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PII: S0022-5347(15)00003-8
DOI: [10.1016/j.juro.2014.12.094](https://doi.org/10.1016/j.juro.2014.12.094)
Reference: JURO 12101

To appear in: *The Journal of Urology*
Accepted Date: 31 December 2014

Please cite this article as: Wuethrich PY, Burkhard FC, Thalmann GN, Stueber F, Studer UE, The impact of pelvic venous pressure on blood loss during open radical cystectomy and urinary diversion: Results from a secondary analysis of a randomized clinical trial, *The Journal of Urology*® (2015), doi: 10.1016/j.juro.2014.12.094.

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The impact of pelvic venous pressure on blood loss during open radical cystectomy and urinary diversion: Results from a secondary analysis of a randomized clinical trial.

P.Y. Wuethrich^{*}, F.C. Burkhard, G.N. Thalmann, F. Stueber, U.E. Studer

Department of Urology (FCB, GNT and UES), and Department of Anesthesiology and Pain Medicine (PYW and FS) University Hospital Bern, Bern, Switzerland

Corresponding Address:

Patrick Wuethrich, M.D.

Department of Anaesthesiology and Pain Medicine, University Hospital Bern, CH-3010 Berne, Switzerland

Phone +41316322725 Fax +416320554 patrick.wuethrich@insel.ch

Words count: abstract 250, text 2475

Running head: pelvic venous pressure and blood loss during cystectomy

Keywords: radical cystectomy, blood loss, fluid management, norepinephrine, pelvic venous pressure

Abstracts

Purpose: Blood loss and blood substitution are associated with higher morbidity after major abdominal surgery. During major liver resection, low local venous pressure, has been shown to reduce blood loss. Ambiguity persists concerning the impact of local venous pressure on blood loss during open radical cystectomy. We aimed to determine the association between intraoperative blood loss and pelvic venous pressure (PVP) and determine factors affecting PVP.

Material and Methods: In the frame of a single-center, double-blind, randomized trial, PVP was measured in 82 patients from a norepinephrine/low-volume group and in 81 from a control group with liberal hydration. For this secondary analysis, patients from each arm were stratified into subgroups with PVP <5 mmHg or \geq 5 mmHg measured after cystectomy (optimal cut-off value for discrimination of patients with relevant blood loss according to the Youden's index).

Results: Median blood loss was 800 ml [range: 300-1600] in 55/163 patients (34%) with PVP <5 mmHg and 1200 ml [400-3000] in 108/163 patients (66%) with PVP \geq 5 mmHg; ($P<0.0001$). A PVP <5 mmHg was measured in 42/82 patients (51%) in the norepinephrine/low-volume group and 13/81 (16%) in the control group ($P<0.0001$). PVP dropped significantly after removal of abdominal packing and abdominal lifting in both groups at all time points (at begin and end of pelvic lymph node dissection, end of cystectomy) ($P<0.0001$). No correlation between PVP and central venous pressure could be detected.

Conclusions: Blood loss was significantly reduced in patients with low PVP. Factors affecting PVP were fluid management and abdominal packing.

Introduction:

During open radical cystectomy (RC) combined with pelvic lymph node dissection (PLND) and urinary diversion (UD), bleeding from the local pelvic venous plexus and capillaries surrounding the bladder and prostate may be substantial despite meticulous surgery. Strategies to reduce blood loss need to be developed aiming to reduce the incidence of blood transfusion and improve postoperative outcome. In the frame of a prospective randomized trial, we recently showed that an intraoperative preemptive norepinephrine administration combined with a restrictive deferred hydration significantly reduces postoperative complications, blood loss and the need for blood transfusion^{1,2}. Whether this is due to a decreased local venous pressure or other factors (vasoconstriction or minimal change in the concentration of coagulation factors) is not known. Local venous pressure in the surgical field may influence blood loss. Low (<5 mmHg) central venous pressure (CVP) is considered a simple and potent method to minimize intraoperative blood loss during liver resection surgery³⁻⁵.

Therefore, we investigated whether blood loss also correlates with pelvic venous pressure (PVP), a surrogate for the local venous pressure around the bladder and prostate, during open RC combined with PLND and UD under two different intraoperative fluid management strategies: a preemptive norepinephrine infusion combined with a restrictive deferred hydration or a more liberal hydration without norepinephrine. In addition, the impact of abdominal packing on PVP was analysed.

Methods

Trial design and participants

This randomized double-blind single-centre study was approved by the local ethics committee (KEK Bern) and registered at Clinicaltrials.gov (NCT01276665). Patients with an ASA score of II to III were included. Exclusion criteria were coagulopathies, significant hepatic and renal dysfunction (Kidney Disease Outcomes Quality Initiative stage ≥ 3), congestive heart failure and contraindication for thoracic epidural analgesia. All patients provided written informed consent. Between November 2009 and September 2012, 167 consecutive patients scheduled for PLND, open RC and UD. Patients were prospectively randomized into two groups: a preemptive administration of norepinephrine combined with a restrictive deferred crystalloid fluid regimen (norepinephrine/low-volume group) or a more liberal i.v. hydration (control group).

