Does Goal-directed Fluid Therapy Affect Postoperative Orthostatic Intolerance?

A Randomized Trial

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ABSTRACT

Background: Early mobilization is important for postoperative recovery but is limited by orthostatic intolerance (OI) with a prevalence of 50% 6 h after major surgery. The pathophysiology of postoperative OI is assumed to include hypovolemia besides dysregulation of vasomotor tone. Stroke volume–guided fluid therapy, so-called goal-directed therapy (GDT), corrects functional hypovolemia, and the authors hypothesized that GDT reduces the prevalence of OI after major surgery and assessed this in a prospective, double-blinded trial.

Methods: Forty-two patients scheduled for open radical prostatectomy were randomized into standard fluid therapy (control group) or GDT groups. Both groups received a fixed-volume crystalloid regimen supplemented with 1:1 replacement of blood loss with colloid, and in addition, the GDT group received colloid to obtain a maximal stroke volume (esophageal Doppler). The primary outcome was the prevalence of OI assessed with a standardized mobilization protocol before and 6 h after surgery. Hemodynamic and hormonal orthostatic responses were evaluated.

Results: Twelve (57%) *versus* 15 (71%) patients in the control and GDT groups ($P = 0.33$), respectively, demonstrated OI after surgery, group difference 14% (CI, −18 to 45%). Patients in the GDT group received more colloid during surgery (1,758 *vs.* 1,057 ml; $P = 0.001$) and reached a higher stroke volume (102 *vs.* 89 ml; $P = 0.04$). OI patients had an increased length of hospital stay (3 *vs.* 2 days; $P = 0.02$) and impaired hemodynamic and norepinephrine responses on mobilization.

Conclusion: GDT did not reduce the prevalence of OI, and patients with OI demonstrated impaired cardiovascular and hormonal responses to mobilization.

What We Already Know about This Topic

- Orthostatic intolerance is a frequent complication that impairs early mobilization after major surgery
- Whether perioperative fluid management using goal-directed therapy decreases orthostatic intolerance after surgery is unknown

What This Article Tells Us That Is New

- This prospective, double-blinded, randomized clinical trial demonstrated that patients with orthostatic intolerance had an increased length of hospital stay after open prostatectomy, but goal-directed therapy did not reduce the prevalence of orthostatic intolerance after surgery

IMMOBILIZATION after surgery is associated with an increased risk of complications including venous thromboembolism, muscle wasting, pneumonia, atelectasis, and reduction in blood volume, thereby impeding convalescence.[1,2] Early mobilization is, therefore, important for enhanced postoperative recovery and integrated in the so-called "fast-track" concept that reduces morbidity and postoperative length of hospital stay (LOS).[3] Early postoperative mobilization may, however, be complicated by orthostatic intolerance (OI) with symptoms including nausea and vomiting, dizziness, blurred vision, feeling of heat, and the patients may even develop a syncope.[4] Thus, OI has a prevalence of approximately 40% 6 h after hip arthroplasty

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and approximately 50% after open radical prostatectomy,[5,6] whereas OI is infrequent after minor surgery.[7] After major surgery, OI has been associated with impaired cardiac output (CO) and peripheral resistance,[5,6] but to what extent such manifestations are related to postoperative hypovolemia or autonomic dysfunction is not known.[8] Hypovolemia is suspected to contribute to postoperative OI, and intraoperative maximization of stroke volume (SV) with fluid, referred to as individualized goal-directed therapy (GDT), is suggested to correct functional hypovolemia and enhance blood flow and oxygen delivery to vital organs and thereby preventing postoperative complications.[9,10] Accordingly, GDT improves postoperative outcome and reduces LOS.[9–12] However, whether GDT affects OI after surgery remains to be established.

We assessed the effect of GDT on OI after open radical prostatectomy and hypothesized that GDT reduces the prevalence of OI. As a secondary measure, we evaluated autonomic control of blood pressure regulation after surgery by determining cardiovascular and relevant hormonal orthostatic responses, and we hypothesized that these responses were affected in OI patients.

