

BMJ Open Plasma pro-atrial natriuretic peptide to indicate fluid balance during cystectomy: a prospective observational study

Kirsten C Rasmussen,¹ Michael Højskov,¹ Birgitte Ruhnau,¹ Lisbeth Salling,² Tom Pedersen,³ Jens P Goetze,⁴ Niels H Secher¹

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¹Departments of Anaesthesiology, Rigshospitalet, Copenhagen, Denmark

²Department of Urology, Rigshospitalet, Copenhagen, Denmark

³Center for Head and Orthopaedic Surgery, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

⁴Department of Clinical Biochemistry, Rigshospitalet, Copenhagen, Denmark

Correspondence to

Dr Kirsten C Rasmussen; dockcr@yahoo.com

ABSTRACT

Objectives: During surgery the volume of administered fluid is debated. Pro-atrial natriuretic peptide (proANP) is released by atrial distension, and we evaluated the relationship between changes in proANP associated with perioperative fluid balance.

Design: Prospective observational study.

Setting: One university/tertiary centre.

Participants: The study included patients who underwent radical cystectomy. Plasma for determination of proANP was obtained before surgery, after resection of the bladder, and at the end of surgery for 20 robotic-assisted radical cystectomy (RARC) and 20 open radical cystectomy (ORC) procedures.

Results: The blood loss was 1871 (95% CI 1267 to 2475) vs 589 mL (378 to 801) in the ORC and RARC groups ($p=0.001$), respectively, and fluid balance was positive by 1518 mL (1215 to 1821) during ORC, and by 1858 mL (1461 to 2255) during RARC ($p=0.163$). Yet, at the end of ORC, plasma proANP was reduced by 23% (14% to 32%, $p=0.001$), while plasma proANP did not change significantly during RARC. Thus, plasma proANP was associated both with the perioperative blood loss ($r=-0.475$ (0.632 to -0.101), $p=0.002$), and with fluid balance ($r=0.561$ (0.302 to 0.740), $p=0.001$), indicating that a stable plasma proANP required a fluid surplus by 2.4 L (2.0 to 2.7).

Conclusions: There was a correlation between intraoperative haemorrhage and a decrease in plasma proANP and, taking plasma proANP to indicate filling of the heart, about 2.5 L surplus volume of lactated Ringer's solution appears to maintain cardiac preload during cystectomy.

Trial registration number: EudraCT (2012-005040-20), Results.

INTRODUCTION

During surgery, blood circulation is supported by a crystalloid, but up to 70% of the administered volume may be lost to the interstitial space even when the circulating blood

Strengths and limitations of this study

- This prospective study demonstrates a correlation between a decrease in plasma proANP and intraoperative haemorrhage.
- Taking plasma proANP to reflect atrial distension, the study advances the idea that fluid balance is directly related to plasma proANP with about 2.5 L surplus lactated Ringer solution needed to secure a stable level in patients undergoing major surgery.
- The study was not randomised to the surgical procedures—robotic-assisted radical cystectomy and open radical cystectomy—and not powered to reveal differences in outcome related to changes in plasma proANP.

volume is reduced due to haemorrhage.^{1 2} Furthermore, a positive postoperative fluid balance may result in gut oedema, contribute to intestinal dysfunction, postoperative complications and extended hospital stay.^{3 4} Thus, maintained fluid balance during surgery is important.

Plasma atrial natriuretic peptide (ANP)—but not B-type natriuretic peptide (BNP)⁵—decreases with reduction of the central blood volume during, for example, head-up tilt⁶ or sitting or standing up⁵ as with pressure breathing⁷ indicating that plasma ANP responds to distension of the atria independently of central venous pressure. Compared with ANP, proANP has a longer half-life in plasma, and proANP is therefore applied to evaluate fluid balance.⁸

We use mainly lactated Ringer's (LR) solution to support the circulation during surgery, and considered the volume of LR required to maintain plasma proANP stable during cystectomy. Both patients going through open radical cystectomy (ORC, expected blood loss >1.5 L) and robotic-assisted radical cystectomy (RARC,

expected blood loss <0.5 L) were included in the evaluation considering that eventual impeded venous return to the heart by abdominal CO₂ inflation is compensated by placing the patients in Trendelenburg's position. The aim of the study was to examine the relationship between changes in proANP associated with perioperative fluid balance. We hypothesised that when a blood loss is replaced by LR, it would require a positive volume balance to maintain plasma proANP.

