Received: 15 March 2022 | Revised: 10 July 2022 | Accepted: 27 July 2022

DOI: 10.1111/aas.14126

RESEARCH ARTICLE

acta Anaesthesiologica Scandinavica

Mid-regional plasma pro-atrial natriuretic peptide and stroke volume responsiveness for detecting deviations in central blood volume following major abdominal surgery

Rune B. Strandby[1] | Niels H. Secher[2] | Rikard Ambrus[1] | Jens P. Gøtze[3] | Amalie Henriksen[1] | Carl C. Kitchen[2] | Michael P. Achiam[1] | Lars B. Svendsen[1]

[1]Department of Surgery and Transplantation, Rigshospitalet, Institute for Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[2]Department of Anesthesia, Rigshospitalet, Institute for Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[3]Department of Clinical Biochemistry, Rigshospitalet, Institute for Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Correspondence
Rune B. Strandby, Department of Surgery and Transplantation, Rigshospitalet, Institute for Clinical Medicine, University of Copenhagen, Inge Lehmanns Vej 7, DK-2100 Copenhagen, Denmark.
Email: runestrandby@hotmail.com

Funding information
Gangstedfonden, Grant/Award Number: A31738 DK; Grosserer Jakob Ehrenreich og Hustru Grete Ehrenreichs Fond; J.E. and G. Ormstrup's Fond; Lundbeckfonden, Grant/Award Number: R230-2016-2727 DK; Rigshospitalet

Abstract

Background: A reduced central blood volume is reflected by a decrease in mid-regional plasma pro-atrial natriuretic peptide (MR-proANP), a stable precursor of ANP, and a volume deficit may also be assessed by the stroke volume (SV) response to head-down tilt (HDT). We determined plasma MR-proANP during major abdominal procedures and evaluated whether the patients were volume responsive by the end of the surgery, taking the fluid balance and the crystalloid/colloid ratio into account.

Methods: Patients undergoing pancreatic ($n = 25$), liver ($n = 25$), or gastroesophageal ($n = 38$) surgery were included prospectively. Plasma MR-proANP was determined before and after surgery, and the fluid response was assessed by the SV response to 10° HDT after the procedure. The fluid strategy was based mainly on lactated Ringer's solution for gastroesophageal procedures, while for pancreas and liver surgery, more human albumin 5% was administered.

Results: Plasma MR-proANP decreased for patients undergoing gastroesophageal surgery (−9% [95% CI −3.2 to −15.3], $p = .004$) and 10 patients were fluid responsive by the end of surgery (ΔSV > 10% during HDT) with an administered crystalloid/colloid ratio of 3.3 (fluid balance +1389 ± 452 ml). Furthermore, plasma MR-proANP and fluid balance were correlated ($r = .352$ [95% CI 0.031–0.674], $p < .001$). In contrast, plasma MR-proANP did not change significantly during pancreatic and liver surgery during which the crystalloid/colloid ratio was 1.0 (fluid balance +385 ± 478 ml) and 1.9 (fluid balance +513 ± 381 ml), respectively. For these patients, there was no correlation between plasma MR-proANP and fluid balance, and no patient was fluid responsive.

Conclusion: Plasma MR-proANP was reduced in fluid responsive patients by the end of surgery for the patients for whom the fluid strategy was based on more lactated Ringer's solution than human albumin 5%.

KEYWORDS
colloids, crystalloid solutions, fluid therapy, human, mid-regional pro-atrial natriuretic peptide, operative, postoperative complications, stroke volume, surgical procedures

Editorial Comment

It is challenging to estimate the optimal amount of intraoperative fluid to be administered to try to achieve optimal patient well-being after surgery. Plasma pro-atrial natriuretic peptide changes were assessed here in relation to different major abdominal surgical procedures, volume responsiveness determined by stroke volume during head-down tilt, and different types and amounts of intravenous fluid administration together with estimated fluid losses. The findings show a complex relationship between these factors and the biomarker level.

1 | INTRODUCTION

Patients are provided fluid and vasopressors during surgery to preserve the central blood volume (CBV) and thereby cardiac output and tissue blood flow. Deviations in CBV may be evaluated by the determination of plasma pro-atrial natriuretic peptide (MR-proANP), a stable precursor of ANP that is released by atrial distention.[1,2] ANP is important for the regulation of blood volume, and deviations in plasma ANP reflect changes in CBV,[3,4] that is, plasma ANP decreases when preload to the heart is reduced[5–7] and, conversely, increases when preload is enhanced.[8] Thus, a stable plasma MR-proANP from start to end of surgery indicates a maintained CBV, which is likely important for avoiding complications associated with hypovolemia[9,10] or fluid excess.[11] Furthermore, a correlation between plasma MR-proANP and perioperative fluid balance is reported during both cystectomy[12] and robot-assisted[5] as well as open esophagectomy.[5,13] Thus, a decrease in plasma MR-proANP may indicate a reduced CBV and the fluid deficit estimated by relating changes in plasma MR-proANP and the perioperative fluid balance.[5,12,13]