For this analysis, only patients with available data on intraoperative PVP measurements were evaluated (Figure 1).

Initial randomization and blinding:

The protocol and design of the original study has been described previously ¹. Briefly, patients were randomly allocated to the norepinephrine/low-volume group or to the control group by using a computer generated permuted block randomization with 1:1 allocation.

Surgeons, patients and data assessors were blinded to the assigned fluid regimens. Crystalloids bags and perfusions pumps were hidden behind a sterile curtain during

surgery. Assessors of the postoperative data had no access to the anesthesiologic patients' data.

Patient management

Standard monitoring included continuous ECG, heart rate, core temperature, S_pO_2 , invasive mean arterial pressure (MAP) and CVP. Before induction of anesthesia, an epidural catheter was placed at the T9/T10 level and activated with bupivacaine 0.25% at a rate of 8 ml/h until the end of the PLND. Anesthesia was induced with propofol, fentanyl, rocuronium and maintained with isoflurane. Ventilation with an inspired oxygen fraction of 60% was mechanically controlled to maintain normocapnia. Normothermia was maintained with an air warming system and fluid warmer.

In the norepinephrine/low-volume group, a preemptive norepinephrine infusion was started at 2 $\mu\text{g}/\text{kg}/\text{h}$ after the induction of anesthesia and 1 ml/kg/h of a balanced crystalloid solution (Ringerfundin®, B. Braun Medical AG, Sempach, Switzerland) was administrated until the bladder had been removed, followed by 3 ml/kg/h of crystalloid until the end of surgery while maintaining the norepinephrine infusion. In case of hypotension (i.e. MAP <60 mmHg), the norepinephrine infusion was titrated accordingly after an initial bolus of 10 μg . In the control group, a bolus of 6 ml/kg of crystalloid was administrated during induction of anesthesia, followed by 6 ml/kg/h of balanced crystalloid solution intraoperatively. In this group, episodes of hypotension were treated with boluses of 250 ml of crystalloid solution. In all patients, blood units were only transfused when the hemoglobin was <8.0 gr/dl ⁶.

Patients were in 30° head-down position during the whole duration of surgery. The surgical technique was standardized ^{7,8}. At least one of 3 senior urologists (FCB, GNT, UES) was present during surgery.

Data collection and outcome measures

Blood loss was assessed **by the anaesthesiologists** based on the amount of blood in the suction device and the blood volume absorbed in the surgical gauzes (**weighed**). Blood loss was assessed separately during the PLND, open RC and UD periods ². The number of patients who received blood unit transfusions during surgery was documented.

During surgery, heart rate, invasive MAP, and CVP were continuously registered and their mean values calculated. Assessment of the pelvic venous pressure (PVP) was done 4 times invasively with a 20G needle placed in the external iliac vein adjacent to the iliac bifurcation. The pressure transducers were calibrated and zeroed separately and levelled to the external iliac vein. PVP measurements were recorded after preparation of the iliac bifurcation (i.e. begin of the PLND), at the end of the pelvic lymph node dissection, after removal of the bladder (i.e. end of the cystectomy part), and finally before closure of the abdominal wall (i.e. end of the UD part). At these defined time points (except before closure of the abdominal wall), PVP was measured first with the gauzes placed in the abdominal cavity (in order to remove the bowel from the surgical field, i.e. abdominal packing) and a second time after removal of the gauzes with the abdominal wall lifted, in order to analyze the impact of the gauzes/packing on venous return. Mean PVP was also calculated.

Patients were analyzed in subgroups according to whether their PVP at the end of the cystectomy part was associated with a clinically relevant blood loss, (i.e. need for blood unit transfusion).

Statistical analysis

Data were analyzed using non-parametric statistical models. Data are expressed as median values with ranges or numbers (%). Categorical data were compared with the chi square test. Relative risks (RR) and 95% CI were also calculated when appropriate. Continuous data were compared using the two-tailed Mann-Whitney *U* test and Kruskal-Wallis H test followed by the Bonferroni correction for multiple comparisons. Within each group, the within patient's PVP values with and without gauzes were analyzed using the Wilcoxon signed rank tests. Spearman correlation tests were used to test the correlation between blood loss and MAP, CVP and PVP at the different time points. Test results were considered significant if $P < 0.05$. Receiver operating characteristic (ROC) curves were constructed to identify the optimal cut-off values for association between blood loss and the need for blood unit transfusion (defined as clinically relevant blood loss) and then between mean PVP and clinically relevant blood loss. The optimal cut-off was defined as the value associated with the highest sum of sensitivity and specificity (Youden's index). Multiple logistic regression analyses using a forward selection procedure were applied to identify independent risk factors for relevant blood loss and reported as adjusted odds ratios (ORs) with 95% CIs. Factors were included if their P values were smaller than 0.10. Confounders considered were mean MAP, CVP and PVP. No interaction terms were included due to the sample size. The fit and predictive power of the model was assessed using the Hosmer–Lemeshow goodness-of-fit test and ROC-area under the curve (ROC-AUC).

