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

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Contributors KCR, BR, JPG and NHS contributed to the conception and design of the work; KCR, MH and BR was responsible for perioperative management and recording clinical characteristics; KCR, MH, BR, LS, TP, JPG and NHS were involved in the analysis and interpretation of 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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Strength and limitations of this study

- This prospective study demonstrated a correlation between intraoperative haemorrhage and a decrease in plasma proANP.
- Taking that proANP reflects atrial distension, the study advanced the idea that fluid balance is directly related to plasma proANP with an about 2.5 l surplus volume needed to secure a stable level in patients undergoing major surgery.
- The study was not randomized 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.

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ABSTRACT

Objectives: During surgery the volume of administered fluid is debated. Pro-atrial natriuretic peptide (proANP) is released by atrial distension and we evaluated how much lactated Ringer's solution needs to be provided for maintaining plasma proANP stable during cystectomy.

Design: Prospective observational study.

Setting: One university/tertiary centre.

Participants: The study included 40 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 (RARC) and 20 open radical cystectomy (ORC) procedures.

Results: The blood loss was 1871 (95% CI 430 to 5420) vs. 589 ml (50 to 2100) in the ORC and RARC group (P=0.001) and fluid balance was positive by 1519 ml (370 to 3060) during ORC and by 1858 ml (690 to 4650) during RARC (P=0.163). Yet, at the end of ORC, plasma proANP was reduced by 23% (14-32; P = 0.004), while plasma proANP did not change significantly during RARC. Thus, plasma proANP was associated both to the perioperative blood loss (r = -0.475 (0.633 to -0.101); P = 0.002) and to fluid balance (r=0.561 (0.302-0.740); 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, an about 2.5 L surplus volume of lactated Ringer's solution appears to maintain cardiac preload during cystectomy.

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INTRODUCTION

During surgery the 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 volume is reduced due to haemorrhage.[1,2] Furthermore, a positive postoperative fluid balance may result in gut edema, 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, e.g. head-up tilt [6] or sitting or standing up [5] as with pressure breathing [7] indicating that plasma ANP responds to distension of the atria independently of central venous pressure. Compared to ANP, proANP has a longer half-life in plasma and proANP is therefore applied to evaluate fluid balance.[8]

We use mainly LR to support the circulation during surgery and considered the volume 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 CO_2 inflation is compensated by Trendelenburg's position.

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METHODS

Patients

The study was based on plasma collected from participants in a colloids vs. crystalloid trial[9] (ClinicalTrials.gov NCT01444508 and EudraCT 2012-005040-20). Forty 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 protocols were approved by the local Ethic Committee (H-2-2011-063 and H-1-2012-135) and monitored by the Agency for Good Clinical Practice at the University of Copenhagen. [13] The Declaration of Helsinki criteria were followed with written informed consent obtained from every patient. Screening and allocation took place between February 2013 and September 2014. 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. Forty out of 133 patients scheduled for elective cystectomy were allocated to intervention with robot assisted radical cystectomy (n=20) or open radical cystectomy (n=20). The reasons for exclusion were not meeting the inclusion criteria (n=24), declining to participate (n=12), investigator absent (n=4), logistic reasons (n=3), fluid therapy with colloids (n=34), and other reasons (n=16). Data were gathered by the investigators and remained confidential throughout the process. All forty patients were followed-up in the postoperative period until discharge. The authors were involved in every stage of manuscript generation and vouched for the completeness and accuracy of the data. No third part influenced the study design, data analysis, or reporting.

Interventions

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The participants consumed solid food up to 6 h and clear fluid until 2 h before surgery. An IV line was established and a catheter placed in the radial artery of the non-dominant arm and connected to a modified Nexfin monitor (Bmeye B.V, Amsterdam, The Netherlands). From the blood pressure recording, SV was estimated by a non-linear three-component model of arterial impedance using Modelflow technology.[14]

For induction of anaesthesia remifentanil infusion was initiated (0.5 µg $kg^{-1} \cdot min^{-1}$) and when the patient reported sedation, propofol (2.0 mg/kg) was administered. Cisatracurium (0.10 to 0.15 mg/kg) facilitated oral tracheal intubation and propofol (5-10 $mg \cdot kg^{-1} \cdot h^{1}$) and remifentanil (1.75-2.25 mg/h) maintained anaesthesia. Ventilation was adjusted to an end-tidal CO2 tension of 28 to 32 mmHg (Dräger CATO; M32040, Lübeck, Germany). An epidural catheter (Th. interspace 9-12) was used for postoperative pain treatment and its placement was tested with 3 ml lidocaine 2% with epinephrine; epidural anaesthesia was established when the operation was completed. A central venous catheter was inserted guided by ultrasound in the right internal jugular vein. With the patient supine, administration of 200 ml lactated Ringer's solution (LR) was continued until SV increased by less than 10% according to the "goal directed fluid therapy" (GDT) paradigm [15]. Both groups of patients received 5% human albumin and blood products if considered in need by the anaesthesiologist.

Patients in the ORC group were supine throughout surgery 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, CA, USA). 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.

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Heart rate (HR), mean arterial pressure (MAP), stroke volume (SV), and cardiac output (CO) were noted after induction of anaesthesia but before surgery (T_1), after resection of the bladder (T_2), and at the end of anaesthesia (T_3) before epidural anaesthesia was activated. If systolic pressure fell below 80 mmHg, 5 to 10 mg of ephedrine was administered.

Arterial blood was drawn at T_1, T_2 and T_3 while the patients were supine, i.e. after end of abdominal CO_2 inflation for RARC. We analyzed blood for proANP to indicate whether the central blood volume was maintained. [16,17] The samples were centrifuged for 10 min at 3.000 rpm at -5˚ C and stored at -80 ˚ C until analyzed. Simultaneously, blood was drawn from the central venous catheter for blood gas variables including S_vO_2 (ABL 825, Radiometer, Copenhagen, Denmark). 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 a immunoassay from our laboratory with excellent performance in non-heart failure patients.[18,19] Fluid balance was defined as intraoperative fluid infusion (LR, human albumin 5%, packed red blood cells, fresh frozen plasma – blood loss and diuresis. Fluid balance was calculated at T_3.