For further validation of a fluid deficit "volume responsiveness" is evaluated by recording stroke volume (SV), cardiac output (CO), or cardiac index during head-down tilt (HDT) by the end of surgery[14] or in the ICU.[15] Patients who respond by an increase >10% in SV are characterized as fluid responsive, indicating that there may be a CBV limitation to SV.[16,17] Thus, volume responsiveness may indicate a fluid deficit in parallel with a decrease in plasma MR-proANP.

We determined plasma MR-proANP during three major abdominal procedures and evaluated whether the patients were volume responsive by the end of the surgery, while fluid balance and the administered crystalloid/colloid ratio were determined. Furthermore, postoperative complications were assessed in relation to deviations in plasma MR-proANP. We hypothesized that patients with a decrease in plasma MR-proANP during surgery would be volume responsive by the end of the procedure.

2 | METHODS

This prospective cohort study was conducted at a single tertiary referral center (2015–2016) as approved by the Scientific-Ethical Committees, Kongens Vænge 2, 3400 Hillerød, Capital Region, Copenhagen (ID: H-3-2014-021, approved August 26, 2015), The Danish Data Protection Agency (ID: RH-2015-232) and registered at Clinicaltrials.gov (ID: NCT02507414). The study was conducted with patients who were simultaneously enrolled in another prospective, observational trial which was registered under the same clinical trial ID.[18] Predefined outcomes were: deviations in plasma MR-proANP and the SV response to HDT (primary) and the applied crystalloid/colloid ratio, fluid balance, as postoperative complications (secondary outcomes). Also, a post hoc variable was defined to allow for a comparison of fluid balance, crystalloid/colloid ratio, and postoperative complications among groups by allocating patients into three percentiles according to their perioperative change in plasma MR-proANP.

Oral and written informed consent was obtained from patients >18 years of age planned for open resection of the liver (≥2 segments), gastroesophageal junction/stomach, or pancreas (Whipple's procedure or total pancreatectomy). Three types of surgery were included in the study due to differences in the applied fluid strategy (see Section 4.1). The exclusion criteria were lack of informed consent, a robot-assisted/laparoscopic procedure, and that the procedure was not completed because of disseminated disease.

3 | EVALUATION OF CBV

Plasma MR-proANP was determined at baseline (after induction of anesthesia) and by the end of surgery (after the closure of the abdomen or thorax). Also, it was evaluated whether the patients were fluid responsive by the end of surgery by exposing them to 10° HDT for 5 min with determination of SV before and after the intervention.[14] Patients who responded with an increase >10% in SV were characterized as fluid responsive. Furthermore, central venous oxygen saturation ($ScvO_2$) was determined before and after HDT.

4 | ANESTHESIA

Before surgery, patients fasted for solid food for 6 h and were not provided clear fluid for 2 h. Induction of anesthesia was by propofol (2.0 $mg\ kg^{-1}$) and remifentanil (0.5 $\mu g\ kg^{-1}$) and cisatracurium facilitated endotracheal intubation. Anesthesia was maintained by infusions of propofol (5–10 mg kg^{-1} h^{-1}) and remifentanil (1.75–2.25 mg h^{-1}). A central venous catheter was inserted in the right internal jugular vein and an epidural catheter was positioned at interspace Th8–Th10. Extravascular or spinal placement was excluded by lack of response to administration of 4 ml 2% lidocaine/adrenaline and epidural anesthesia activated by 3–4 ml bupivacaine 0.5% followed by continuous infusion (bupivacaine 0.25% or 0.5% at 4–5 ml h^{-1}). Intraoperative hemodynamic variables (mean arterial pressure [MAP], heart rate [HR], SV, and CO) were obtained by pulse contour analysis (Nexfin, BMEYE BV) from a catheter in the radial artery of the non-dominant arm. Also, intraoperative hypotension was noted and expressed as minutes below 90 (systolic) or 60 (MAP) mmHg.

4.1 | Fluid and hemodynamic management

The fluid strategy depended on the type of operation according to department standards. For pancreatic resections, a goal-directed fluid therapy-based regime was applied perioperatively guided by SV. After induction of anesthesia, infusion of 250 ml HA 5% was repeated in increments until SV remained within ≤10% of the previous value,[19,20] and the fluid challenge was repeated every hour or if SV decreased >10% below the maximal SV. In addition to HA, patients were supplemented by a background infusion of lactated Ringer's solution (LR; 1 ml kg^{-1} h^{-1}).