Results

PVP was assessed in 82 in the norepinephrine/low-volume group and 81 patients in the control group (Figure 1). Baseline data were equally distributed between the subgroups within the groups (Table 1).

The ROC-AUC for mean PVP was 0.753 (95% CI 0.659-0.847) according to the occurrence of blood loss requiring blood unit transfusions. The optimal cut-off value for mean PVP was 5.1 mmHg (84% sensitivity and 64% specificity) for discrimination of patients with a relevant blood loss. According to multiple logistic regression analysis, PVP (<5 vs \geq 5 mmHg) was the only independent predictor for clinically relevant blood loss (OR 0.373 [95% CI 0.165-0.842]; $P=0.018$). MAP (OR 1.054 [95% CI 0.984-1.130]; $P=0.130$) and CVP (OR 1.094 [95% CI 0.974-1.230]; $P=0.115$) did not significantly correlate. The model accorded well with the Hosmer–Lemeshow test ($P=0.801$) and the ROC-AUC was 0.701.

Independent of the groups, median blood loss was 800 ml [range: 300, 1600] in 55/163 patients (34%) who had a PVP <5 mmHg and 1200 ml [400, 2800] in 108/163 patients (66%) with a PVP \geq 5 mmHg; ($P<0.0001$). Independent of the groups, PVP were found to be significantly correlated with blood loss at the end of PLND at $r^2=0.234$ ([95% CI: 0.096-0.397], $P=0.004$). At the end of the cystectomy part, CVP and PVP significantly correlated with blood loss during this period at $r^2=0.241$ ([95% CI: 0.085-0.384], $P=0.006$) and $r^2=0.344$ ([95% CI: 0.155-0.469], $P<0.0001$), respectively. At the end of the UD period, PVP significantly correlated with blood loss during this period at $r^2=0.190$ ([95% CI: 0.022-0.371], $P=0.022$) (Figure 2). CVP and PVP were not significantly correlated, with the exception of a weak correlation which was observed at the end of cystectomy $r^2=0.134$ ([95% CI: 0.019-0.259], $P=0.025$).

In the norepinephrine/low-volume group, PVP significantly correlated with blood loss at the end of the cystectomy part and at the end of the UD part at $r^2=0.244$ ([95% CI: 0.021-0.461], $P=0.032$) and $r^2=0.269$ ([95% CI: 0.024-0.495], $P=0.019$), respectively. In the control group, no significant correlation could be detected between PVP values and blood loss during the different time periods.

PVP was significantly lower in the norepinephrine/low-volume group during all periods assessed compared to the control group (Table 2). A PVP <5 mmHg at the end of the cystectomy part was present in 42/82 patients (51%) in the norepinephrine/low-volume group and in 13/81 patients (16%) in the control group [RR: 0.58 (95% CI: 0.46-0.74), $P<0.0001$]. A PVP <5 mmHg at the end of the cystectomy part was associated with significantly less intraoperative blood loss in both groups: Median total blood loss for the subgroup PVP with a <5 mmHg in the norepinephrine/low-volume group was 800 ml [300, 1200] vs 900 ml [500, 1800] in the subgroup with a PVP ≥ 5 mmHg; $P=0.004$. In the control group, the subgroup PVP <5 mmHg had a median blood loss of 1000 ml [600, 1600] compared to 1300 ml [400, 3000] in the subgroup with a PVP ≥ 5 mmHg; $P=0.006$ (Figure 3).

PVP dropped significantly ($P<0.0001$) after removal of the gauzes from the abdominal cavity and lifting of the abdominal wall in both groups at any measurement time point (Table 2).

There was a significant difference in the rate of blood unit transfusion given between the patients with a PVP <5 mmHg and patients with a PVP ≥ 5 mmHg (5/55 patients (9%) vs 28/108 patients (26%); RR: 0.72, 95% CI: 0.10 to 0.79, $P=0.013$), but no difference between the subgroups within each randomized group (norepinephrine/low-volume group: subgroup PVP <5 mmHg 3/42 patients (7%) vs 4/40 patients (10%) in the subgroup PVP ≥ 5 mmHg; $P=0.709$ and control group:

subgroup PVP <5 mmHg 2/13 patients (15%) vs 24/68 patients (35%) patients in the subgroup PVP \geq 5 mmHg; $P=0.206$).

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Discussion

Total intraoperative blood loss was significantly lower in patients with a low PVP (<5 mmHg) compared to patients with a PVP \geq 5 mmHg. A significantly larger number of patients with a preemptive infusion of norepinephrine combined with a restrictive deferred hydration had a PVP <5 mmHg. Even in this group, increased PVP was associated with an increased blood loss. This suggests that fluid management can influence PVP and consequently impact blood loss.