Statistical Analysis

As an exploratory study of the proANP response to surgery no power analysis was performed. We used two-sided or unadjusted chi-square 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% confidence interval (CI) is provided. Test for differences used the non-parametric Spearman's test, $\chi 2$ test for categorical data

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and analysis of variance or Mann-Whitney *U*-test and Wilcoxon signed ranks test for continuous data when appropriate. For intraoperative bleeding, multivariate linear 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.[20] Statistical analyses were performed using SPSS V.20.0 (SPSS Inc, Chicago, Illinois, USA).

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RESULTS

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

Haemorrhage, fluid administration and haemodynamics

The intraoperative lost blood was 1871 ml (CI 1267 to 2475) during ORC vs. 589 ml (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 vs. only 5% in the RARC group, *P*=0.008 (Table 1). Table 2 presents administration of IV fluids: total fluid infusion was by 3580 (2989 to 4171) vs. 2762 ml (2266 to 3258), (*P*=0.033) in the ORC and RARC group, 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, hemoglobin 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 vs. one patient during RARC, resulting in administration of 325 (73 to 577) vs. 61 ml (0 to 189) packed red blood cells (*P*=0.058), respectively, however with no marked differences between observations at T_2 and T_3.

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_vO_2 was higher during RARC (82±5% vs. 73±6%), (*P*=0.001). MAP increased by approximately 10% (from 63±15 to 69±14 mmHg), (*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

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increase in HR (from 63±13 to 81±14 bpm in RARC patients and from 63±12 to 76±16 bpm in ORC patients).

ProANP

During ORC plasma proANP was reduced by 23% (14-32), *P* = 0.004), 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) and to fluid balance (*r*=0.561 (0.302-0.740), *P*=0.001), (Fig. 1). Thus a stable plasma proANP during surgery appeared to require fluid surplus of 2.4 l (2.0 - 2.7). By multiple regression analysis only plasma proANP was independently associated with the perioperative blood loss (Table 4).

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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 plasma space depletion. For patients going through open (ORC) and robotic assisted (RARC) radical cystectomy, plasma proANP was related to the volume load at the end of surgery and a stable value was established with a 2.4 (2.0 to 2.7) l surplus.

Plasma proANP correlated not only to the total volume balance, it also demonstrated a negative correlation to the loss of blood. Thus, with a blood loss of approximately 300 ml, there was no change in plasma proANP with a 2000 ml positive fluid balance during surgery (Fig. 1). On the other hand, 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 to RARC [10-12] as confirmed here and only ORC patients demonstrated a significant decrease in plasma proANP.

We optimized the intravascular volume before surgery according to GDT criteria [15] and aimed to maintain a maximal SV, CO, and S_vO_2 throughout surgery although the late evaluation was not protocolled. Yet, for the RARC patients, CO increased in Trendelenburg's position indicating a central blood volume deficit at that time. [21] 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 remaining cardiovascular variables supported that the ORC patients were hypovolaemic. That was the case although the fluid

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balance at the end of surgery was positive by 1.9 l for ORC patients and similar (1.5 l) for RARC patients.

Here it is considered how fluid balance is estimated. Based on a 1:5 volume ratio between the intravascular and interstitial fluid space, [2] a separate calculation may be made for colloids and crystalloids. If only 25% of the administered 2762 ml of LR remained in plasma space (690 mL) together with 5% human albumin and packed red blood cells, the fluid balance is on an average positive by 30 ml for the RARC patients and for the ORC patients the similar calculated 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 a (central) volume deficit. Fluid administration was standardized with patients receiving LR and substitution of the blood loss with packed red blood cells and eventually human albumin.[22] Thus, the 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.[23] The largest values for plasma proANP were for patients with the highest Acute Physiology and Chronic Health Evaluation (APACHE) score and for non-survivors. In order to discriminate 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 randomized to the two surgical procedures, however the history of the patients was similar. Also the study was not powered to reveal differences in outcome related to changes in plasma proANP. Yet, there were fewer postoperative complications in the RARC than in the ORC patients and maintained vs.

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reduced fluid balance as indicated by plasma proANP may be important in that regard. Other means of evaluating cardiac filling during surgery including, e.g. echocardiography may be required to generalize the present findings and the evaluation could be extended to include frequent evaluation of plasma proANP during surgery. However, values determined during surgery (T_2) were not deviating from those obtained at T_3 and therefore not detailed. We could have recorded central venous pressure, but plasma ANP relates to atrial stretch rather than to atrial pressure. [7]

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 haemorrhage and a decrease in plasma proANP while fluid balance based mainly on LR was directly related to plasma proANP with an about 2.5 l surplus volume needed to secure a stable level in patients undergoing radical cystectomy.

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Legends to Figure.

Figure 1. 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 circle) or open radical cystectomy (ORC) (black angle), *r*=-0.475 (95%CI -0.632 to -0.101), *P*=0.002 (A) and *r*=0.561 (0.302-0.740), *P*=0.001 (B). Regression lines shown with 95% confidence interval. Horizontal ditched lines indicate no change in plasma proANP.