Materials and Methods

This prospective, double-blinded, placebo-controlled trial was approved by the local Regional Ethics Committee, Copenhagen, Denmark (H-D-2008–051), and by the Danish Data Protection Agency. The trial was registered on ClinicalTrials.gov under the U.S. National Library of Medicine (NCT00771966). Patients were randomized in a 1:1 ratio for parallel arms to a (1) standard care group or (2) a GDT group using computer-generated allocation (www.randomization.com). A total of 44 sealed and opaque envelopes were prepared for the trial by staff who had no other involvement in the trial. All included patients provided written informed consent. The study was conducted at the Copenhagen University Hospital, Rigshospitalet, Denmark.

Patients scheduled for open radical prostatectomy were screened for inclusion (fig. 1). Inclusion required an age of greater than 18 and less than 90 yr, and exclusion criteria were the American Society of Anesthesiologists physical status class greater than III, need for sedative premedication, psychiatric disease, alcohol abuse (>35 units/week), kidney disease, coagulation impairment, daily opioid consumption, history of orthostatic hypotension/OI, use of β-blockers, need for intraoperative infusion of vasopressor or inotropic agents other than ephedrine, and contraindication to esophageal Doppler use.

Orthostatic Challenge

Guided by ultrasound, the patients were provided with a central venous catheter through the right internal jugular vein, and its position was confirmed by chest radiograph. A mobilization procedure was carried out in the afternoon on the day before surgery and 6 h after the operation, defined as the time from tracheal extubation. The mobilization procedure included supine rest (5 min), 30° leg elevation (3 min), followed by rest (5 min) before mobilization to sitting on the hospital bed with the feet on the floor (3 min), and in an upright position while the patient was encouraged to stand on the toes and move body weight from one leg to the other to activate the muscle pump (3 min).[5–7] Blood pressure, referred to heart level, was measured with a cuff on the middle part of the third finger (Finometer®; FMS, Finapres Medical Systems BV, Amsterdam, The Netherlands). With a nonlinear three-component model of the arterial impedance (Modelflow®, Finapres Medical Systems BV, Amsterdam, The Netherlands), continuous SV, CO, and total peripheral resistance (TPR) were calculated.[13] In addition, muscle and frontal lobe oxygenation (S_MO_2 and S_{CO_2}, respectively) were assessed at 10-s intervals by near-infrared spectroscopy (NIRS; INVOS®, cerebral oximeter; Somanetics, Troy, OH) with optodes placed above the biceps muscle and high and lateral on the forehead. NIRS has been validated as a measure of tissue oxygenation in both surgical and nonsurgical settings.[14] After surgery, the patients graded pain on a 0- to 10-point verbal rating scale during the mobilization procedure. The mobilization procedure was discontinued if the patient experienced OI or developed a considerable decrease (>30 mmHg) in systolic arterial pressure (SAP). Blood samples for hormonal analysis were obtained from the central venous access when the patient was at supine and at the end of the standing period, or immediately in the case where the mobilization procedure had to be discontinued due to OI. Blood samples were collected in tubes with EDTA and aprotinin, stored on ice, and centrifuged within 20 min at 4°C. Plasma was stored at −80°C until analysis for angiotensin II, atrial natriuretic peptide, epinephrine, norepinephrine, and vasopressin concentrations.[15]

Orthostatic Classification

The orthostatic challenge was terminated if OI appeared, defined as intolerable dizziness, nausea and vomiting, feeling of heat, or blurred vision.[4] Accordingly, patients with OI in the sitting position did not proceed to standing. To prevent the development of syncope, the procedure was also terminated in the case where SAP decreased more than 30 mmHg. Patients were classified as having orthostatic hypotension if SAP decreased 20 mmHg or more and/or diastolic arterial pressure (DAP) decreased 10 mmHg or more.[16]

Anesthesia, Surgery, and Pain Management

Before admission to the operating room, the patients were assigned to the control or the GDT group. For both groups of patients, anesthesia was induced with propofol 2.0–2.5 mg/kg and fentanyl 0.25 mg and maintained with propofol 5–10 $mg \cdot kg^{-1} \cdot h^{-1}$ and remifentanil 1.75–2.25 mg/h *via* the central venous access. Orotracheal intubation was facilitated with