METHODS

Patients

The study included patients undergoing resection of the urine bladder due to cancer, was approved by the local ethics committee (H-1-2012-135), and the ORC patients were part of a randomised controlled study (RCT) registered in EudraCT (2012-005040-20). For the 20 ORC patients included consecutively between February 2013 and July 2014,⁹ plasma proANP and fluid balance were determined. Furthermore, we analysed a second group of 20 patients undergoing RARC, who were prospectively included in the same period, where plasma proANP and fluid balance were determined as well. Patients selected for ORC and RARC were included in the study to supposedly represent a markedly different blood loss with a similar surgical intervention.^{10–12} The Declaration of Helsinki criteria were followed, and the study was monitored by the Agency for Good Clinical Practice at the University of Copenhagen.¹³ At least 24 h before surgery written informed consent was obtained from the patients. We excluded patients from this investigator-initiated, prospective trial if consent was withdrawn. Data were gathered by the investigators and remained confidential throughout the process. The patients were followed-up until discharge, and the authors were involved in every stage of manuscript generation and vouched for the completeness and accuracy of the data. No third party influenced the study design, data analysis or reporting.

Interventions

Monitoring and fluid administration for the patients during anaesthesia has been published.^{9 14} An intravenous line was established, and a catheter placed in the left radial artery and connected to a modified Nexfin monitor (Bmeye BV, Amsterdam, The Netherlands). From the blood pressure recording, heart rate (HR) was determined and stroke volume (SV) estimated by a non-linear model of arterial impedance using Modelflow technology and cardiac output (CO) calculated.¹⁵

For induction of anaesthesia, remifentanyl infusion was initiated (0.5 µg/kg/min) and when the patient reported sedation, propofol (2.0 mg/kg) was administered. Cisatracurium (0.10–0.15 mg/kg) facilitated oral tracheal intubation, and propofol (5–10 mg/kg/h) and remifentanyl (1.75–2.25 mg/h) maintained anaesthesia. With the patient supine, administration of 200 mL LR

was continued until SV increased by <10% according to the 'goal directed fluid therapy' (GDT) paradigm.¹⁶ Both groups of patients received 5% human albumin and blood products if considered in need by the anaesthesiologist.

Patients in the ORC group were bent to expose the lower abdominal organs, while RARC patients were in 30° Trendelenburg's position during resection of the bladder and lymph node exeresis using a da Vinci System (5.0 robotic, Intuitive Surgical Inc., Sunnyvale, California, USA). For RARC patients, bladder reconstruction was established via a lower mini laparotomy with the patient supine. Two surgeons performed the ORC procedures, while two other surgeons performed the RARC procedures.

The HR, mean arterial pressure (MAP), SV and CO were noted after induction of anaesthesia before surgery (T₁), after resection of the bladder (T₂), and at the end of anaesthesia (T₃) before epidural anaesthesia was activated for ORC patients. If systolic pressure fell below 80 mm Hg, 5–10 mg of ephedrine was administered.

Arterial blood was drawn at T₁ and T₃, that is, before and after abdominal CO₂ inflation with the patient supine, and at T₂ a few minutes after resection of the bladder, when the patient in the ORC group was bent. We analysed plasma for proANP to indicate whether the central blood volume was maintained.^{17 18} The samples were centrifuged for 10 min at 3.000 rpm at –5°C and stored at –80°C until analysed. Simultaneously, blood was drawn from the central venous catheter for blood gas variables including haemoglobin oxygen saturation (S_vO₂, ABL 825, Radiometer, Copenhagen, Denmark). Plasma proANP was measured with an automated method from Thermo-Fisher (the Kryptor Plus platform), where the antibody is directed against epitopes within the mid-region of the precursor (MR-proANP). We validated this method against an immunoassay from our laboratory with excellent performance in non-heart failure patients.^{19 20} Fluid balance was defined as intraoperative fluid infusion (LR, human albumin 5%, packed red blood cells, fresh frozen plasma) minus blood loss and diuresis.