For gastroesophageal resection, the fluid strategy was based mainly on LR to maintain intravascular volume (3 ml kg^{-1} h^{-1}) and HA replaced the blood loss 1:1. For liver surgery, the fluid administration was restricted to keep central venous pressure <6 mmHg to limit the blood loss and administration of HA and LR was at the discretion of the anesthesiologist.

Blood products were administered if hemoglobin dropped to 4.3 mmol L^{-1} (77 g L^{-1}) or 5.0 mmol L^{-1} (90 g L^{-1}) if the patient presented ischemic heart disease. Moreover, for pancreatic resection, blood products replaced colloid if administration of HA exceeded 25 ml kg^{-1}. In case of bleeding red blood cells, fresh frozen plasma, and thrombocytes were administered in a 3:3:1 ratio guided by thromboelastography.

If MAP decreased to <60 mmHg, ephedrine (0.1–0.2 ml [50 mg ml^{-1}]) and/or phenylephrine (0.1–0.2 ml [1 mg ml^{-1}]) were administered and supplemented by continuous infusion of either noradrenaline or phenylephrine if considered indicated by the anesthesiologist. Fluid balance was calculated by the end of surgery as the difference between the administered LR, HA, and blood products versus the diuresis and blood loss.

4.2 | Postoperative complications

Postoperative complications were expressed by the Dindo-Clavien classification[21] and the score graded by two reviewers: pharmacological treatment and interventions that did not require general anesthesia were classified as Grade 1–3a (minor complications). Alike, complications requiring surgical, endoscopic, or radiological intervention under general anesthesia as admission to the ICU and death were classified as Grade 3b–5 (major complications). Also, a comprehensive complication index was calculated in which the sum of all complications as severity is weighted.[22]

4.3 | Plasma MR-proANP

Blood for plasma MR-proANP was obtained from the arterial line in EDTA tubes and centrifuged at 3000 rpm at 4°C for 10 min and stored at −80°C until analysis. Plasma MR-proANP was measured by an automated method from Thermo-Fisher (the Kryptor Plus platform)[23] that aims at the mid-region (amino acids 53–90) where little proteolytic degradation is assumed to occur, and plasma MR-proANP is, therefore, more stable in plasma than mature ANP[24] but is released in equimolar amounts.[24,25] The applied test has an inter-assay reproducibility of 2.5%–4.5% and an inter-assay of 6.5% when evaluated according to CLSI guideline EP 5-A2.

4.4 | Statistical analysis

Statistical evaluation was by SPSS (IBM SPSS Statistics for Windows, Version 22) and graphs were constructed by GraphPad Prism Software (Version 7). Data were tested for normality using histograms and are presented as mean (SD) or median (interquartile range). Changes in plasma MR-proANP within groups are expressed in percentual change from baseline (95% CI) and evaluated by a paired *t* test or one-way repeated measures ANOVA with Bonferroni correction. To detect differences in variables between the three groups, a one-way ANOVA or Kruskal–Wallis *H* test with Bonferroni correction was applied for normally and non-normally distributed data, respectively. The association between plasma MR-proANP and fluid balance/HA was examined by linear regression and presented with Pearson's correlation coefficient (95% CI). Hemodynamic variables were calculated over 30 s, and a *p* value ≤.05 was considered statically significant.

Within 1 h after major surgery, 39% of patients are fluid responders as determined by HDT.[14] Assuming that plasma MR-proANP decreases during surgery in fluid responders and is maintained in non-responders, a power calculation (power: 0.8 and α level: .05) predicted that 15 patients were required in each group, and we decided to include at least 25 patients in each group before the final analysis.

5 | RESULTS

Patients undergoing gastroesophageal ($n = 38$), pancreas ($n = 25$), and liver surgery ($n = 25$) were included (Figure 1). Patients' baseline characteristics are presented in Table 1.