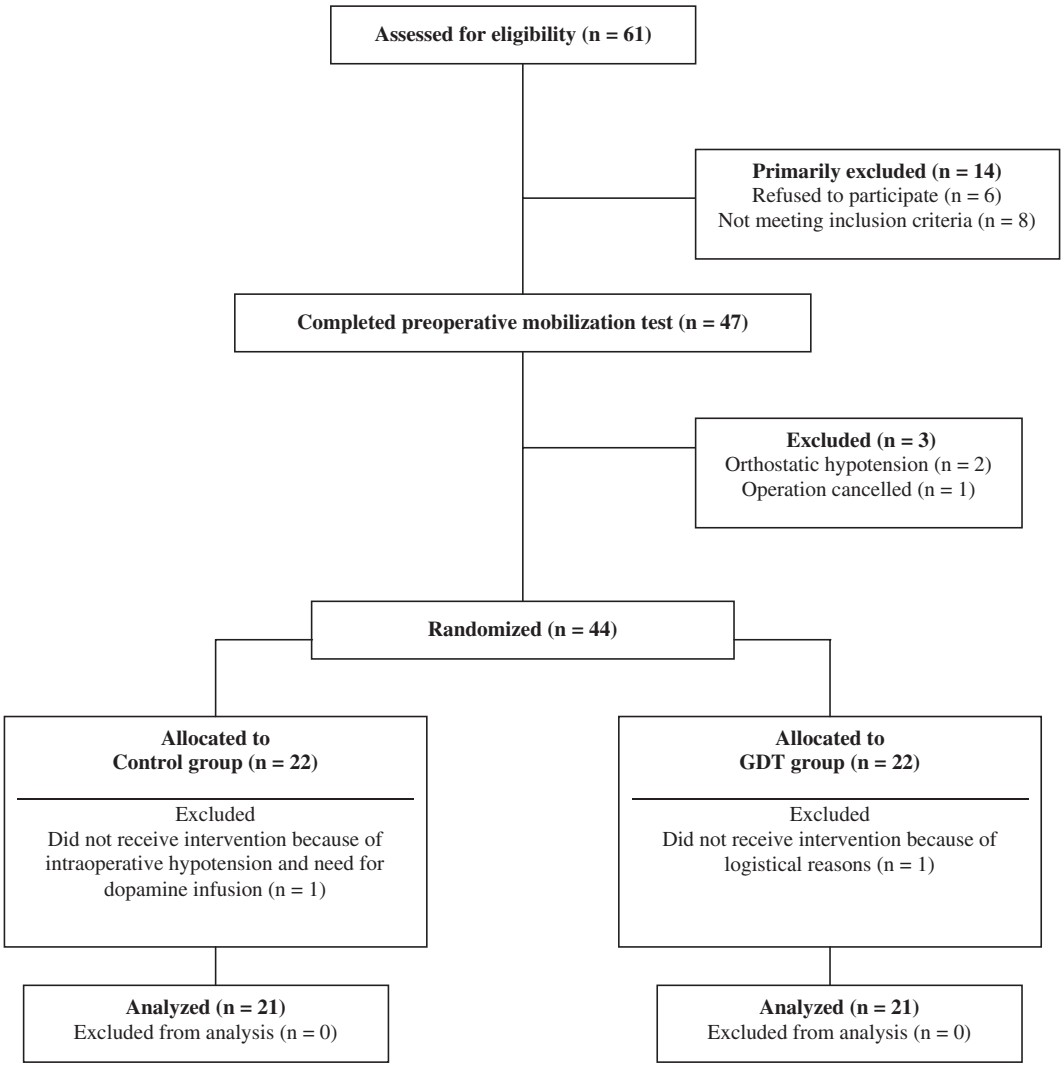

Fig. 1. Flow diagram. GDT = goal-directed therapy.