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Table 1. Patient characteristics and intraoperative data

Variable	Overall (n=40)	*RARC (n=20)*	*ORC (n=20)*	*P*-value
Age, yrs.	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 & 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. BMI, body mass index; ASA class, American Society of Anesthesiologists

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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 (1600-7340)	*2762 (1600-6100)*	*3580 (2075-7340)*	0.033
Ringer's solution (ml)	2393 (2186-2599)	*2336 (1994-2677)*	*2450 (2186-2714)*	0.58
PRBC* (ml)	193 (52-334)	*61 (0-189)*	*325 (73-576)*	0.058
Albumin (ml)	319 (197-440)	*188 (51-323)*	*450 (254-646)*	0.027
Total Fluid loss (ml) #	1486 (200-1165)	*905 (200-2400)*	*2068 (550-5320)*	0.001
Diuresis (ml)	260 (202-319)	*321 (228-413)*	*201 (132-270)*	0.037
Blood loss (ml)‡	1230 (50-5420)	*589 (50-2100)*	*1871 (430-5420)*	0.001
Total fluid balance (ml)¤	1688 (370-4650)	*1858 (690-4650)*	*1518 (370-3060)*	0.16

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 (robotic assisted radical cystectomy) and ORC (open radical cystectomy) groups are given.

† Fluid administered during anaesthesia; * packed red blood cells; # Blood and urine lost during anaesthesia; ‡ Blood loss during anaesthesia and ¤ Fluid balance= fluid infusion – fluid lost during anaesthesia

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Table 3. Plasma proANP during open radical cystectomy (ORC) and robotic assisted cystectomy (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

T_1 = before start of surgery; T_2 = after resection of the urinary bladder; T_3 = at the end of anaesthesia. Data are mean (SD), *P*-value determined by univariate analysis. *t- test* compared differences in hormones between the RARC and ORC group. + $P<0.05$ difference from anaesthesia induction within the group; ‡ $P<0.01$ difference from anaesthesia induction within the group; and † $P<0.001$ difference from anaesthesia induction within the group (Wilcoxon Signed Ranks test).

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Table 4. Multiple Logistic Regression Analysis of Changes in plasma proANP (< vs. ≥80% of T1 value) during anaesthesia in relation to blood loss and fluid excess.

Variable	Regression coefficient (β)	Standard errors (SE)	*P*-value	Odds ratio (e^{β})	95% CI
Pro-ANP					
Blood loss >1500 ml vs < 1500 ml	-1.84	0.86	0.034	0.16	0.03-0.87
Fluid balance <2000 ml vs ≥ 2000 ml	1.69	1.21	0.163	5.43	0.50-58.59
Constant	-1.22	1.14	0.286		

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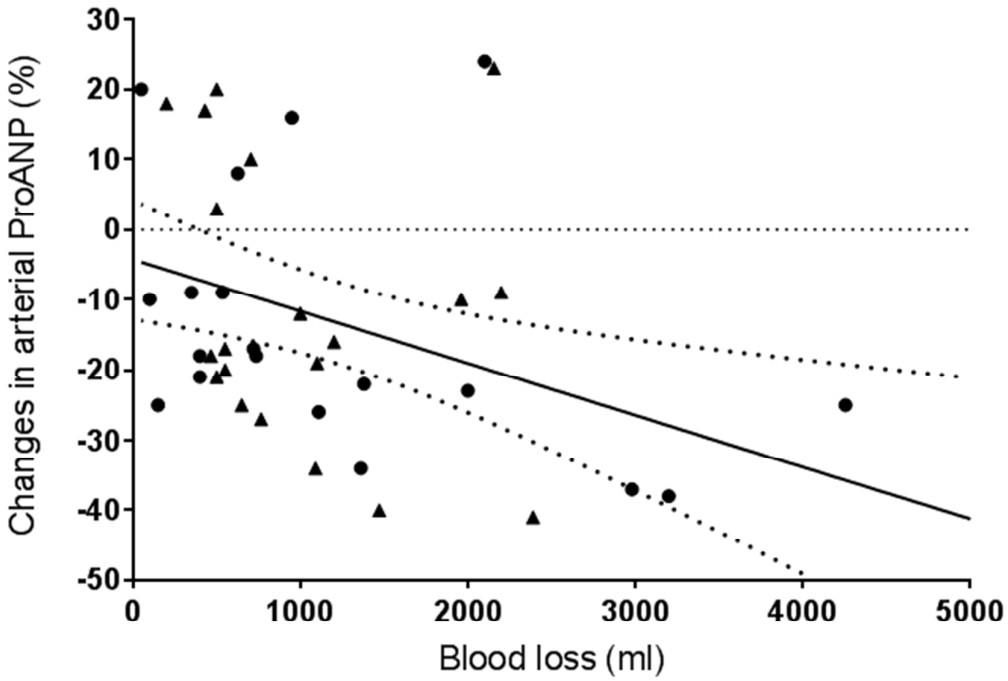
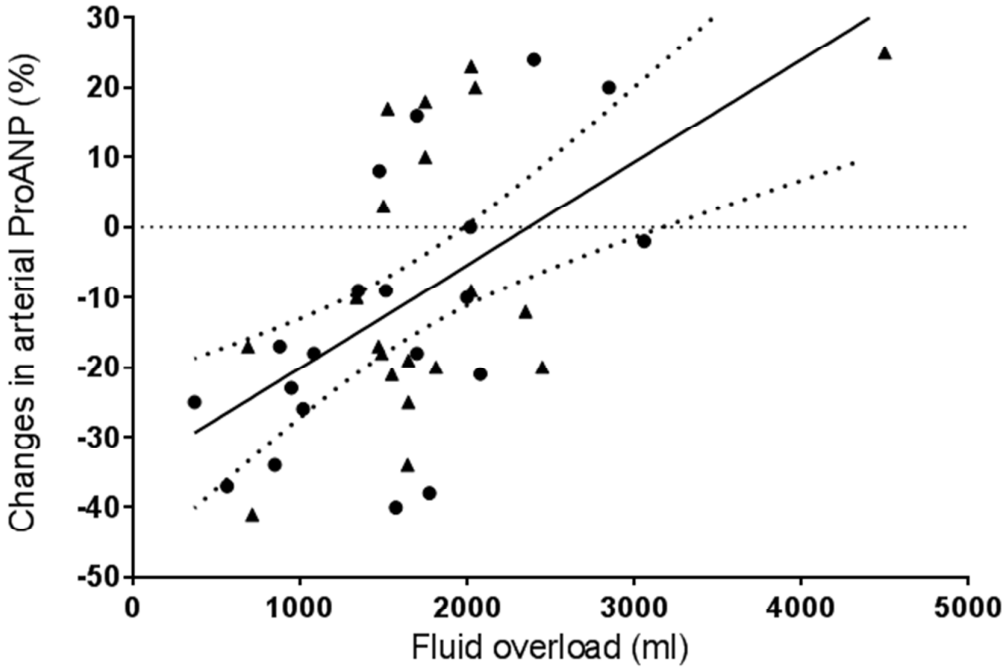
Figure 1