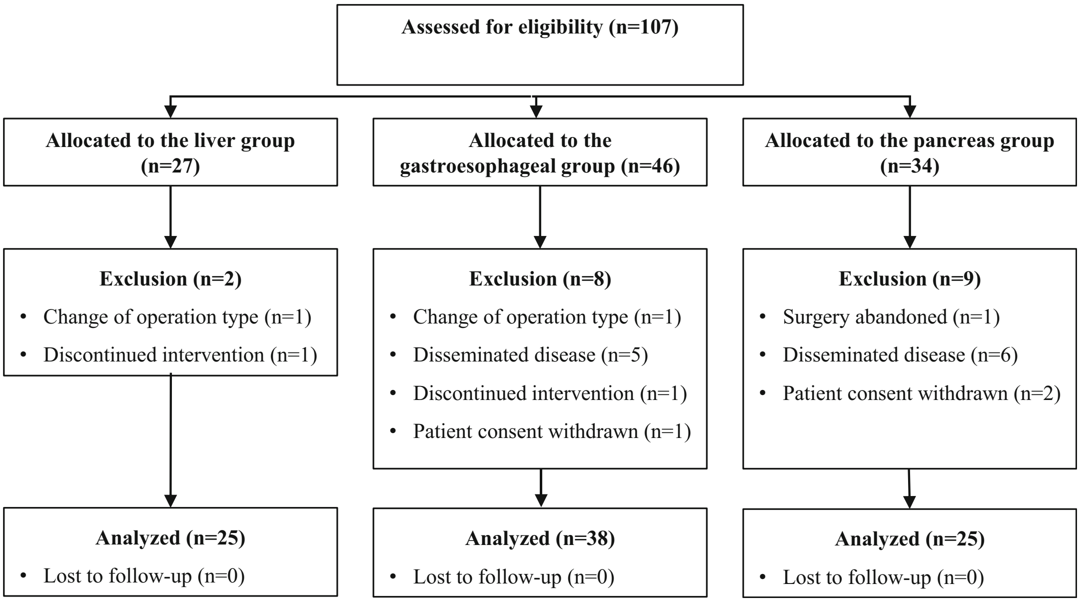

FIGURE 1 Patient flow chart

TABLE 1 Baseline characteristics

Baseline characteristics	Liver	Pancreas	Gastroesophageal	All patients
No. of patients	25	25	38	88
Age, years	63 (±9.1)	66 (±9.8)	66 (±11.0)	65 (±10.2)
Gender, no. (%)				
Male	17 (68.0)	10 (40.0)	30 (78.9)	65 (10.2)
BMI, kg cm^2	26.4 (±4.0)	23.8 (±4.1)	26.1 (±4.4)	25.5 (±4.3)
Smoking, no. (%)				
No	9 (36.0)	9 (36.0)	7 (18.4)	25 (28.4)
Earlier use	8 (32.0)	2 (8.0)	20 (52.6)	30 (34.1)
Active	7 (4.0)	14 (56.0)	11 (28.9)	32 (36.4)
Missing	1 (4.0)	0 (0.0)	0 (0.0)	1 (1.1)
Alcohol, no (%)				
None	5 (20.0)	7 (28.0)	9 (23.7)	21 (23.9)
Yes, not abuse	18 (72.0)	14 (56.0)	22 (57.9)	54 (61.4)
Yes, abuse	1 (4.0)	4 (16.0)	7 (18.4)	12 (13.6)
Missing	1 (4.0)	0 (0.0)	0 (0.0)	1 (1.1)
ASA, no. (%)				
1	5 (20.0)	4 (16.0)	7 (18.4)	16 (18.2)
2	11 (44.0)	14 (56.0)	22 (57.9)	47 (53.4)
3	9 (36.0)	6 (24.0)	8 (21.1)	23 (26.1)
4	0 (0.0)	1 (4.0)	0 (0.0)	1 (1.1)
Missing	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.1)

Note: Values are mean (±SD) or frequency (%).
Abbreviations: ASA, American Society of Anesthesiologists classification; BMI, body mass index.

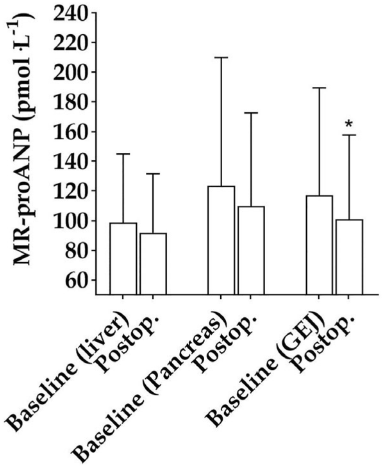

FIGURE 2 Change in plasma MR-proANP from start to end of surgery according to type of procedure. Values are mean ± SD. *Different from the baseline value, $p = .004$. GEJ, gastroesophageal; MR-proANP, mid-regional pro-atrial natriuretic peptide

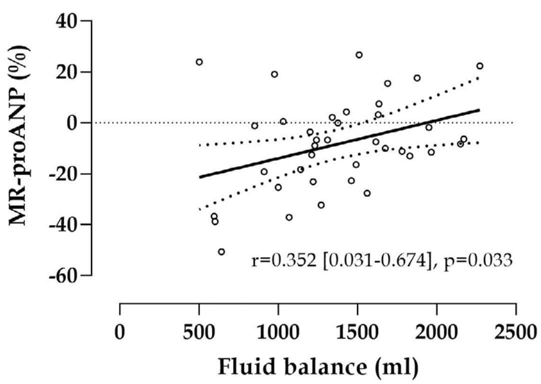

FIGURE 3 Change in plasma MR-proANP in relation to the perioperative fluid balance for patients undergoing gastroesophageal resection. Regression line with 95% CI is shown ($n = 38$). The horizontal broken line indicates no change in mid-regional plasma pro-atrial natriuretic peptide (MR-proANP)