cisatracurium (0.1 mg/kg) except in one patient for whom it was considered to require rapid-sequence induction because of gastroesophageal reflux and thus succinylcholine (1 mg/kg) was used. *Via* nasal access an esophageal Doppler probe (Deltex Medical, Chichester, United Kingdom) was placed in the mid esophagus guided by visual and auditory signals from the descending aorta. A CardioQ monitor (Deltex Medical) was used to measure flow velocity to calculate SV from a nomogram based on the subject's height, weight, and age.[17] In addition, a corrected flow time was estimated, representing the time of the systole corrected to a heart rate (HR) of 60 beats/min.[17] Baseline values included the noninvasively determined pressure and esophageal Doppler obtained SV, HR, CO, and corrected flow time, each averaged over 10 cardiac cycles.[18] In the GDT group, a fluid optimization algorithm was used to maximize SV by warmed IV colloid (hydroxyethyl starch [HES] 130/0.4; Voluven; Fresenius Kabi AB, Uppsala, Sweden) boluses (3 ml/kg) until SV did not increase 10% or more (fig. 2). Esophageal Doppler measurements were repeated every 15 min after skin incision, and for the GDT group, colloid 3 ml/kg was administered if SV decreased more than 10%. Both groups of patients received a fixed-volume crystalloid regimen supplemented with 1:1 replacement of blood loss with artificial colloid (HES 130/0.4) to a maximum of 50 ml/kg.[6] Blood transfusion was administered if hemoglobin decreased to less than 7 g/dl and in that case no further artificial colloid was administered. If blood was transfused, thrombelastography assessed the need for transfusion of platelets and plasma according to the local guidelines.[19] Blood samples were taken from the central venous line to measure hemoglobin concentration and central venous oxygenation (ABL-700; Radiometer Medical, Copenhagen, Denmark) hourly or more frequently in case of bleeding. Tracheal extubation was carried out when the patient gained consciousness and was able to breathe adequately.

Oxycodone 0.1 mg/kg was administered 30 min before the end of surgery and 40 ml bupivacaine (2.5 mg/ml) was infiltrated at the incision site at the end of surgery. In both groups of patients, pain management consisted of

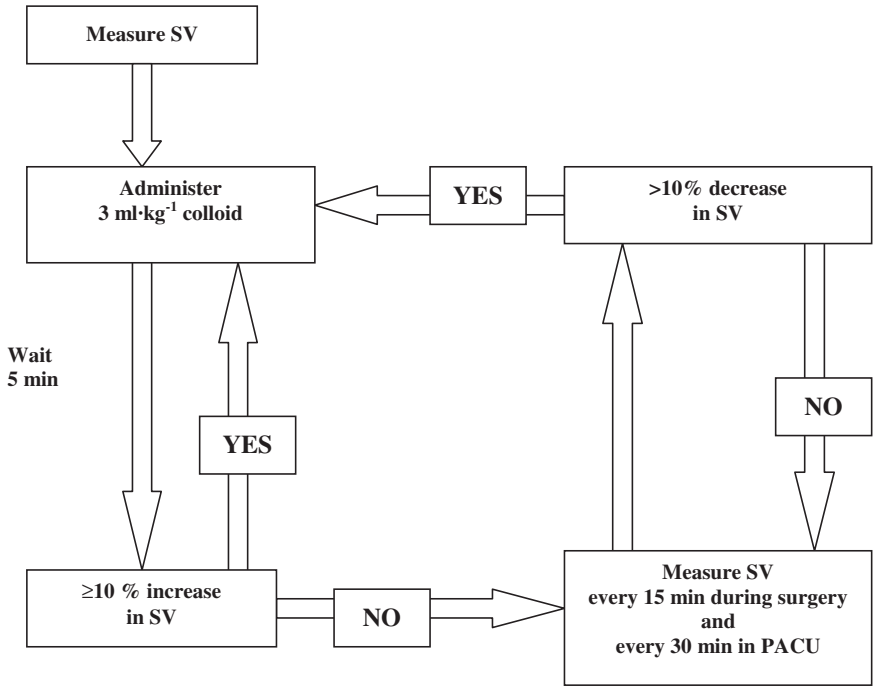

Fig. 2. Individualized goal-directed fluid administration algorithm for stroke volume (SV) optimization during surgery and at the postanesthetic care unit (PACU).

acetaminophen 1 g, gabapentin 600 mg, and oxycodone 20 mg before the operation and continuing acetaminophen 4 g, oxycodone 40 mg, and ibuprofen 1,800 mg daily thereafter.