The outcome variable was postoperative morbidity and length of hospital stay in the ORC and RARC groups. Complications were defined as need for postoperative treatment of cardiopulmonary infections or surgical complications until discharge from hospital.

Statistical analysis

As an exploratory study of the plasma proANP response to surgery, no power analysis was performed. We used two-sided or unadjusted χ^2 tests, t test and Fisher's exact test for continuous and dichotomous variables, respectively. Results are presented as mean (SD) or median, as appropriate, and the 95% CI is provided. Test for differences used the non-parametric Spearman's test, χ^2 test for categorical data, and analysis of variance or Mann-Whitney U test and Wilcoxon signed-rank test for

continuous data when appropriate. For intraoperative bleeding, multivariate logistic regression analysis was performed to define whether plasma proANP was independently associated with intraoperative bleeding with 1.5 L considered to represent an approximately 30% loss of blood volume and, thereby, potentially affecting blood pressure.²¹ Statistical analyses were performed using SPSS V.20.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

There was no significant intergroup difference in baseline data including preoperative diseases between the two groups of patients (table 1). After induction of anaesthesia, 59% of the participants were normovolaemic according to the GDT criteria.

Haemorrhage, fluid administration and haemodynamics

The intraoperative lost blood was 1871 mL (CI 1267 to 2475) during ORC vs 589 mL (CI 378 to 801) in the RARC group ($p=0.0001$). Significant haemorrhage was also more frequent during ORC as 45% of these patients lost more than 1500 mL of blood versus only 5% in the RARC group, $p=0.008$ (table 1). Table 2 presents administration of intravenous fluids: total fluid infusion was by 3580 (2989 to 4171) vs 2762 mL (2266 to 3258) ($p=0.033$) in the ORC and RARC groups, respectively. The net fluid balance was positive in both groups: by 1518 mL (1215 to 1821) during ORC and by 1858 mL (1461 to 2255) during RARC ($p=0.163$). Accordingly, haemoglobin was more reduced (by 13%) during ORC than during RARC (by 7%, $p=0.001$). Seven patients in the ORC group were provided with transfusion of blood versus one patient during RARC, resulting in administration of 325 (73 to 577) vs 61 (0 to 189) mL packed red blood cells ($p=0.058$), respectively, with no marked differences between observations at T₂ and T₃.

The CO increased almost 50% during RARC (from 4.6±1.2 to 6.3±1.5 L/min) ($p=0.001$), and was higher

than in ORC patients ($p=0.001$); and also S_vO₂ was higher during RARC (82±5% vs 73±6%, $p=0.001$). The MAP increased by approximately 10% (from 63±15 to 69±14 mm Hg, $p<0.05$) in both groups of patients, and without difference in the total dose of administered ephedrine. In the two groups of patients, there was a similar increase in HR (from 63±13 to 81±14 bpm in RARC patients, and from 63±12 to 76±16 bpm in ORC patients).

Plasma proANP

During ORC, plasma proANP was reduced by 23% (14% to 32%, $p=0.001$), but remained unchanged during RARC (table 3). Changes in plasma proANP were related to the blood loss ($r=-0.475$ (-0.632 to -0.101), $p=0.002$) (figure 1A) and to fluid balance ($r=0.561$ (0.302 to 0.740), $p=0.001$) (figure 1B). Thus, a stable plasma proANP during surgery appeared to require a fluid surplus of 2.4 L (2.0 to 2.7). By multiple regression analysis, only plasma proANP was independently associated with the perioperative blood loss (table 4).

Postoperative observations

There was no significant difference in postoperative complications between the surgical groups, that is, four patients in the ORC and the RARC groups were treated due to postoperative complications. The length of hospital stays were similar, 7 days (6–92) in the ORC group vs 7 days (5–21) in the RARC group ($p=0.33$).