A



B



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STROBE Statement—checklist of items that should be included in reports of observational studies

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

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **p.3**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **p.3**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **p.5**
Objectives	3	State specific objectives, including any prespecified hypotheses **p.5**
Methods		
Study design	4	Present key elements of study design early in the paper **p.6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **p.6**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **p.6** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **-** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **p.7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **p.8**
Bias	9	Describe any efforts to address potential sources of bias **p.8**
Study size	10	Explain how the study size was arrived at **p.6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **-**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **p.8**
		(*b*) Describe any methods used to examine subgroups and interactions **-**
		(*c*) Explain how missing data were addressed **p.6**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **p.6** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of

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		sampling strategy
		(*e*) Describe any sensitivity analyses -

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **p.10**
		(b) Give reasons for non-participation at each stage **p.6**
		(c) Consider use of a flow diagram -
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **p.10 and table 1**
		(b) Indicate number of participants with missing data for each variable of interest -
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **p.10**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Table 3**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **p.10-11**
		(*b*) Report category boundaries when continuous variables were categorized **p. 10,Table 2-3**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **p.11 and table 4**
Discussion		
Key results	18	Summarise key results with reference to study objectives **p.12**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **p.13-14**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **p.14**
Generalisability	21	Discuss the generalisability (external validity) of the study results **p.13-14**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **p.2**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Keywords:	Anaesthesia in urology < ANAESTHETICS, Bladder disorders < UROLOGY, Clinical chemistry < PATHOLOGY

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

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ABSTRACT

Objectives: During surgery the volume of administered fluid is debated. Pro-atrial natriuretic peptide (proANP) is released by atrial distension and we evaluated how much lactated Ringer's solution needs to be provided for maintaining plasma proANP stable during cystectomy.

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 (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 group (P=0.001) 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% (14-32%; 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 (0.302-0.740), P = 0.001) indicating that a stable plasma proANP required a fluid surplus by 2.4 litre (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, an

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about 2.5 litre surplus volume of lactated Ringer's solution appears to maintain cardiac preload during cystectomy.

Strength 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 an about 2.5 litre surplus lactated Ringer solution needed to secure a stable level in patients undergoing major surgery.
- The study was not randomized 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.

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INTRODUCTION

During surgery the 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 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, e.g. head-up tilt [6] or sitting or standing up [5] as with pressure breathing [7] indicating that plasma ANP responds to distension of the atria independently of central venous pressure. Compared to 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 solution (LR) to support the circulation during surgery and considered the volume required to maintain plasma proANP stable during cystectomy. Both patients going through open radical cystectomy (ORC, expected blood loss >1.5 litre) and robotic assisted radical cystectomy (RARC, expected blood loss <0.5 litre) were included in the evaluation considering that eventual impeded venous return to the heart by abdominal CO_2 inflation is compensated by placing the patients in Trendelenburg's position.

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METHODS

Patients

The study included patients undergoing resection of the urine bladder due to cancer, was approved by the local Ethic Committee (H-1-2012-135), and the ORC patients were part of a randomized controlled study (RCT) registered in EudraCT (2012-005040-20). For the 20 ORC patients included consecutively between February 2013 to July 2014,[9] plasma proANP and fluid balance were determined. Furthermore, we analyzed 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 part influenced the study design, data analysis, or reporting.

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Interventions

Monitoring and fluid administration for the patients during anaesthesia has been published.[9,14] An IV line was established and a catheter placed in the left radial artery and connected to a modified Nexfin monitor (Bmeye B.V, 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 remifentanil infusion was initiated (0.5· μg kg^{-1}·min^{-1}) and when the patient reported sedation, propofol (2.0 mg/kg) was administered. Cisatracurium (0.10 to 0.15 mg/kg) facilitated oral tracheal intubation and propofol (5-10 mg· kg^{-1}· h^{1}) and remifentanil (1.75-2.25 mg/h) maintained anaesthesia. With the patient supine, administration of 200 mL LR was continued until SV increased by less than 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, CA, 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 (T_1), after resection of the bladder (T_2), and at the

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end of anaesthesia (T_3) before epidural anaesthesia was activated for ORC patients. If systolic pressure fell below 80 mmHg, 5 to 10 mg of ephedrine was administered.

Arterial blood was drawn at T_1 and T_3 i.e. before and after abdominal CO2 inflation with the patient was supine, and at T_2 few minutes after resection of the bladder when the patient was bend for ORC patients. We analyzed 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 analyzed. Simultaneously, blood was drawn from the central venous catheter for blood gas variables including haemoglobin oxygen saturation (S_vO_2; 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 a 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 chi-square tests, *t*-test and Fisher's exact test for continuous and dichotomous variables, respectively. Results are presented as

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mean (SD) or median as appropriate and the 95% confidence interval (CI) is provided. Test for differences used the non-parametric Spearman's test, χ2 test for categorical data and analysis of variance or Mann-Whitney *U*-test and Wilcoxon signed ranks 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 litre 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).

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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 criterion.

Haemorrhage, fluid administration and haemodynamics

The intraoperative lost blood was 1871 mL (CI 1267 to 2475) during ORC vs. 589 mL (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 vs. only 5% in the RARC group, *P*=0.008 (Table 1). Table 2 presents administration of IV fluids: total fluid infusion was by 3580 (2989 to 4171) vs. 2762 mL (2266 to 3258) (*P*=0.033) in the ORC and RARC group, 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 vs. 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 T_2 and T_3.