Postoperative Care

Lactated Ringer's solution (3 ml·kg^{-1}·h^{-1}) was administered in the postanesthetic care unit (PACU). HES 130/0.4 (3 ml/kg) was administered if two of the following criteria were fulfilled: (1) diuresis less than 0.5 ml·kg^{-1}·h^{-1}, (2) mean arterial pressure less than 60 mmHg, or (3) HR more than 110 beats/min. The esophageal Doppler probe was kept in place during the PACU stay to obtain the mentioned hemodynamic variables every 30 min, and in the GDT group HES 130/0.4 was administered according to the algorithm if SV decreased 10% or more compared with the initial optimized SV in the operating theater (fig. 2). Blood samples were obtained hourly from the central venous line to measure hemoglobin concentration and central venous oxygenation (ABL-700; Radiometer Medical). If pain on a verbal rating scale (0–10) was more than 3 at rest and/or more than 5 during movement, additional oxycodone was administered. The patients were discharged from the PACU according to the modified Aldrete criteria.[20]

Outcome Measures

The primary outcome measure was the prevalence of OI in sitting or standing positions at 6 h after tracheal extubation. Secondary outcome measures were the prevalence of orthostatic hypotension, LOS, vasoactive hormonal and hemodynamic responses, and changes in tissue oxygenation during postoperative mobilization. Variables were analyzed according to randomization group and orthostatic competence.

Data Analysis

The finger arterial pressure curves and the derived cardiovascular variables acquired during the mobilization procedure were analyzed using Beatscope software (Finapres Medical Systems BV). Each curve was inspected for artifacts which were excluded. For both Finometer® and NIRS variables, estimates representing supine rest were averaged over 5 min, whereas estimates representing mobilization periods were averaged over the last 10 s before termination of each posture, both for patients completing the mobilization procedure and for patients for whom the procedure was terminated.[5,18]

Statistical Analysis

The prevalence of OI is reported to be 50% at 6 h after open radical prostatectomy.[6] This study was conducted as a superiority trial and 42 patients were needed to show a reduction in the OI prevalence to 10% with a power of 0.8 (1-β) and an α of 0.05. Thus, 44 eligible patients were randomized (fig. 1). The primary outcome was analyzed using the chi-square test, whereas other differences between treatment groups were analyzed using the chi-square or Fisher exact test for categorical data. Continuous variables were examined for normal distribution and compared between groups using the independent samples *t* test for normally distributed variables and the Mann–Whitney U test for variables with a nonnormal distribution.

Table 1. Demographic Data for Patients Included in the Study

	Control (n = 21)	GDT (n = 21)
Age, yr	64 (61 to 66)	63 (60 to 66)
BMI, kg/m^2	26 (25 to 28)	26 (24 to 29)
ASA		
I	12 (57)	14 (67)
II	9 (43)	7 (33)
Comorbidity		
Hypertension	8 (38)	6 (29)
Other cardiovascular disease	0 (0)	1 (5)
Pulmonary disease	1 (5)	1 (5)

Data are median (inter quartile range) or number (%).
ASA = American Society of Anesthesiologists; BMI = body mass index; GDT = goal-directed therapy.

Hemodynamic responses, changes in tissue oxygenation, and hormones were compared within and between each mobilization session using a mixed-model ANOVA for repeated measures. Subjects were included as random effects, whereas body position and mobilization time point (pre- *vs.* postoperative) were included as fixed effects in the model. Pair-wise comparisons were carried out using differences in least-square means only if a significant overall type-III effect was observed and adjusted using the Dunnett-correction with supine rest as control level. Concentrations of hormones were transformed by the natural logarithm to obtain normal distributed data. Statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC) with a two-sided *P* value of 0.05 representing statistical significance and CI presented with a 95% confidence level.

Results

From October 8, 2008 to October 12, 2009, 44 of 61 eligible patients were enrolled in the study and randomized to standard therapy or GDT (fig. 1 and table 1). Two patients were excluded from the study after the randomization: one for logistical reasons (GDT group) and one because of intraoperative hypotension considered to require an infusion of dopamine (control group).