5.1 | Plasma MR-proANP and fluid administration

From start to end of surgery, plasma MR-proANP decreased in the gastroesophageal group (−9.3% [−3.2 to −15.3], $p = .004$) while it remained stable in the pancreas (−4.2% [−6.8 to 15.1], $p = .438$) and liver groups (−4.0% [−5.5 to 13.6], $p = .391$) (Figure 2). Accordingly, plasma MR-proANP was correlated to fluid balance in gastroesophageal patients ($r = .352$ [95% CI 0.031–0.674], $p < .001$) (Figure 3), but not in the pancreas ($r = .004$ [−0.394 to 0.387], $p = .985$) and liver groups ($r = .285$ [−0.128 to 0.699], $p = .167$).

For the gastroesophageal group, the crystalloid/colloid ratio was 3.3 ± 2.2 (HA: 628 ± 432 ml and LR: 1810 ± 396 ml) as compared to 1.0 ± 0.34 in the pancreas group (HA: 1175 ± 445 ml and LR: 1063 ± 212 ml), and 1.9 ± 1.2 in the liver group (HA: 680 ± 640 ml and LR: 1301 ± 544 ml) (Table 2). The gastroesophageal patients had a more positive fluid balance after surgery (+1389 ± 452 ml) than the pancreas (+385 ± 478 ml) and liver patients (+513 ± 381 ml). The mean MAP during surgery was as intended >60 mmHg for all patients but for the gastroesophageal patients, hypotension lasted longer than for the two other groups of patients.

5.2 | Volume responsiveness

Ten patients (11.4%), all in the gastroesophageal group, responded by an increase of >10% in SV during HDT by the end of surgery (Table 3). For fluid responders, also CO increased but the increase in $ScvO_2$ did not reach statistical significance ($p = .085$). For non-responders ($n = 78$) SV and CO decreased while $ScvO_2$ increased by about 2% and 3% in the gastroesophageal and pancreas groups but remained unchanged in the liver group.

5.3 | Plasma MR-proANP percentiles and crystalloid/colloid ratio

To further evaluate differences in crystalloid and colloid administration in relation to changes in plasma MR-proANP, the patients were allocated into three percentiles depending on the peroperative MR-proANP response (Table 4): first (≤−17%, $n = 29$), second (−17 to 0%, $n = 30$), and third (≥0%, $n = 29$). Patients from the gastroesophageal, liver, and pancreas groups were allocated equally into the percentiles ($p = .794$). Administration of HA was lowest in the first compared with the third percentile (563 ± 484 vs. 1027 ± 595 ml, $p = .004$), and these patients were treated by a smaller amount of phenylephrine as compared with those in the third percentile ($p = .015$), and also total fluid administration tended to be lower ($p = .094$). There was no difference in the administered LR volume ($p = .136$) or fluid balance ($p = .115$) between the groups and mean MAP ($p = 1.0$) and minutes of intraoperative hypotension were also similar ($p = .216$). The crystalloid/colloid ratio was approximately 2.4, 2.0, and 1.4 in the first, second, and third percentiles, respectively, that is, plasma MR-proANP became stable when more colloid is administered. Accordingly, there was a correlation between plasma MR-proANP and HA administration ($r = .438$ [0.231–0.603], $p < .001$) (Figure 4).

5.4 | Postoperative complications

No differences were found for length of stay in hospital ($p = .765$), in the rate of minor ($p = .717$) and major postoperative complications ($p = .724$), or in the comprehensive complication index ($p = .147$) between patients allocated into the three plasma MR-proANP percentiles (Table 4). Moreover, no difference in outcomes was found when adjusted for type of operation (results not shown). Refer to Table S1 for specified complication categories.

6 | DISCUSSION

Plasma MR-proANP was stable during liver and pancreatic surgery, indicating a maintained CBV as supported by lack of volume responsiveness when these patients were exposed to HDT after surgery. In