DISCUSSION

Plasma proANP is released in response to atrial distension independently of central venous pressure, and we considered an increase to reflect intravascular volume expansion and, conversely, a reduction to indicate a reduced central blood volume. For patients going through ORC and RARC, plasma proANP was related to

Table 1 Patient characteristics and intraoperative data

Variable	Overall (n=40)	RARC (n=20)	ORC (n=20)	p Value
Age, years	66.6 (7.7)	64.8 (8.5)	68.6 (6.5)	0.12
Male sex	32 (40)	18 (90)	14 (70)	0.24
BMI, kg/m ²	25.5 (5.5)	25.8 (3.3)	25.1 (7.1)	0.70
ASA classification, I and II/III	32/8	17/3	15/5	0.69
Cardiopulmonary disease	23 (58)	11 (55)	12 (60)	1.00
Hypertension	16 (40)	9 (45)	7 (35)	0.37
Chronic heart failure	2 (5)	1 (5)	1 (5)	0.76
Diabetes	5 (13)	1 (5)	4 (20)	0.17
Smokers (current and former)	32 (80)	17 (85)	15 (75)	0.70
Duration of surgery, min	255 (82)	325 (37)	184 (45)	0.001
Ephedrine, mg	32.8 (17)	31.0 (19)	34.6 (16)	0.03
Blood loss >1500 mL	10 (25)	1 (5)	9 (45)	0.008
Blood administration	8 (20)	1 (5)	7 (35)	0.044

Values are mean±SD or numbers (%). p Value by univariate analysis.

ASA class, American Society of Anesthesiologists; BMI, body mass index; ORC, open radical cystectomy; RARC, robotic-assisted radical cystectomy.

Table 2 Fluid administration and balance during anaesthesia

Variable	Overall (n=40)	RARC (n=20)	ORC (n=20)	p Value
Total fluid infusion (mL)*	3171 (2780 to 3563)	2762 (2266 to 3258)	3580 (2988 to 4171)	0.033
Ringer's solution (mL)	2393 (2186 to 2599)	2336 (1994 to 2677)	2450 (2186 to 2714)	0.58
PRBC (mL)	193 (52 to 334)	61 (0 to 189)	325 (73 to 576)	0.058
Albumin (mL)	319 (197 to 440)	188 (51 to 323)	450 (254 to 646)	0.027
Total fluid loss (mL)†	1486 (1126 to 1847)	905 (665 to 1145)	2068 (1470 to 2667)	0.001
Diuresis (mL)	260 (202 to 319)	321 (228 to 413)	201 (132 to 270)	0.037
Blood loss (mL)‡	1230 (861 to 1599)	589 (378 to 801)	1871 (1267 to 2475)	0.001
Total fluid balance (mL)□	1688 (1444 to 1933)	1858 (1461 to 2255)	1518 (1215 to 1821)	0.163

Values for fluid balance are expressed as means with 95% CI. Also p value determined by ANOVA test compared differences in fluid volume between the RARC and ORC groups are given.

*Fluid administered during anaesthesia.

†Blood and urine lost during anaesthesia.

‡Blood loss during anaesthesia and fluid balance=fluid infusion–fluid lost during anaesthesia.

□ANOVA, analysis of variance; ORC, open radical cystectomy; PRBC, packed red blood cells; RARC, robotic-assisted radical cystectomy.

the volume load at the end of surgery and a stable value was established with a 2.4 L (2.0–2.7) surplus.

Plasma proANP correlated not only to volume balance, it also demonstrated a negative correlation to the loss of blood. Thus, with a blood loss by approximately 300 mL, there was no change in plasma proANP, with a 2000 mL positive fluid balance during surgery (figure 1). On the contrary, with a 3300 mL blood loss, plasma proANP decreased by about 40% despite a 500 mL positive volume balance. Perioperative haemorrhage and need for transfusion is larger during ORC compared with RARC^{10–12} as confirmed here, and only ORC patients demonstrated a significant decrease in plasma proANP.