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_vO_2 was higher during RARC (82±5% vs. 73±6%; *P*=0.001). The MAP increased by approximately 10% (from 63±15 to 69±14 mmHg; *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

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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% (14-32%; *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 (0.302-0.740), *P*=0.001) (Figure 1b). Thus a stable plasma proANP during surgery appeared to require a fluid surplus of 2.4 litre (2.0 - 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, i.e. 4 patients in both the ORC and the RARC group were treated due to postoperative complications. The length of hospital stays was similar, 7 (6-92) in the ORC group vs. 7 days (5-21) in the RARC group (*P*=0.33).

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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 open (ORC) and robotic assisted (RARC) radical cystectomy, plasma proANP was related to the volume load at the end of surgery and a stable value was established with a 2.4 (2.0 to 2.7) litre 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 (Fig. 1). On the other hand, 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 to RARC [10-12] as confirmed here and only ORC patients demonstrated a significant decrease in plasma proANP.

We optimized 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 protocolled. 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 litre for ORC patients and similar (1.5 litre) for RARC patients.

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It should be considered how fluid balance is estimated. There may be a 1:5 volume ratio between the intravascular and interstitial fluid space [2] 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 an 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 standardized with patients receiving LR and substitution of the blood loss with packed red blood cells and eventually human albumin.[23] Thus, the 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 (APACHE) score and for non-survivors. In order to discriminate 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 randomized 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, e.g. echocardiography or a determination of blood volume may be required to

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generalize the present findings and the evaluation could be extended to include frequent evaluation of plasma proANP during surgery. However, values determined during surgery (T_2) were not deviating from those obtained at T_3 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 an about 2.5 litre 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.

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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 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.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Legends to Figure.

Figure 1. 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 (0.302-0.740), *P*=0.001 (B). Regression lines shown with 95% confidence interval. Horizontal ditched lines indicate no change in plasma proANP.

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Table 1. Patient characteristics and intraoperative data

Variable	Overall (n=40)	*RARC (n=20)*	*ORC (n=20)*	*P*-value
Age, yrs.	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 & 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. BMI, body mass index; ASA class, American Society of Anesthesiologists

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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 (2780-3563)	*2762 (2266-3258)*	*3580 (2988-4171)*	0.033
Ringer's solution (mL)	2393 (2186-2599)	*2336 (1994-2677)*	*2450 (2186-2714)*	0.58
PRBC* (mL)	193 (52-334)	*61 (0-189)*	*325 (73-576)*	0.058
Albumin (mL)	319 (197-440)	*188 (51-323)*	*450 (254-646)*	0.027
Total Fluid loss (mL) #	1486 (1126-1847)	*905 (665-1145)*	*2068 (1470-2667)*	0.001
Diuresis (mL)	260 (202-319)	*321 (228-413)*	*201 (132-270)*	0.037
Blood loss (mL)‡	1230 (861-1599)	*589 (378-801)*	*1871 (1267-2475)*	0.001
Total fluid balance (mL)¤	1688 (1444-1933)	*1858 (1461-2255)*	*1518 (1215-1821)*	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 (robotic assisted radical cystectomy) and ORC (open radical cystectomy) groups are given.

† Fluid administered during anaesthesia; * packed red blood cells; # Blood and urine lost during anaesthesia; ‡ Blood loss during anaesthesia and ¤ Fluid balance= fluid infusion – fluid lost during anaesthesia

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Table 3. Plasma proANP during open radical cystectomy (ORC) and robotic assisted cystectomy (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

T_1 = before start of surgery; T_2 = after resection of the urinary bladder; T_3 = at the end of anaesthesia. Data are mean (SD), *P*-value determined by univariate analysis. * *t- test* compared differences in hormones between the RARC and ORC group. ‡ *P*<0.01 difference from anaesthesia induction within the group; and † *P*<0.001 difference from anaesthesia induction within the group (Wilcoxon Signed Ranks test).

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Table 4. Multiple Logistic Regression Analysis of Changes in plasma proANP (< vs. ≥80% of T1 value) during anaesthesia in relation to blood loss and fluid excess.

Variable	Regression coefficient (β)	Standard errors (SE)	*P*-value	Odds ratio (e^{β})	95% CI
Pro-ANP					
Blood loss >1500 mL vs. < 1500 mL	-1.84	0.86	0.034	0.16	0.03-0.87
Fluid balance <2000 mL vs. ≥ 2000 mL	1.69	1.21	0.163	5.43	0.50-58.59
Constant	-1.22	1.14	0.286		

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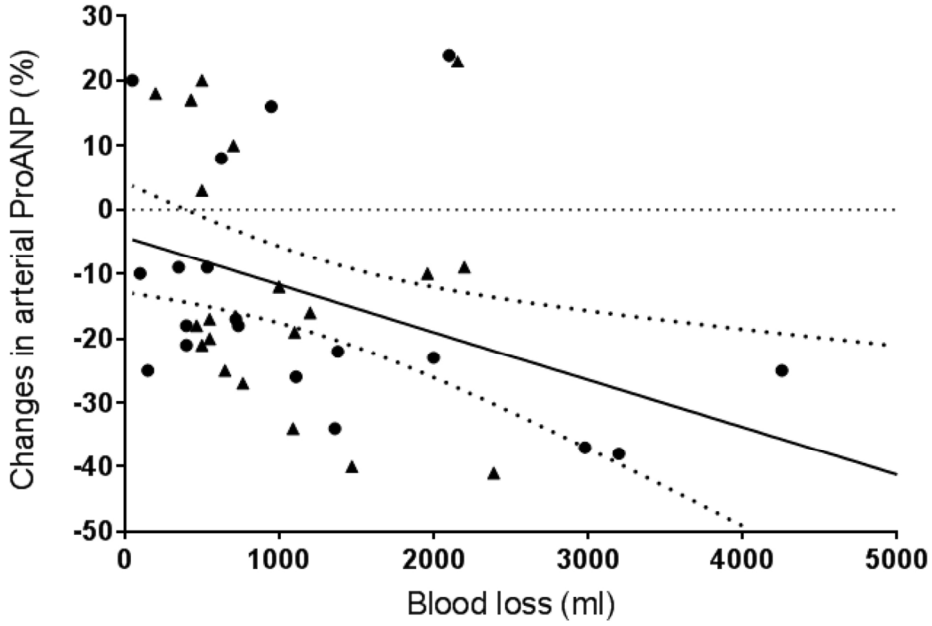