TABLE 2 Fluid input/output, vasopressor treatment, and intraoperative variables

Intraoperative characteristics	Liver ($n = 25$)	Pancreas ($n = 25$)	Gastroesophageal ($n = 38$)	All patients ($n = 88$)
Duration of procedure, min	184 (±67)	281 (±52)	231 (±60)	232 (±70)
MAP, mean, mmHg	68 (±7)	65 (±4)	66 (±6)	66 (±6)
HR, mean, beats min^{-1}	65 (±7)	69 (±12)	67 (±10)	67 (±10)
Intraoperative hypotension, min	38 (±21)	49 (±35)	75 (±48)	57 (±41)
LR, ml	1301 (±544)	1063 (±212)	1810 (±396)	1453 (±517)
HA 5%, ml	680 (±640)	1175 (±445)	628 (±432)	796 (±552)
Blood products, ml	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Total fluid administration, ml	1800 (1200–3000)	2045 (1843–2809)	2350 (2048–2949)	2200 (1776–2877)
Blood loss, ml	885 (±632)	1289 (±1168)	672 (±428)	906 (±791)
Urine output, ml	611 (±464)	779 (±491)	424 (±235)	577 (±414)
Total fluid loss, ml	1497 (±865)	2068 (±1300)	1095 (±566)	1484 (±983)
Fluid balance, ml	513 (±381)	385 (±478)	1389 (±452)	854 (±641)
Noradrenalin infusion				
No. of patients, μg kg^{-1} min^{-1}	$N = 10$ 0.000 (0.000–0.026)	$N = 24$ 0.043 (0.020–0.068)	$N = 2$ 0.000 (0.000–0.000)	$N = 36$ 0.000 (0.000–0.028)
Phenylephrine infusion				
No of patients, mg min^{-1}	$N = 10$ 0.000 (0.000–0.026)	$N = 0$ 0.000 (0.000–0.000)	$N = 25$ 0.004 (0.000–0.014)	$N = 35$ 0.00 (0.00–0.0053)
Phenylephrine boli				
No of patients, mg	$N = 17$ 0.10 (0.00–0.30)	$N = 12$ 0.05 (0.00–0.20)	$N = 32$ 0.00 (0.00–0.01)	$N = 61$ 0.00 (0.00–0.01)
Ephedrin boli				
No of patients, mg	$N = 19$ 15 (5–28)	$N = 19$ 10 (10–19)	$N = 32$ 10 (10–25)	$N = 70$ 10 (10–25)

Note: Values are mean (±SD) or median (interquartile range). Intraoperative hypotension was defined as systolic pressure <90 mmHg or MAP <60 mmHg. Abbreviations: fluid balance = fluid administration − fluid loss; HA 5%, human albumin 5%; HR, heart rate; LR, lactated Ringer's solution; MAP, mean arterial pressure.

TABLE 3 Volume responsiveness evaluated by head-down tilt by the end of surgery

	Responders (gastroesophageal, $n = 10$)		Non-responders (pancreas, $n = 25$)		Non-responders (liver, $n = 25$)		Non-responders (gastroesophageal, $n = 28$)	
	Baseline 0°	HDT 10°	Baseline 0°	HDT 10°	Baseline 0°	HDT 10°	Baseline 0°	HDT 10°
SV, ml	59 (±10.2)	68 (±10.7)[a]	72 (±13.9)	67 (±13.0)[a]	76 (±17.1)	71 (±14.6)[a]	73 (±15.2)	69 (±15.1)[a]
$ScvO_2$, %	71.8 (±8.8)	74.8 (±6.9)	78.8 (±4.1)	81 (±4.3)[a]	77.1 (±5.4)	77.9 (±5.3)	74 (±6.6)	75.7 (±5.9)[a]
CO, l min^{-1}	4.6 (±1.0)	5.1 (±1.3)[a]	4.7 (±1.4)	4.5 (±1.4)[a]	4.9 (±0.9)	4.5 (±1.0)[a]	4.6 (±1.5)	4.4 (±1.4)[a]

Note: The values are mean (±SD). An increase by >10% in SV in response to head-down tilt was taken to indicate fluid responsiveness.
Abbreviations: CO, cardiac output; HDT, head-down tilt; $ScvO_2$, mixed central venous saturation; SV, stroke volume.
[a]Different from baseline within groups, $p < .05$.

contrast, plasma MR-proANP decreased during esophagectomy, and 10 of these patients were volume responsive by the end of surgery. The surgical procedures were not similar, but the allocation of patients into plasma MR-proANP percentiles showed that a stable perioperative plasma MR-proANP depends on the administered amount of colloid rather than on the surgical procedure.