We optimised the intravascular volume before surgery according to GDT criteria,¹⁶ and aimed to maintain a maximal SV, CO and S_vO_2 throughout surgery although the late evaluation was not a protocol. Yet, for the RARC patients, CO increased in Trendelenburg's position indicating a central blood volume deficit at that time.²² Furthermore, CO and S_vO_2 were larger for RARC than for ORC patients, and although HR did not differ between the two groups of patients, the other cardiovascular variables supported that the ORC patients were

hypovolaemic. That was the case although the fluid balance at the end of surgery was positive by 1.9 L for ORC patients and similar (1.5 L) for RARC patients.

Table 3 Plasma proANP during ORC and RARC

Variable	All (n=40)	RARC (n=20)	ORC (n=20)	p Value*
ProANP (pmol/L)				
T ₁	130 (66)	106 (37)	153 (79)	0.094
T ₂	114† (49)	108 (40)	120‡ (60)	0.787
T ₃	107‡ (47)	104 (33)	115‡ (59)	0.646

T₁=before start of surgery; T₂=after resection of the urinary bladder; T₃=at the end of anaesthesia. Data are mean (SD), p value determined by univariate analysis.

*† Test compared differences in hormones between the RARC and ORC group.

†p<0.01 difference from anaesthesia induction within the group.

‡p<0.001 difference from anaesthesia induction within the group (Wilcoxon signed-rank test).

ORC, open radical cystectomy; proANP; pro-atrial natriuretic peptide; RARC, robotic-assisted radical cystectomy.

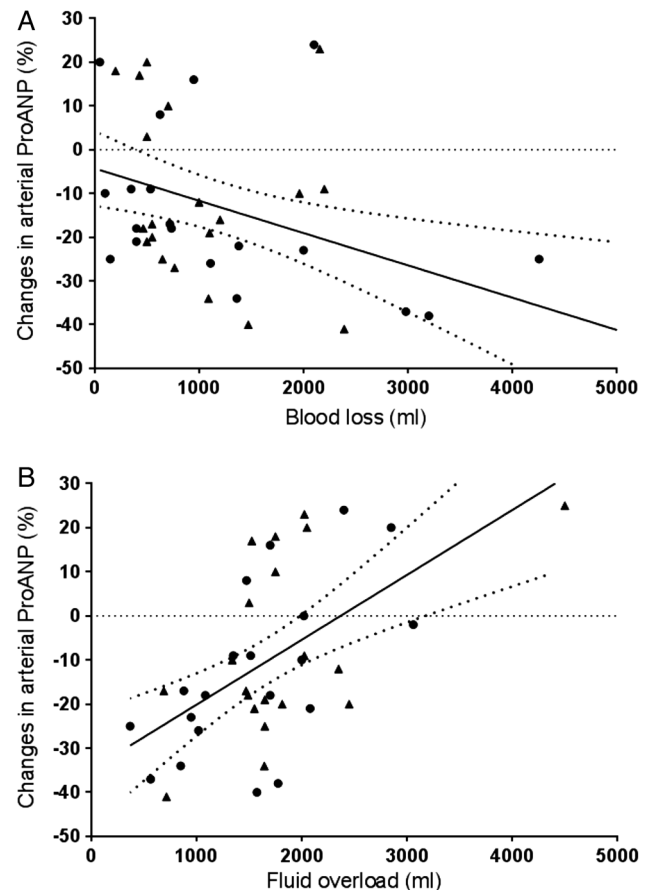


Figure 1 Pro-atrial natriuretic peptide ProANP in relation to intraoperative blood loss and fluid balance. Change in plasma proANP from start (T₁) to end of anaesthesia (T₃) in patients during robotic-assisted (RARC) (black angle) or open radical cystectomy (ORC) (black circle), $r=-0.475$ (95% CI -0.632 to -0.101), $p=0.002$ (A) and $r=0.561$ (0.302 to 0.740), $p=0.001$ (B). Regression lines shown with 95% CI. Horizontal broken lines indicate no change in plasma proANP.