Blood loss during open RC with UD has an impact on postoperative outcome and increases postoperative morbidity⁹⁻¹². Blood unit transfusion following excessive blood loss carries the risk of transfusion associated lung injury, postoperative transfusion associated fluid overload, increased wound infection rates and has been postulated to promote cancer recurrence¹³⁻¹⁵. Consequently, intraoperative strategies aiming to reduce blood loss may have vital consequences.

Little is known about the impact of the venous pressure in the surgical site on blood loss. Substantial literature could already demonstrate that a significant reduction in blood loss can be achieved by maintaining a CVP lower than 5 mmHg in patients undergoing liver dissection and thus making control of vascular injury easier^{3,4}. In this study we could demonstrate that preemptive use of norepinephrine with a restrictive deferred fluid management lead to a significant reduction in PVP and blood loss when compared with a more liberal fluid regimen.

The question remains whether the decreased blood loss is attributable to the reduced intravenous fluid administration and the vasoconstriction induced by norepinephrine resulting in a lower PVP. The correlation between blood loss and PVP independent of the amount of fluid administered emphasizes that PVP significantly impacts blood

loss. Even within the control group, in which patients received a more generous fluid administration, a PVP <5 mmHg at the end of cystectomy was associated with a significant decrease in blood loss.

An additional important observation was that lifting of the abdominal wall significantly reduced PVP. This suggests that avoiding abdominal packing, for example by using a table-fixed self-retaining retractor to lift up the abdominal wall, may help reduce intraoperative PVP. The potential hemodynamic impact of an abdominal wall-lifting retractor compared to conventional abdominal packing in patients undergoing open abdominal surgery is less well studied than in laparoscopic surgery. In laparoscopic surgery an abdominal wall lifting device has a positive effect on blood loss and CVP both in animal models and in patients undergoing cholecystectomy. An abdominal wall lifting device resulted in an increased cardiac index compared to **carbon dioxide** insufflation without affecting systemic vascular resistance in healthy patients undergoing laparoscopic cholecystectomy and showed less side effects such as postoperative nausea and vomiting and right shoulder pain^{16,17}. For these reasons this approach has been recommended for high-risk patients¹⁷⁻²⁰.

Another important observation was the lack of correlation between PVP and CVP, with the exception of a weak correlation at the end of the cystectomy part. Thus, standard CVP assessment may not be a reliable surrogate for PVP, a factor which has to be taken into account.

In some of our patients negative PVPs were measured which could potentially be a risk for air emboli. However, a Trendelenburg's position of 30 degrees and packing of the pelvis with wet gauzes after removing the bladder should limit the risk of air emboli. In addition, no fall in end-tidal carbon dioxide could be detected, thus making clinically relevant air emboli unlikely.

Limitations: The main limitation is the lack of a specific power analysis concerning the reduction in blood loss as this study is a secondary analysis. In addition, PVP measurements were only done punctually and not continuously. However, continuous monitoring of PVP would imply catheterization of the veins resulting in a higher risk of thrombosis.

Conclusion:

Our results suggest that low PVP during PLND, RC and UD significantly reduces intraoperative blood loss. Techniques to decrease PVP, such as the use of a norepinephrine/low-volume regimen and avoidance of compression of the vena cava, **(e.g. by intraabdominal packing)**, should be established for open RC and UD.

Conflict of interest

None declared.

Funding

Else Kröner Fresenius Foundation (2010_A80), Bad Homburg, Germany, institutional research funds of the Department of Anesthesiology and Pain Medicine and of the Department of Urology, University Hospital Bern, Bern, Switzerland. The funding sources had no role in the design and conduct of the study, the collection, management, analysis and interpretation of the data; or in the preparation, review or approval of the manuscript.

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Figure legends:

Figure 1: Modified Consort flow-chart:

Figure 2: Correlation between pelvic venous pressure (mmHg) and blood loss (ml) during the different time periods including fit lines with 95% confidence intervals; sphere size depends on the number of patients (scale).

Figure 3: Total blood loss according to randomization group and stratified according to pelvic venous pressure (PVP); in white norepinephrine/low-volume group and in grey the control group:

Table 1: Baseline characteristics according to the randomization group and stratified according to pelvic venous pressure (PVP) into subgroups “PVP <5mmHg and PVP ≥5mmHg”. Data are presented with median values and ranges:

	Norepinephrine/low-volume Group (n=82)				Control Group (n=81)			
	PVP < 5mmHg		PVP ≥ 5mmHg		PVP < 5mmHg		PVP ≥ 5mmHg	
Number of patients	n=42	51%	n=40	49%	n=13	16%	n=68	84%
Age (yr)	71	[38-86]	67	[40-88]	67	[42-88]	70	[47-88]
Gender								
Male (n)	28	67%	27	68%	10	77%	48	71%
Female (n)	14	33%	13	32%	3	23%	20	29%
BMI (kg.m ⁻²)	23.5	[18-31]	24	[19-42]	25	[21-28]	24	[20-39]
ASA								
II	23	55%	28	70%	7	54%	39	57%
III	19	45%	12	30%	6	46%	29	43%
Biomarkers:								
Brain natriuretic peptide (pg.ml ⁻¹)	39.5	[5-350]	22	[5-146]	38	[5-68]	29	[5-341]
Haemoglobin (g.dl ⁻¹)	13	[9.4-15.6]	13	[8.4-15.9]	13.4	[10-16.2]	12.6	[7.3-16.7]
Thrombocytes (G.l ⁻¹)	244	[127-386]	258	[122-576]	250	[173-513]	255	[111-770]
Prothrombin time (%)	99	[51-100]	100	[66-100]	100	[95-100]	100	[51-100]
C reactive proteine (mg.l ⁻¹)	4	[3-95]	3	[3-197]	3	[3-72]	3	[3-73]
Albumin (g.l ⁻¹)	35	[27-48]	34.5	[19-45]	33	[22-39]	34	[21-49]
Glasgow prognostic score								
0	19	45%	17	43%	3	23%	25	37%
1	13	31%	15	38%	7	54%	31	46%
2	10	24%	8	19%	3	23%	12	17%
Preoperative use of aspirin								
Yes	15	36%	6	15%	1	8%	14	21%
No	27	64%	34	85%	12	92%	54	79%
Duration of surgery (min)	393	[240-560]	378	[300-540]	390	[210-585]	390	[240-585]
Type of urinary diversion								
Ileal conduit	19	45%	13	33%	6	46%	32	47%
Orthotopic ileal bladder substitute	23	55%	27	67%	7	54%	35	53%
pT stage								
pT1-2	23	55%	30	75%	6	46%	42	62%
pT3-4	19	45%	10	25%	7	54%	26	38%
Neoadjuvant therapy								
Yes	3	71%	8	20%	1	8%	12	18%
No	39	29%	32	80%	12	92%	56	82%

Table 2: Pelvic venous pressure (PVP) in mmHg according to the randomization groups; data are presented with median values and ranges.* $P < 0.0001$ for within-group P value derived from the Wilcoxon signed rank test for within-patient or without and with abdominal lifting at the endpoint starting the PLND, end of the PLND and end of the cystectomy part, with Bonferroni adjustment.

	Overall (n=183)	Norepinephrine / Low-Volume Group (n=82)	Control Group (n=81)	P -value
Starting PLND	7 [0-16]	5 [0-13]*	8 [0-16]*	< 0.0001
with abdominal wall lifting		2 [0-12]	3 [0-12]	0.007
P -value within		< 0.0001	< 0.0001	
End of PLND	6 [0-15]	4 [0-12]*	8 [0-15]*	< 0.0001
with abdominal wall lifting		2 [-1-4]	3 [-2-9]	< 0.0001
P -value within		< 0.0001	< 0.0001	
End of cystectomy part	6 [-1-14]	4 [-1-12]*	7 [0-14]*	< 0.0001
with abdominal wall lifting		1 [-2-6]	3 [0-8]	< 0.0001
P -value within		< 0.0001	< 0.0001	
After urinary diversion	5 [-1-13]	2 [-1-8]	6 [0-13]	< 0.0001

Table 3: Blood loss, hemodynamic data and intraoperative blood unit transfusion rate according to the subgroups. Data are presented with median values and ranges or number and %. *P*-values: * $P < 0.0001$ norepinephrine/low-volume group with PVP < 5mmHg vs control group with PVP \geq 5 mmHg; # $P < 0.05$ norepinephrine/low-volume group with PVP < 5 mmHg vs control group with PVP < 5mmHg; ° $P < 0.0001$ norepinephrine/low-volume group with PVP \geq 5 mmHg vs control group with PVP \geq 5 mmHg; ± $P < 0.0001$ norepinephrine/low-volume group with PVP \geq 5 mmHg vs control group with PVP < 5 mmHg.