Plasma MR-proANP decreased by 9% in the gastroesophageal group despite a higher fluid balance (by +1400 ml) as compared with the liver and pancreas groups (by +500 ml and +400 ml, respectively) and 10 of 38 gastroesophageal patients were fluid responsive when exposed to HDT. Thus, the findings indicate that CBV was not maintained in the gastroesophageal patients for whom the fluid strategy was based primarily on LR. By plotting changes in plasma MR-proANP against fluid balance an estimated fluid surplus of 2000 ml LR seems required to maintain plasma MR-proANP stable, that is, about 600 ml more than administered on average (Figure 3). The higher accumulation of intraoperative hypotensive minutes for gastroesophageal patients may be related to the apparent volume deficit. In contrast, as

TABLE 4 Fluid input/output, vasopressor treatment, and postoperative complications according to changes in plasma MR pro-atrial natriuretic peptide

Variable	MR-proANP ≤ −17%	MR-proANP 0% to −17%	MR-proANP ≥0%	*p*
Procedure				.794
Pancreas, no. (%)	10 (35)	6 (20)	9 (31)	
Liver, no. (%)	8 (28)	8 (27)	9 (31)	
Gastroesophageal, no. (%)	11 (37)	16 (53)	11 (38)	
HA 5%, ml	563 (±484)	798 (±492)	1027 (±595)[a]	.006
LR, ml	1346 (±456)	1602 (±587)	1401 (±473)	.136
Total fluid administration, ml	2032 (±986)	2497 (±944)	2472 (±720)	.094
Blood loss, ml	803 (±938)	916 (±770)	999 (±656)	.653
Urine output, ml	573 (±417)	583 (±433)	576 (±406)	.995
Fluid balance, ml	657 (±550)	999 (±697)	896 (±635)	.115
Phenylephrine boli, mg	0.13 (±0.17)	0.33 (±0.34)[a]	0.30 (±0.28)[a]	.015
Intraoperative hypotension, min	47 (±44)	57 (±33)	67 (±45)	.216
LOS, days	8.9 (±5.4)	10.3 (±9.6)	9.7 (±6.4)	.765
CCI	16.3 (±16.2)	16.0 (±17.7)	24.1 (±19.1)	.147
Minor complications (Dindo-Clavien Grade 1–3a), no. of patients (%)	26 (89.7)	26 (86.7)	27 (93.1)	.717
Major complications (Dindo-Clavien Grade 3b–4), no. of patients (%)	3 (10.3)	4 (13.3)	2 (6.9)	.724
Total no. of complications	80	94	123	.135
No. of patients with more than one complication, no. (%)	13 (44.8)	18 (60)	13 (44.8)	.492

Note: Values are frequency (%) or mean (±SD).
Abbreviations: CCI, comprehensive complication index; fluid balance = fluid input − fluid output; HA 5%, human albumin 5%; LOS, length of stay; LR, lactated Ringer's solution; MR-proANP, mid-regional pro-atrial natriuretic peptide.
[a]Different from ≤−17%, *p* < .05.

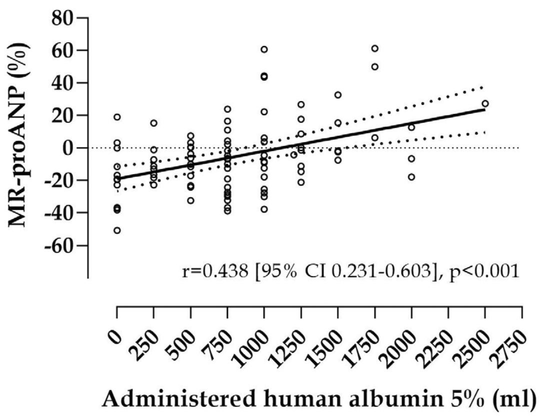

FIGURE 4 Change in plasma MR-proANP in relation to the administered volume of human albumin 5%. Regression line with 95% CI is shown (*n* = 88). The horizontal broken line indicates no change in plasma pro-atrial natriuretic peptide (MR-proANP)

MR-proANP did not change in the liver and pancreas groups, no correlation to fluid balance was found.

A similar decrease in plasma MR-proANP is reported during open esophagectomy[5] (by 11%) for whom the crystalloid/colloid ratio (∼4) and the fluid balance (+1528 ml) were comparable to the gastroesophageal patients in this study. That study also evaluated plasma MR-proANP during robot-assisted esophagectomy, where a decrease by 21% was found at a similar fluid balance as in the open procedures (+1705 ml). The discrepancy in plasma MR-proANP between the two procedures was likely due to the 15° head-up tilt during robot-assisted resection. Thus, preload to the heart is limited by gravity as demonstrated in healthy volunteers by a plasma ANP decrease during head-up tilt[4] and sitting or standing-up.[26] During cystectomy with the fluid strategy aiming at a maximal SV by administering LR, plasma MR-proANP correlates to both the blood loss (*r* = −.475, *p* = .002) and fluid balance (*r* = .561, *p* = .001).[12] Likewise, plasma MR-proANP decreases when thoracic epidural anesthesia is activated early rather than late during open esophagectomy,[13] indicating a reduced CBV due to inhibition of splanchnic sympathetic tone. Taken together, changes in plasma MR-proANP reflect perioperative deviations in CBV and may qualify for retrospective evaluation of how well a chosen fluid strategy maintains CBV. In addition, a fluid deficit may be estimated by plotting plasma MR-proANP against the perioperative fluid balance.[5,12,13]