Table 4 Multiple logistic regression analysis of changes in plasma proANP (<80% vs ≥80% of T1 value) during anaesthesia in relation to blood loss and fluid excess

Variable	Regression coefficient (β)	SE	p Value	OR (e ^β)	95% CI
ProANP					
Blood loss >1500 vs <1500 mL	-1.84	0.86	0.034	0.16	0.03 to 0.87
Fluid balance <2000 vs ≥2000 mL	1.69	1.21	0.163	5.43	0.50 to 58.59
Constant	-1.22	1.14	0.286		

proANP; pro-atrial natriuretic peptide.

It should be considered how fluid balance is estimated. There may be a 1:5 volume ratio between the intravascular and interstitial fluid space² and a separate calculation may be conducted for colloids and crystalloids. If only 25% of the administered 2762 mL of LR remained within the plasma space (690 mL) together with 5% human albumin and packed red blood cells, the intravascular fluid balance is, on average, positive by 30 mL for the RARC patients. For the ORC patients, a similar calculated intravascular fluid balance becomes negative by 400 mL. Thus, a calculation of fluid balance based on distinction between colloids and LR, supports that ORC patients were exposed to an intravascular volume deficit. Fluid administration was standardised with patients receiving LR and substitution of the blood loss with packed red blood cells and, eventually, human albumin.²³ Thus, according to plasma proANP, established intravascular volume deficit—despite a positive volume balance—reflects distribution of LR to the extravascular space.

Plasma proANP indicates a volume surplus for patients in septic shock.²⁴ The largest values for plasma proANP were for patients with the highest Acute Physiology and Chronic Health Evaluation score and for non-survivors. In order to discriminate between survivors and non-survivors, the proANP cut-off concentration was 221 pmol/L (with a high sensitivity, but a low specificity; likelihood ratio 2.0). In the present study, plasma proANP was only about half that level, and decreased further for the ORC patients.

The participants were not randomised to the two surgical procedures, however, the history of the patients was similar. Also, the study was not considered to reveal differences in postoperative outcome—neither related to changes in plasma proANP, nor between the surgical methods. Other means of evaluating cardiac filling during surgery, including, for example, echocardiography or a determination of blood volume, may be required to generalise the present findings, and the evaluation could be extended to include frequent evaluation of plasma proANP during surgery. However, values determined during surgery (T₂) were not deviating from those obtained at T₃ and, therefore, not detailed. We could have recorded central venous pressure, but plasma ANP relates to atrial stretch rather than to atrial pressure.⁷

A critical consideration for this study is how fluid balance is estimated. If a separate calculation is made

for colloids (blood and albumin) and crystalloids, the ORC patients had a colloid deficit of 1518 vs 422 mL for the RARC patients, but the two groups of patients were supported by an almost identical crystalloid surplus (by 1771 vs 1478 mL, table 2). The calculation, thereby, supports that the volume load was small for the ORC patients, but we admit that a determination of blood volume or the central blood volume was not established.

Taking that (pro)ANP reflects atrial distension, we advance the idea that fluid balance during surgery can be evaluated in relation to cardiac preload. We demonstrate a correlation between a decrease in plasma proANP and haemorrhage, while fluid balance based mainly on LR was directly related to plasma proANP with about 2.5 L surplus volume needed to secure a stable level in patients undergoing radical cystectomy. In consequence, it remains to be established whether the clinical outcome would be improved by administration of some colloid rather than base fluid support on LR only.

Contributors KCR, BR, JPG and NHS contributed to the conception and design of the work; KCR, MH and BR were responsible for perioperative management and recording clinical characteristics; KCR, MH, BR, LS, TP, JPG and NHS were involved in the analysis and interpretation of the data; KCR, MH, BR, LS, TP, JPG and NHS were involved in the drafting of the manuscript and its revision for important intellectual content, and gave final approval for the manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The ethic committee in the capital region of Denmark (H-1-2012-135).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Additional data can be accessed via the Dryad data repository at <http://datadryad.org/> with the doi:10.5061/dryad.56np2.

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