinal mucosa, despite increasing overall cardiac output[16]. In a clinical setting, De Backer and colleagues observed that NOR alone can have variable effects on splanchnic blood flow in septic patients, often requiring addition of DOBU to improve regional perfusion[17]. Taken together, evidence suggests that NOR, while critical for supporting blood pressure, tends to restrict blood flow to the liver and gut. NOR's effect might also be context-dependent – for example, in a profoundly hypotensive patient, raising MAP from very low levels with NOR can improve organ perfusion initially, but beyond a certain point further increases in vasopressor dose may reduce flow by excessive vasoconstriction[16]. Our data reflect a scenario of relatively stable patients where additional NOR primarily exerted a flow-restrictive effect on the liver.

Despite the clear hemodynamic differences we observed, it must be acknowledged that the translation of such physiological effects into clinical outcomes is not straightforward. To date, studies targeting splanchnic perfusion have had mixed results in improving patient outcomes. As noted in a prior review, various interventions that increased splanchnic blood flow or improved regional perfusion markers did not conclusively reduce mortality or organ failure in septic shock[13]. For example, a patient's outcome will also depend on control of the underlying cause (infection, bleeding, etc.), global oxygen delivery, and cellular ability to utilize oxygen. Thus, our findings should be viewed as highlighting an important physiological distinction and a potential consideration in management, rather than an endorsement that one drug is universally superior to the other. Further clinical research is needed to determine whether strategies that favor hepatic perfusion (such as concomitant use of inotropes, or targeting a slightly lower vasopressor dose when feasible) result in better outcomes in specific scenarios.

Several limitations of our study warrant discussion. First, the study was conducted in a controlled intraoperative environment on a relatively homogeneous patient population (elective pancreaticoduodenectomy cases). While this model was advantageous for obtaining reliable paired measurements, it may limit the generalizability of the results. Patients in critical care settings or with different surgical procedures (e.g. hepatic resections, trauma) might respond differently. Hemodynamic responses can vary with underlying pathophysiology. Future research should investigate how NOR and DOBU affect hepatic perfusion in patients with compromised liver function or in the presence of systemic inflammatory states. Second, we measured hepatic blood flows only during the procedure and did not assess any post-operative liver function or long-term outcomes. Thus, we cannot directly link the observed hemodynamic changes to clinical endpoints such as liver enzyme release, bile production, or patient recovery. It would be valuable to know if the greater HBF under DOBU translated into better liver function (e.g., lower post-op transaminases or faster clearance of drugs) or if the reduced flow under NOR had any detectable harms. These questions remain unanswered in our study and should be explored in future trials. Third, our two drug groups were not part of a single randomized trial but rather derived from two sequentially conducted cohorts. This led to an unequal sample size and potential baseline differences between groups. We attempted to mitigate bias by using a linear mixed-effects model. A post-hoc power analysis indicated that the sample was sufficient to detect

the observed difference in total hepatic blood flow at the highest doses with over 90% power. However, being a post-hoc analysis, this is merely supportive and cannot replace a priori sample size calculation. Additionally, because patients were not randomized, there is a risk of selection bias or unrecognized confounders. We did note that baseline MAP and HR were slightly higher in the DOBU group, and the total dose of intraoperative opioids was higher in the NOR. This highlights the need for caution when comparing results. Finally, the use of somatostatin, as mentioned earlier, could confound absolute portal flow values as shown by van Limmen et al[10]; we mitigated this by ensuring both groups had similar exposure, but individual variability in response to somatostatin might still influence hepatic flow reserve.

In light of these limitations, the next logical step would be a prospective, randomized controlled trial directly comparing NOR versus DOBU (or perhaps a combination of both) in terms of hepatic perfusion and clinical outcomes. Such a study could stratify patients by risk factors (for example, patients with cirrhosis, vs. normal livers, vs. septic shock patients) to see if certain subpopulations benefit more from one approach. It would also allow balanced group sizes and random allocation to eliminate selection bias.