The amount of crystalloid and colloid required to maintain plasma MR-proANP during surgery was evaluated by allocating patients into three percentiles. A crystalloid/colloid ratio of 1.4 and a positive fluid balance by 900 ml maintained plasma MR-proANP (>0%; third percentile) together with more treatment by phenylephrine. In comparison, patients for whom plasma MR-proANP decreased ≤−17%, a small volume of colloid was administered while the provided LR volume and the fluid balance were similar. Accordingly, a correlation between MR-proANP and administered albumin was found (Figure 4). Thus, the results confirm that albumin expands the intravascular space more efficiently than crystalloids, and that perioperative maintenance of plasma MR-proANP depends on the volume of administered colloid rather than on the surgical procedure.[27,28] A systematic review examined the perioperative crystalloid versus colloid volume needed to achieve resuscitation endpoints for patients admitted to the intensive care unit or during surgery.[29] The overall crystalloid/colloid ratio for 48 studies was 1.5 (95% CI 1.36–1.65) which is comparable to our findings when applying plasma MR-proANP to reflect CBV.

SV and CO decreased both by about 6% in non-responders during 10° HDT (Table 3) suggesting impaired cardiac function despite CBV was expanded. A similar decrease in SV by about 12% was shown for healthy subjects exposed to HDT by 90° while left ventricular end-diastolic volume increased concomitantly by 16%.[30] This observation seems to reflect that CO may be compromised when CBV is expanded, and even more so in anesthetized patients, in accordance with the observation that a fluid overload may have harmful effects postoperatively.[11,31]

No difference was found in minor and major complications, length of hospital stay, or comprehensive complication index between patients allocated into the three MR-proANP percentiles, that is, between patients with or without an assumed intravascular volume deficit by the end of surgery. This conclusion should be interpreted with caution because the accumulated fluid balance on the first days after surgery was not calculated. Thus, whether an intravascular volume deficit was compensated by additional administration of fluid after surgery was not evaluated. The focus of the study was limited to the intraoperative period, and postoperative outcomes should be evaluated in a cohort with power to detect a difference.

A limitation of the study is the non-randomized design. The surgical procedures are not similar and the extent of, for example, surgical stress or duration of surgery could affect the response to administration of fluid as vasopressor requirements. Thus, the intraoperative variables were described only according to the surgical procedure, and no differences between groups were evaluated. Yet, to allow for a comparison between groups, the patients were divided into MR-proANP percentiles and changes were applied to account for age and comorbidity-related deviations. MR-proANP was considered because the plasma concentration changes in parallel to CBV as determined by scintigraphy[3,32] as thoracic impedance[4] and MRI/echocardiography-determined atrial volume.[1,33] Furthermore, plasma ANP is related to changes in cardiac volume measures, but not filling pressure, which is an advantage since central filling pressures of the heart, e.g., central venous pressure and pulmonary artery wedge pressure, do not correlate to CBV.[3,4,34,35] HDT is feasible[14] and a reliable method for expanding CBV (AUC 0.9 95% CI 0.8–1.0 when using the cardiac index)[15] and chosen rather than a fluid challenge to prevent providing non-responders with excess fluid, that is, patients who were unlikely to benefit from additional fluid administration. The passive leg-raising test is an alternative to HDT but we considered the method challenging to perform on anesthetized patients in the operating room.

7 | CONCLUSION

Plasma MR-proANP was reduced in fluid responsive patients by the end of surgery for the patients for whom the fluid strategy was based on more lactated Ringer's solution than human albumin 5%.

AUTHOR CONTRIBUTION

RBS, NHS, RA, JPG, MPA, and LBS contributed to the design and conception of the study. RBS, AH, and CCK were responsible for acquisition of data. All authors contributed to the interpretation and analyses of data. RBS drafted the article with subsequent critical revision of its important intellectual context by all coauthors. All authors gave final approval for publication.

ACKNOWLEDGMENTS

This study was supported by the Lundbeck Fonden (R230-2016-2727, DK), Ehrenreich's Fond (DK), Gangstedfonden (A31738, DK), Rigshospitalet's Fond (DK), and J.E. and G. Ormstrup's Fond (DK). The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request.

ORCID

Rune B. Strandby https://orcid.org/0000-0002-7684-7780

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Strandby RB, Secher NH, Ambrus R, et al. Mid-regional plasma pro-atrial natriuretic peptide and stroke volume responsiveness for detecting deviations in central blood volume following major abdominal surgery. *Acta Anaesthesiol Scand*. 2022;66(9):1061-1069. doi:10.1111/aas.14126