ProANP in relation to intraoperative blood loss and fluid balance.
Change in plasma proANP from start (T1) to end of anaesthesia (T3) in patients during robotic assisted (RARC) (black angle) or open radical cystectomy (ORC) (black circle), r=-0.475 (95%CI -0.632 to -0.101), P=0.002 (Figure 1A) and r=0.561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

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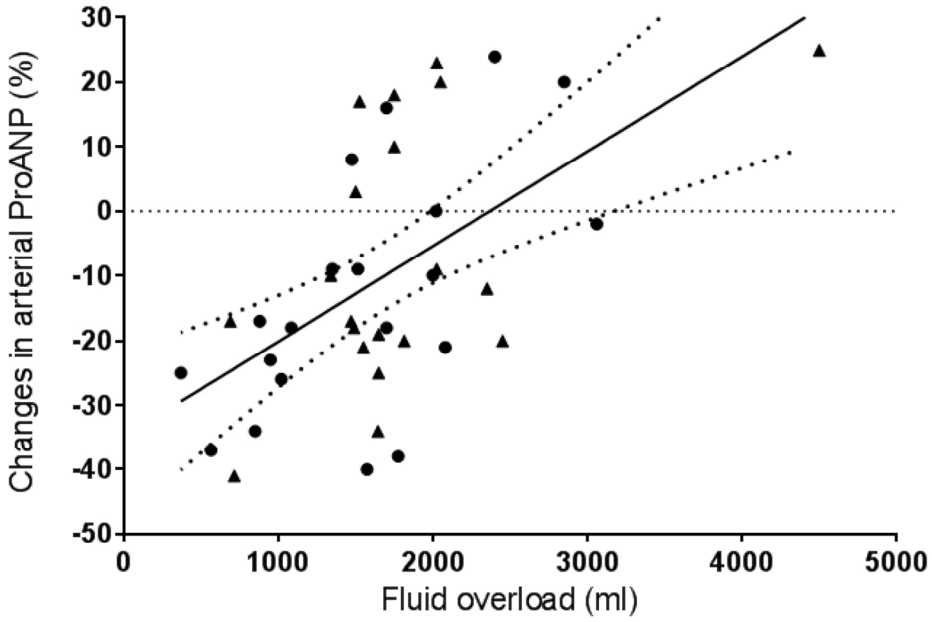

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STROBE Statement—checklist of items that should be included in reports of observational studies

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

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **p.3**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **p.3**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **p.5**
Objectives	3	State specific objectives, including any prespecified hypotheses **p.5**
Methods		
Study design	4	Present key elements of study design early in the paper **p.6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **p.6**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **p.6** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **-** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **p.7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **p.8**
Bias	9	Describe any efforts to address potential sources of bias **p.8**
Study size	10	Explain how the study size was arrived at **p.6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **-**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **p.8**
		(*b*) Describe any methods used to examine subgroups and interactions **-**
		(*c*) Explain how missing data were addressed **p.6**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **p.6** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of

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		sampling strategy
		(*e*) Describe any sensitivity analyses -

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **p.10**
		(b) Give reasons for non-participation at each stage **p.6**
		(c) Consider use of a flow diagram -
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **p.10 and table 1**
		(b) Indicate number of participants with missing data for each variable of interest -
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **p.10**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Table 3**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **p.10-11**
		(*b*) Report category boundaries when continuous variables were categorized **p. 10,Table 2-3**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **p.11 and table 4**
Discussion		
Key results	18	Summarise key results with reference to study objectives **p.12**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **p.13-14**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **p.14**
Generalisability	21	Discuss the generalisability (external validity) of the study results **p.13-14**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **p.2**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Urology
Keywords:	Anaesthesia in urology < ANAESTHETICS, Bladder disorders < UROLOGY, Clinical chemistry < PATHOLOGY

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02 February 2016

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

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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 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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ABSTRACT

Objectives: During surgery the volume of administered fluid is debated. Pro-atrial natriuretic peptide (proANP) is released by atrial distension and we evaluated how much lactated Ringer's solution needs to be provided for maintaining plasma proANP stable during cystectomy.

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 (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 group (p=0.001) 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 to32%, 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 to0.740), p = 0.001) indicating that a stable plasma proANP required a fluid surplus by 2.4 litre (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, an

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about 2.5 litre surplus volume of lactated Ringer's solution appears to maintain cardiac preload during cystectomy.

Strength 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 an about 2.5 litre surplus lactated Ringer solution needed to secure a stable level in patients undergoing major surgery.
- The study was not randomized 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.

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INTRODUCTION

During surgery the 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 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, e.g. head-up tilt [6] or sitting or standing up [5] as with pressure breathing [7] indicating that plasma ANP responds to distension of the atria independently of central venous pressure. Compared to 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 solution (LR) to support the circulation during surgery and considered the volume of RL required to maintain plasma proANP stable during cystectomy. Both patients going through open radical cystectomy (ORC, expected blood loss >1.5 litre) and robotic assisted radical cystectomy (RARC, expected blood loss <0.5 litre) were included in the evaluation considering that eventual impeded venous return to the heart by abdominal CO_2 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 hypothesized that when a blood loss is replaced by LR, it would require a positive volume balance to maintain plasma proANP.

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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 randomized controlled study (RCT) registered in EudraCT (2012-005040-20). For the 20 ORC patients included consecutively between February 2013 to July 2014,[9] plasma proANP and fluid balance were determined. Furthermore, we analyzed 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.