OI and Hypotension

Twenty-seven (64%) patients failed to complete the mobilization procedure after surgery because of OI. In the control group, 12 (57%; CI, 34–78%) patients (8 while sitting) compared with 15 (71%; CI, 48–89%) patients (11 while sitting) in the GDT group developed OI (*P* = 0.33). Therefore, in the control group 13 were able to sit and 9 were able to stand and in the GDT group 10 were able to sit and 6

Table 2. Perioperative Data together with Drugs and Fluid Administration/Losses

Variable	Control (n = 21)	GDT (n = 21)	*P* Value
Anesthesia, min	208 (189 to 228)	220 (205 to 235)	0.32
Surgery, min	149 (130 to 168)	164 (148 to 180)	0.22
PACU stay, min	181 (139 to 223)	140 (112 to 168)	0.10
Intraoperative			
RL, ml	1,636 (1,428 to 1,843)	1,879 (1,205 to 2,052)	0.07
HES, ml	1,057 (778 to 1,336)	1,758 (1,441 to 2,076)	0.001
Packed erythrocytes, n	2 (10%)	3 (14%)	0.23
Blood loss, ml	1,152 (774 to 1,530)	1,285 (875 to 1,696)	0.62
Urine output, ml	178 (115 to 241)	261 (178 to 345)	0.11
Propofol, mg	1,330 (1,118 to 1,542)	1,461 (1,296 to 1,625)	0.31
Remifentanil, mg	4.9 (4.0 to 5.8)	5.0 (4.3 to 5.7)	0.79
Ephedrine, mg	15 (8 to 22)	9 (4 to 13)	0.10
PACU			
RL, ml	661 (509 to 812)	525 (429 to 621)	0.12
HES, n	2 (10%)	3 (15%)	0.66
Packed erythrocytes, n	1 (5%)	0 (0%)	0.97
Oral intake, ml	208 (120 to 297)	163 (71 to 255)	0.46
Drain output, ml	51 (12 to 90)	56 (20 to 92)	0.85
Urine output, ml	446 (311 to 582)	476 (344 to 606)	0.75
Ward (arrival to 6 h postoperative)			
Oral intake, ml	339 (131 to 547)	423 (317 to 529)	0.44
Drain output, ml	21 (4 to 40)	22 (4 to 39)	0.97
Urine output, ml	299 (185 to 413)	385 (281 to 488)	0.25

Data are mean (95% CI) or number (%) of patients receiving infusion.
GDT = goal-directed therapy; HES = hydroxyethyl starch 130/0.4; PACU = postanesthetic care unit; RL = Ringer's lactate.

Table 3. Hemodynamic Data from the Intraoperative Period and during the Stay at the Postanesthetic Care Unit

Variable	Control (n = 21)	GDT (n = 21)	*P* Value
Intraoperative			
SV, ml	89 (81 to 96)	102 (91 to 113)	0.04
CO, l	4.9 (4.4 to 5.3)	5.3 (4.6 to 6.0)	0.25
FTc, ms	309 (299 to 317)	321 (311 to 330)	0.06
MAP, mmHg	63 (60 to 66)	65 (62 to 68)	0.22
HR, beats/min	55 (51 to 59)	52 (49 to 55)	0.24
Hb, g/dl	10.5 (9.8 to 11.2)	9.9 (9.2 to 10.6)	0.19
$ScvO_2$, %	77 (75 to 79)	77 (76 to 79)	0.76
Postanesthetic care unit			
SV, ml	97 (89 to 105)	107 (96 to 117)	0.15
CO, l	6.8 (5.9 to 7.6)	7.6 (6.7 to 8.5)	0.17
FTc, ms	345 (332 to 358)	358 (348 to 367)	0.10
MAP, mmHg	84 (80 to 89)	89 (85 to 93)	0.11
HR, beats/min	69 (63 to 76)	71 (67 to 75)	0.61
Hb, g/dl	11.0 (10.4 to 11.7)	10.8 (10.2 to 11.3)	0.52
$ScvO_2$, %	77 (75 to 80)	78 (75 to 81)	0.90

Data are mean (95% CI) of measurements taken every 15 min after optimization during surgery and every 30 min during stay at the postanesthetic care unit except for hemoglobin concentration and $ScvO_2$, which are reported as mean (95% CI) of the last measured value intraoperatively and at the postanesthetic care unit, respectively.