	Norepinephrine/low-volume Group (n=82)		Control Group (n=81)		<i>P</i> -value
	PVP < 5mmHg n=42	PVP \geq 5mmHg n=40	PVP < 5mmHg n=13	PVP \geq 5mmHg n=68	
blood loss total (ml)	800 [300-1200]*#	900 [500-1800]°	1000 [600-1600]	1300 [400-2800]	<0.0001
blood loss per min (ml/min)	1.8 [0.7-2.9]*#	2.0° [1.2-3.5]°	2.7 [1.5-3.7]	3.2 [2.9-3.5]	0.005
blood loss PLND (ml)	100 [0-400] *	145 [0-300]°	150 [50-300]	200 [50-2000]	<0.0001
blood loss cystectomy (ml)	480 [200-850] *#	550 [300-1200]°	650 [500-1200]	900 [300-2300]	<0.0001
blood loss urinary diversion (ml)	100 [0-410]	200 [0-500]	150 [50-500]	200 [0-700]	0.049
heart rate PLND (1.min ⁻¹)	66 [50-94]	66 [45-92]	60 [52-85]	65 [45-90]	0.167
heart rate cystectomy (1.min ⁻¹)	70 [47-102]	67 [43-100]	65 [44-78]	63 [40-90]	0.123
heart rate urinary diversion (1.min ⁻¹)	74 [50-107]	77 [41-100]	75 [55-90]	70 [40-98]	0.210
MAP PLND (mmHg)	70 [60-85]	70 [60-93]	70 [60-84]	68 [60-90]	0.577
MAP cystectomy (mmHg)	70 [60-85]	71 [60-93]	73 [60-81]	70 [60-100]	0.438
MAP urinary diversion (mmHg)	72 [62-94]	72 [60-100]	70 [60-85]	70 [60-92]	0.684
CVP baseline (mmHg)	12 [7-20]	13 [6-21]	14 [5-20]	13 [5-21]	0.132
CVP PLND (mmHg)	12 [7-19]	13 [5-21]	15 [10-20]	15 [5-23]	<0.0001
CVP cystectomy (mmHg)	11 [4-23]	12 [2-23]	16 [10-20]	15 [2-25]	<0.0001
CVP urinary diversion (mmHg)	9 [3-22]	11 [4-19]	15 [9-20]	14 [3-29]	<0.0001
crystalloid (ml)	1500 [700-2500]*#	1800 [800-4000]±	3800 [3000-6100]	4450 [2800-6200]	<0.0001

Figure 1:

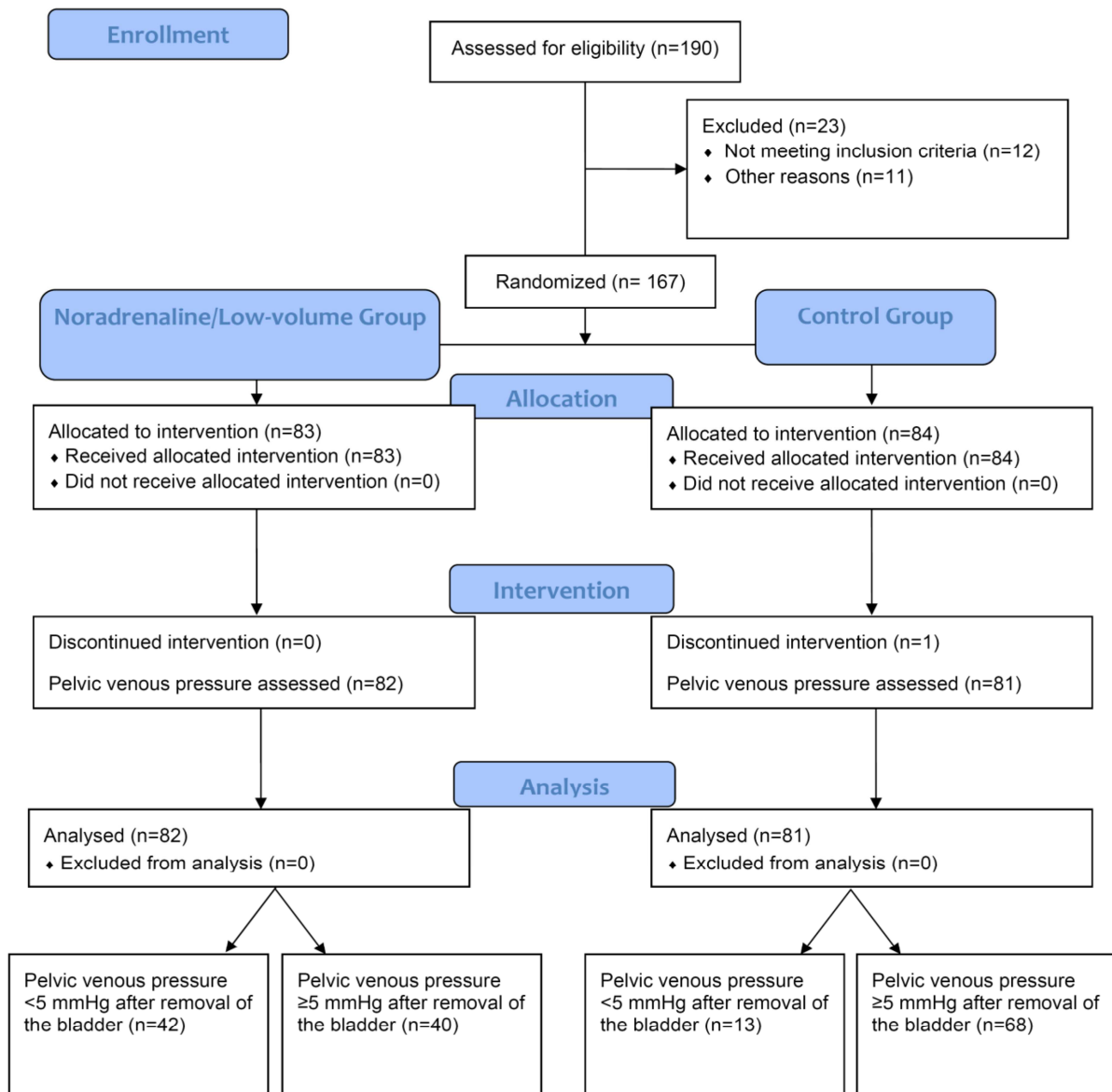


Figure 2:

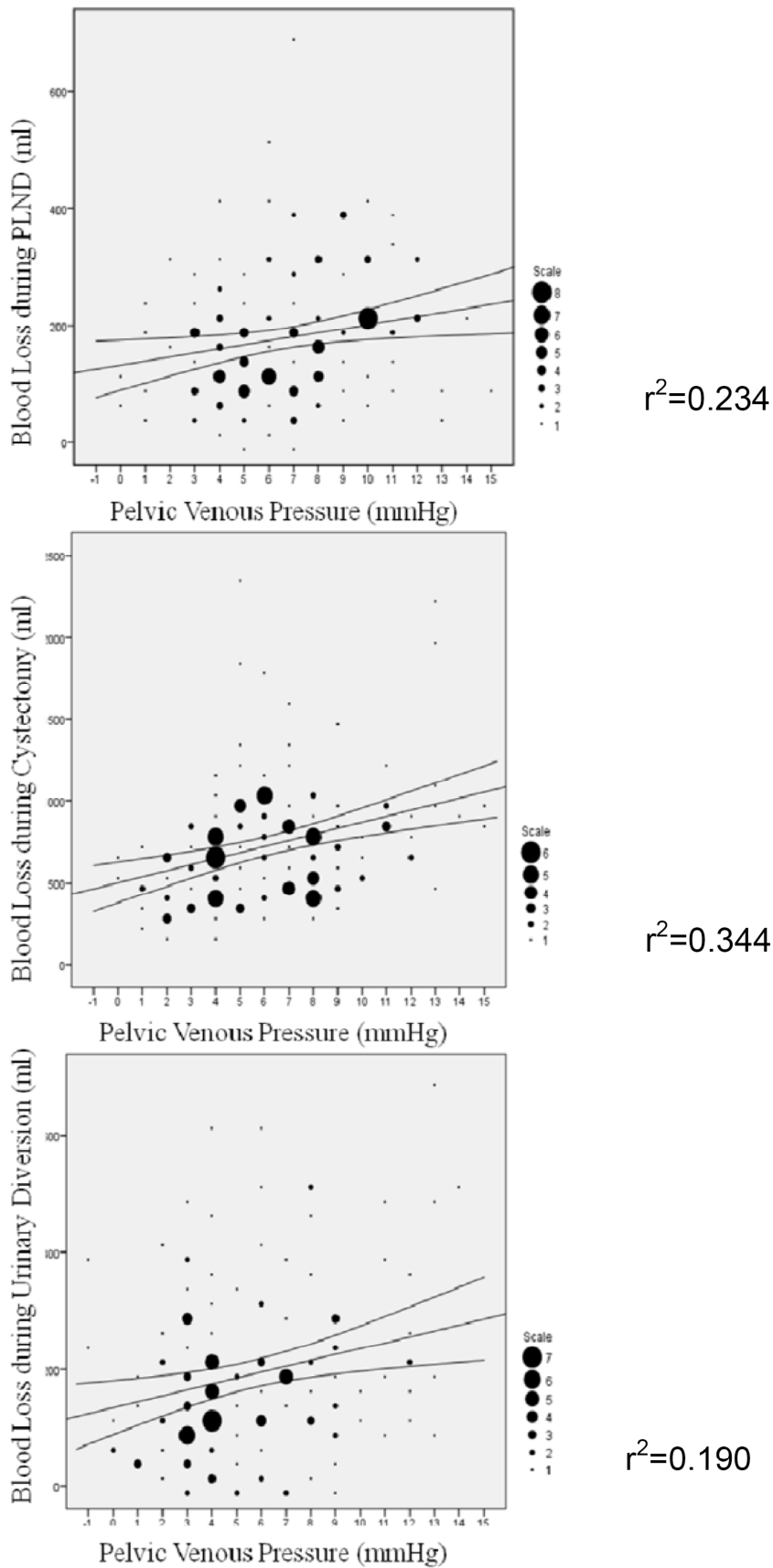
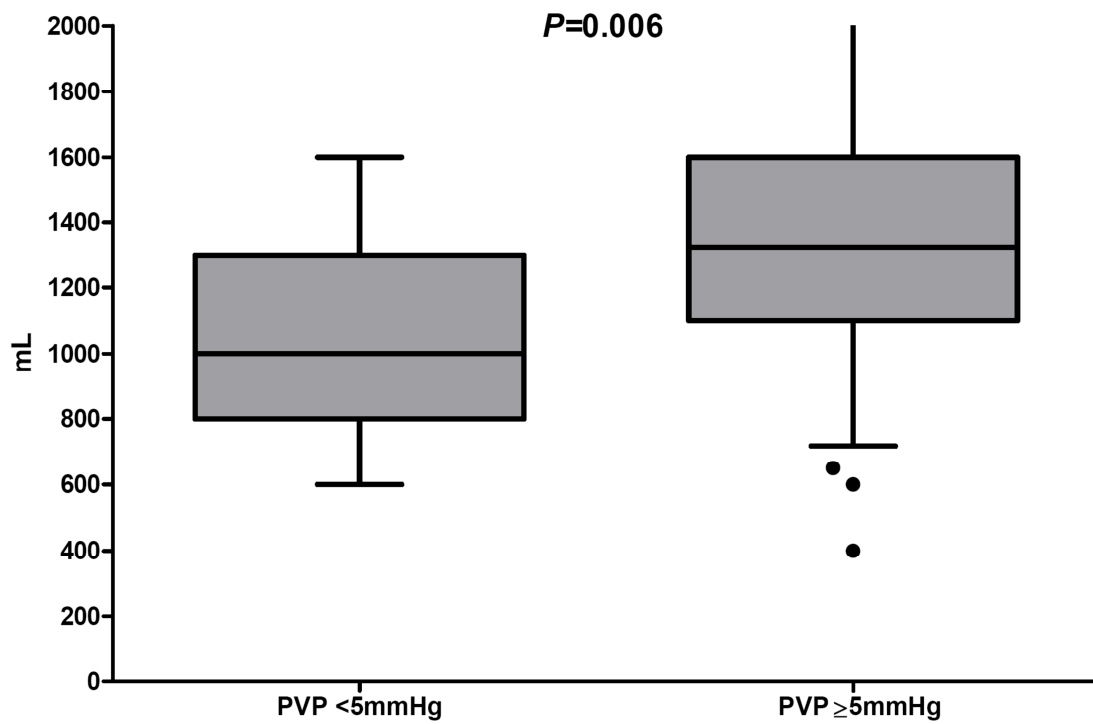
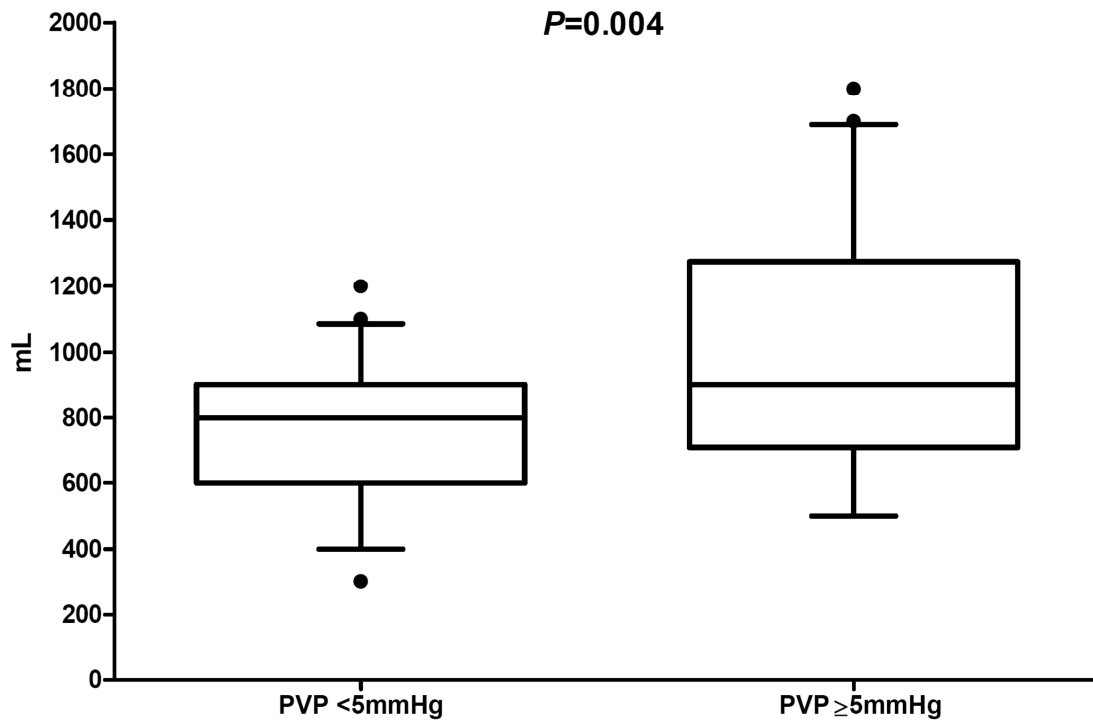


Figure 3:



Abbreviations and Acronyms:

PLND = pelvic lymph node dissection

RC = radical cystectomy

UD = urinary diversion

CVP = central venous pressure

PVP = pelvic venous pressure

MAP = mean arterial pressure

RR = relative risk

CI = confidence intervals

OR = odds ratios

ROC-AUC = receiver operating characteristic-area under the curve