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Interventions

Monitoring and fluid administration for the patients during anaesthesia has been published.[9,14] An IV line was established and a catheter placed in the left radial artery and connected to a modified Nexfin monitor (Bmeye B.V, 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 remifentanil infusion was initiated (0.5· μg kg^{-1}·min^{-1}) and when the patient reported sedation, propofol (2.0 mg/kg) was administered. Cisatracurium (0.10 to 0.15 mg/kg) facilitated oral tracheal intubation and propofol (5 to10 mg· kg^{-1}· h^{1}) and remifentanil (1.75 to2.25 mg/h) maintained anaesthesia. With the patient supine, administration of 200 mL LR was continued until SV increased by less than 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, CA, 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 (T_1), after resection of the bladder (T_2), and at the

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end of anaesthesia (T_3) before epidural anaesthesia was activated for ORC patients. If systolic pressure fell below 80 mmHg, 5 to 10 mg of ephedrine was administered.

Arterial blood was drawn at T_1 and T_3 i.e. before and after abdominal CO2 inflation with the patient was supine, and at T_2 few minutes after resection of the bladder when the patient in the ORC group was bend. We analyzed 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 analyzed. Simultaneously, blood was drawn from the central venous catheter for blood gas variables including haemoglobin oxygen saturation (S_vO_2, 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 a 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 chi-square tests, *t*-test and Fisher's exact test for continuous and dichotomous variables, respectively. Results are presented as

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mean (SD) or median as appropriate and the 95% confidence interval (CI) is provided. Test for differences used the non-parametric Spearman's test, χ2 test for categorical data and analysis of variance or Mann-Whitney *U*-test and Wilcoxon signed ranks 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 litre 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).

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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 (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 vs. only 5% in the RARC group, p=0.008 (table 1). Table 2 presents administration of IV fluids: total fluid infusion was by 3580 (2989 to 4171) vs. 2762 mL (2266 to 3258) (p=0.033) in the ORC and RARC group, 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 vs. 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 T_2 and T_3.

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_vO_2 was higher during RARC (82±5% vs. 73±6%, p=0.001). The MAP increased by approximately 10% (from 63±15 to 69±14 mmHg, 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

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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 to32%, 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 litre (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, i.e. 4 patients in both the ORC and the RARC group were treated due to postoperative complications. The length of hospital stays was similar, 7 (6 to 92) in the ORC group vs. 7 days (5 to 21) in the RARC group (p=0.33).

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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 open (ORC) and robotic assisted (RARC) radical cystectomy, plasma proANP was related to the volume load at the end of surgery and a stable value was established with a 2.4 (2.0 to 2.7) litre 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 other hand, 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 to RARC [10-12] as confirmed here and only ORC patients demonstrated a significant decrease in plasma proANP.

We optimized 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 protocolled. 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

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balance at the end of surgery was positive by 1.9 litre for ORC patients and similar (1.5 litre) for RARC patients.

It should be considered how fluid balance is estimated. There may be a 1:5 volume ratio between the intravascular and interstitial fluid space [2] 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 an 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 standardized with patients receiving LR and substitution of the blood loss with packed red blood cells and eventually human albumin.[23] Thus, the 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 (APACHE) score and for non-survivors. In order to discriminate 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 randomized 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

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between the surgical methods. Other means of evaluating cardiac filling during surgery including, e.g. echocardiography or a determination of blood volume may be required to generalize the present findings and the evaluation could be extended to include frequent evaluation of plasma proANP during surgery. However, values determined during surgery (T_2) were not deviating from those obtained at T_3 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 an about 2.5 litre 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.

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Legends to Figure.

Figure 1. 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 to0.740), p=0.001 (B). Regression lines shown with 95% confidence interval. Horizontal broken lines indicate no change in plasma proANP.

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Table 1. Patient characteristics and intraoperative data

Variable	Overall (n=40)	*RARC (n=20)*	*ORC (n=20)*	*p*-value
Age, yrs.	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 & 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. BMI, body mass index; ASA class, American Society of Anesthesiologists

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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 (2780-3563)	*2762 (2266-3258)*	*3580 (2988-4171)*	0.033
Ringer's solution (mL)	2393 (2186-2599)	*2336 (1994-2677)*	*2450 (2186-2714)*	0.58
PRBC* (mL)	193 (52-334)	*61 (0-189)*	*325 (73-576)*	0.058
Albumin (mL)	319 (197-440)	*188 (51-323)*	*450 (254-646)*	0.027
Total Fluid loss (mL) #	1486 (1126-1847)	*905 (665-1145)*	*2068 (1470-2667)*	0.001
Diuresis (mL)	260 (202-319)	*321 (228-413)*	*201 (132-270)*	0.037
Blood loss (mL)‡	1230 (861-1599)	*589 (378-801)*	*1871 (1267-2475)*	0.001
Total fluid balance (mL)¤	1688 (1444-1933)	*1858 (1461-2255)*	*1518 (1215-1821)*	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 (robotic assisted radical cystectomy) and ORC (open radical cystectomy) groups are given.

† Fluid administered during anaesthesia; * Packed red blood cells; # Blood and urine lost during anaesthesia; ‡ Blood loss during anaesthesia and ¤ Fluid balance= fluid infusion – fluid lost during anaesthesia

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Table 3. Plasma proANP during open radical cystectomy (ORC) and robotic assisted cystectomy (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

T_1 = before start of surgery; T_2 = after resection of the urinary bladder; T_3 = at the end of anaesthesia. Data are mean (SD), p-value determined by univariate analysis. * *t- test* compared differences in hormones between the RARC and ORC group. ‡ $p<0.01$ difference from anaesthesia induction within the group; and † $p<0.001$ difference from anaesthesia induction within the group (Wilcoxon Signed Ranks test).