CO = cardiac output; FTc = systolic flow time corrected to an HR of 60 beats/min; GDT = goal-directed therapy; Hb = hemoglobin; HR = heart rate; MAP = mean arterial pressure; $ScvO_2$ = central venous oxygenation; SV = stroke volume.

were able to stand. The difference in OI between treatment groups was consequently 14% (CI, −18 to 45%). Twenty-six (96%) patients with OI terminated the procedure because of OI symptoms alone or OI symptoms combined with a decrease in SAP of more than 30 mmHg, leaving one patient for whom the procedure was aborted only because of a decrease in SAP more than 30 mmHg that reached 40 mmHg before the patient was supine.

Both in the control and GDT groups, nine (43%) patients developed orthostatic hypotension. Two and one patient(s) were unclassifiable in the control and GDT group, respectively, because no data were available when the mobilization procedure was discontinued because of OI. Accordingly, there was no difference in the prevalence of orthostatic hypotension between randomization groups ($P = 0.83$). In addition, LOS was similar with median 3 days (interquartile range, 2–3) in the standard group compared with 3 days (3–4) in the GDT group ($P = 0.2$). However, LOS was 3 days (3–4) in OI patients compared with 2 days (2–3) in orthostatic-tolerant patients ($P = 0.02$).

Perioperative Management and Hemodynamic Data

Perioperative data, administered drugs, and fluid administration and losses are shown in table 2. The only difference between randomization groups was in the administered volume of colloid (HES 130/0.4), which was, 701 ml (CI, 292–1,110 ml), greater in the GDT group compared with the control group ($P = 0.001$).

The initially measured SV after induction of anesthesia was 85 ml (CI, 79–91 ml) in the control group compared with 78 ml (CI, 69–87 ml) in the GDT group ($P = 0.20$). In the GDT group, the first optimization increased SV by 23 ml (CI, 16–30 ml; $P < 0.0001$). Perioperative hemodynamic data including the surgical period and the PACU stay are shown in table 3 as means of measurements obtained every 15 min after optimization. During surgery, SV was the only variable differing significantly between randomization groups ($P = 0.04$). At the PACU stay, no significant differences in hemodynamic data were observed ($P > 0.05$).

Pain and Opioid Requirements

Postoperative pain scores at the mobilization test were 2 (1–2), 2 (1–4), and 3 (1–3) when the patients were at rest, sitting, and standing, respectively, and they were not different between the randomization groups (all $P > 0.05$). Three patients in the control group and two patients in the GDT group required supplemental opioids in the PACU and these patients received oxycodone 5 mg (5–5) with no difference between randomization groups ($P = 0.70$) or with regard to orthostatic competence ($P = 0.70$). Pain scores during mobilization did not differ between OI and orthostatic-tolerant patients (table 4; $P > 0.05$).

Orthostatic Hemodynamic and Hormonal Responses

Baseline hemodynamic values, tissue oxygenation, and plasma hormones during supine rest, before, and after surgery are presented in table 5. There were no differences between the control and GDT groups before or after surgery ($P > 0.05$). However, for both groups of patients, baseline SAP, DAP, mean arterial pressure, TPR, and S_CO_2 were lower after surgery, whereas HR and plasma vasopressin level were higher ($P < 0.05$). In the control group, SV and CO

were higher postoperatively, but for the GDT group these differences did not reach statistical significance. For the GDT group, the epinephrine concentration was lower in the postoperative evaluation ($P = 0.02$).

Before surgery, the hemodynamic response to standing did not differ between the control and GDT groups and were characterized by an increase in DAP and HR and a decrease in SV, S_CO_2, and S_MO_2 ($P < 0.05$), whereas SAP, CO, and TPR did not change significantly ($P > 0.05$; fig. 3). Compared with supine rest, no hemodynamic variables changed during passive leg raise for both treatment groups before and after surgery ($P > 0.05$).

After surgery, the responses from supine to standing included a decrease in SAP, SV, and S_CO_2 compared with the preoperative evaluation ($P < 0.05$; fig. 3). In addition, the S_MO_2 response to standing was reduced in the control group compared with the GDT group after surgery ($P < 0.05$), whereas no other hemodynamic- and tissue oxygenation responses differed between the control and GDT groups. Furthermore, the hormonal responses on mobilization did not differ significantly between randomization groups, neither before nor after surgery ($P > 0.05$; data not shown). However, the increase in plasma vasopressin level was larger after than before surgery: 182 *versus* 1 pg/ml ($P < 0.0001$) for the GDT group and 124 *versus* 2 pg/ml ($P = 0.006$) for the control group. A similar pattern was observed for epinephrine: 0.7 *versus* 0.0 pmol/ml ($P = 0.02$) for the GDT group and 1.0 *versus* 0.1 pmol/ml ($P = 0.003$) for the control group.