In conclusion, this comparative analysis strengthens our understanding of how DOBU and NOR differentially influence the liver's circulation. DOBU increases HBF (predominantly via the portal vein), whereas NOR can compromise hepatic perfusion by reducing arterial inflow. These differences are clinically relevant and suggest that the choice of hemodynamic support could be tailored to the patient's needs, balancing the benefits of improved systemic pressure with regional perfusion optimization. Continued research and clinical observation will help clarify how best to apply these insights to improve patient outcomes in both surgical and critical care contexts.

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References

1. Nicklas JY, Diener O, Leistenschneider M, Sellhorn C, Schön G, Winkler M, et al. Personalised haemodynamic management targeting baseline cardiac index in high-risk patients undergoing major abdominal surgery: a randomised single-centre clinical trial. Br J Anaesth. 2020;125(2):122–32.
2. Ryan EG, Harrison EM, Pearse RM, Gates S. Perioperative haemodynamic therapy for major gastrointestinal surgery: the effect of a Bayesian approach to interpreting the findings of a randomised controlled trial. BMJ Open. 2019;9(3):e024256.
3. Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, et al. Effect of a perioperative, cardiac output–guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. JAMA. 2014;311(21):2181–90.
4. Guimarães S, Moura D. Vascular adrenoceptors: an update. Pharmacol Rev. 2001;53(2):319–56.
5. Gelman S, Mushlin PS, Weiskopf RB. Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. Anesthesiology. 2004;100(2):434–9.
6. Vollmar B, Menger MD. The hepatic microcirculation: mechanistic contributions and therapeutic targets in liver injury and repair. Physiol Rev. 2009;89(4):1269–339.
7. Lautt WW. Regulatory processes interacting to maintain hepatic blood flow constancy: vascular compliance, hepatic arterial buffer response, hepatorenal reflex, liver regeneration, escape from vasoconstriction. Hepatology Research. 2007;37(11):891–903.
8. Eipel C, Abshagen K, of BVW journal, 2010 undefined. Regulation of hepatic blood flow: the hepatic arterial buffer response revisited. ncbi.nlm.nih.govC Eipel, K Abshagen, B VollmarWorld journal of gastroenterology: WJG, 2010•ncbi.nlm.nih.gov [Internet]. [cited 2024 Apr 24]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3012579/
9. El Hadi H, Di Vincenzo A, Vettor R, Rossato M. Relationship between heart disease and liver disease: a two-way street. Cells. 2020;9(3):567.
10. van Limmen J, Iturriagagoitia X, Verougstraete M, Wyffels P, Berrevoet F, Abreu de Carvalho LF, et al. Effect of norepinephrine infusion on hepatic blood flow and its interaction with somatostatin: an observational cohort study. BMC Anesthesiol. 2022 Dec 1;22(1).
11. DuBois D. A formula to estimate the approx-imate surface area if height and weight be known. Arch intern med. 1916;17:863–71.
12. Kainuma M, Kimura N, Nonami T, Kurokawa T, Ito T, Nakashima K, et al. The effect of dobutamine on hepatic blood flow and oxygen supply-uptake ratio during enflurane nitrous oxide anesthesia in humans undergoing liver resection. Anesthesiology. 1992;77(3):432–8.
13. Asfar P, De Backer D, Meier-Hellmann A, Radermacher P, Sakka SG. Clinical review: influence of vasoactive and other therapies on intestinal and hepatic circulations in patients with septic shock. Crit Care. 2003;8:1–10.
14. Joly LM, Monchi M, Cariou A, Chiche JD, Bellenfant F, Brunet F, et al. Effects of dobutamine on gastric mucosal perfusion and hepatic metabolism in patients with septic shock. Am J Respir Crit Care Med. 1999;160(6):1983–6.
15. Creteur J, De Backer D, Vincent JL. A dobutamine test can disclose hepatosplanchnic hypoperfusion in septic patients. Am J Respir Crit Care Med. 1999;160(3):839–45.
16. Krejci V, Hiltebrand LB, Sigurdsson GH. Effects of epinephrine, norepinephrine, and phenylephrine on microcirculatory blood flow in the gastrointestinal tract in sepsis. Crit Care Med. 2006;34(5):1456–63.
17. De Backer D, Creteur J, Silva E, Vincent JL. The hepatosplanchnic area is not a common source of lactate in patients with severe sepsis. Crit Care Med. 2001;29(2):256–61.

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