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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)	Standard errors (SE)	p-value	Odds ratio (e^{β})	95% CI
Pro-ANP					
Blood loss >1500 mL vs. < 1500 mL	-1.84	0.86	0.034	0.16	0.03-0.87
Fluid balance <2000 mL vs. ≥ 2000 mL	1.69	1.21	0.163	5.43	0.50-58.59
Constant	-1.22	1.14	0.286		

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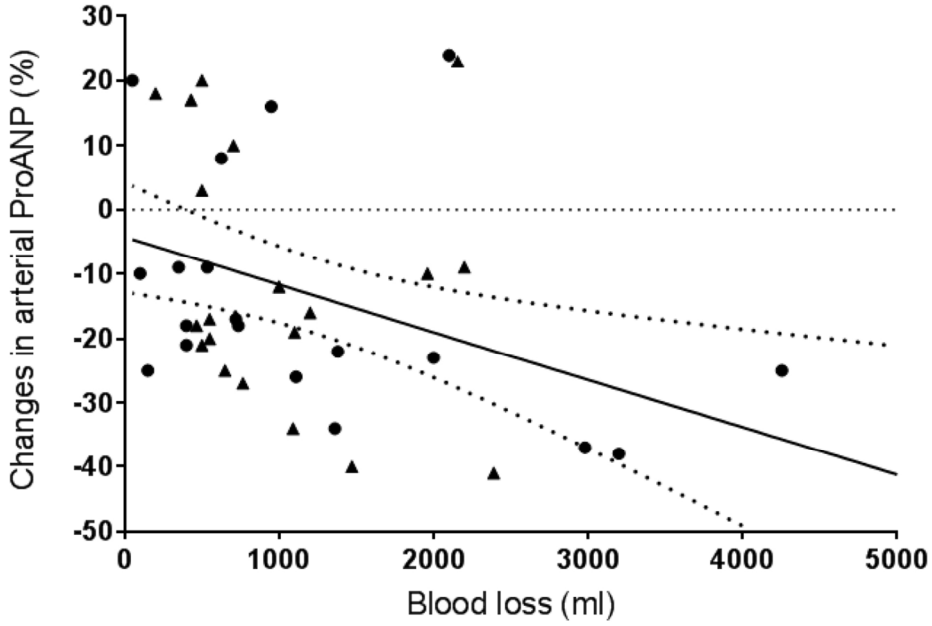

ProANP in relation to intraoperative blood loss and fluid balance.
Change in plasma proANP from start (T1) to end of anaesthesia (T3) in patients during robotic assisted (RARC) (black angle) or open radical cystectomy (ORC) (black circle), r=-0.475 (95%CI -0.632 to -0.101), P=0.002 (Figure 1A) and r=0.561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

173x117mm (300 x 300 DPI)

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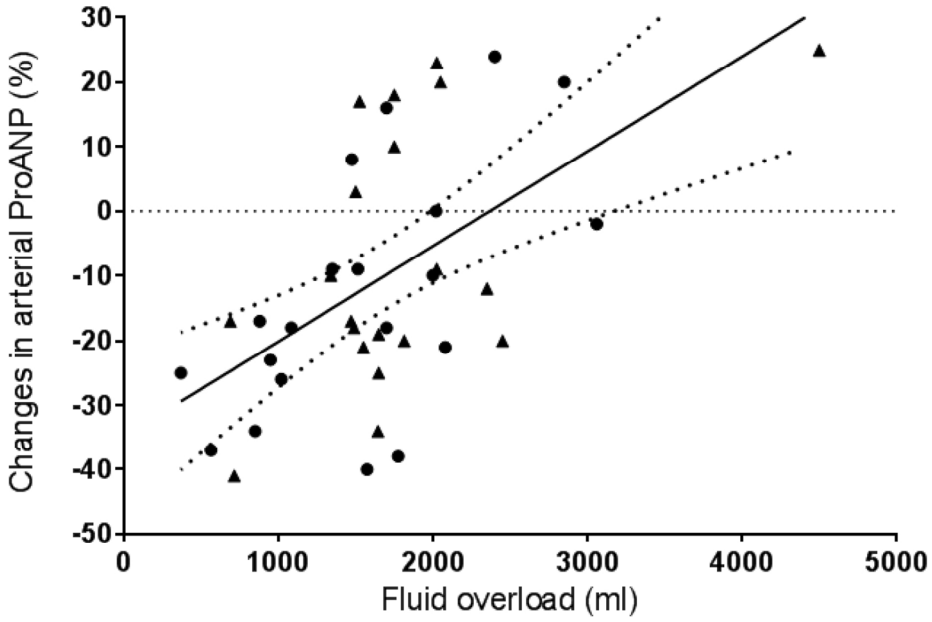

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STROBE Statement—checklist of items that should be included in reports of observational studies

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

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **p.3**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **p.3**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **p.5**
Objectives	3	State specific objectives, including any prespecified hypotheses **p.5**
Methods		
Study design	4	Present key elements of study design early in the paper **p.6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **p.6**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **p.6** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **-** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **p.7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **p.8**
Bias	9	Describe any efforts to address potential sources of bias **p.8**
Study size	10	Explain how the study size was arrived at **p.6**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **-**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **p.8**
		(*b*) Describe any methods used to examine subgroups and interactions **-**
		(*c*) Explain how missing data were addressed **p.6**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **p.6** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of

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		sampling strategy
		(*e*) Describe any sensitivity analyses -

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **p.10**
		(b) Give reasons for non-participation at each stage **p.6**
		(c) Consider use of a flow diagram -
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **p.10 and table 1**
		(b) Indicate number of participants with missing data for each variable of interest -
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **p.10**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Table 3**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **p.10-11**
		(*b*) Report category boundaries when continuous variables were categorized **p. 10,Table 2-3**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **p.11 and table 4**
Discussion		
Key results	18	Summarise key results with reference to study objectives **p.12**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **p.13-14**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **p.14**
Generalisability	21	Discuss the generalisability (external validity) of the study results **p.13-14**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **p.2**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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