Table 4 compares the hemodynamic and hormonal responses to mobilization before *versus* after surgery between orthostatic tolerant and OI patients. For the orthostatic-tolerant patients, the only variable that differed was SV that decreased more after compared with before surgery. In contrast, the OI patients showed large decreases in SAP, DAP, mean arterial pressure, SV, and CO and an attenuated increase in HR during mobilization after surgery. In accordance with these findings, the responses in SAP, DAP, mean arterial pressure, and HR in the OI patients differed from the orthostatic-tolerant patients. In addition, the vasopressin and epinephrine responses were increased in both OI and orthostatic-tolerant patients, but these increases reached statistical significance only in the OI group. The norepineprhine response was attenuated in OI patients

Table 4. Changes in Hemodynamic Variables, Tissue Oxygenation, Hormones, and Pain Scores from Supine to Termination of the Mobilization Procedure during Sitting or Standing 6 Hours after Surgery Grouped by Orthostatic Competance before and after Operation

		6 h Postoperative	
Variable	Preoperative (n = 42)	OT (n = 15)	OI (n = 27)
Hemodynamic variables			
ΔSAP, mmHg	1 (–3 to 6)	–5 (–16 to 6)	–29 (–40 to –18)*#
ΔDAP, mmHg	3 (1 to 5)	2 (–2 to 7)	–10 (–15 to –5)*#
ΔMAP, mmHg	2 (–1 to 5)	–1 (–7 to 5)	–17 (–24 to –10)*#
ΔHR, beats/min	9 (7 to 11)	13 (5 to 20)	2 (–4 to 9)*#
ΔSV, ml	–6 (–11 to –1)	–20 (–30 to –9)*	–22 (–31 to –12)*
ΔCO, l/min	0.3 (0 to 0.7)	–0.4 (–1.1 to 0.4)	–1.3 (–2.2 to –0.4)*
ΔTPR, $mmHg \cdot s^{-1} \cdot ml^{-1}$	–0.03 (–0.11 to 0.05)	0.08 (–0.03 to 0.18)	0.05 (–0.11 to 0.2)
Tissue oxygenation			
ΔS_MO_2, %	–7 (–10 to –4)	–8 (–12 to –4)	–4 (–6 to –1)
ΔS_CO_2, %	–3 (–4 to –2)	–7 (–9 to –4)	–6 (–9 to –3)
Hormones			
ΔAngiotensin II, pg/ml	0.5 (0.0 to 1.1)	0.9 (–0.4 to 2.1)	0.6 (–0.8 to 2.0)
ΔANP, pg/ml	–6.4 (–12.9 to 0.0)	–3.2 (–17.6 to 11.3)	5.0 (–1.9 to 11.9)
ΔVasopressin, pg/ml	2 (1 to 2)	89 (9 to 170)	188 (107 to 270)*
ΔEpinephrine, pmol/ml	0.0 (–0.1 to 0.2)	0.6 (0.3 to 0.9)	0.9 (0.4 to 1.5)*
ΔNorepinephrine, pmol/ml	2.1 (1.8 to 2.4)	2.8 (1.8 to 3.7)	1.2 (0.8 to 1.6)*#
Pain scores			
Supine rest (VRS)	—	1 (1)	2 (1)
Termination of mobilization (VRS)	—	2 (2)	3 (3)

Data presented as mean (95% CI) or median (inter quartile range).

*$P < 0.05$ compared with preoperative; #$P < 0.05$ compared with OT; —, not applicable.

ANP = atrial natriuretic peptide; CO = cardiac output; DAP = diastolic arterial pressure; HR = heart rate; MAP = mean arterial pressure; OI = orthostatic intolerant; OT = Orthostatic tolerant; SAP = systolic arterial pressure; S_CO_2 = frontal lobe cerebral oxygenation; S_MO_2 = muscle tissue oxygenation; SV = stroke volume; TPR = total peripheral resistance; VRS = verbal rating scale 0 to 10.

Table 5. Baseline Values of Hemodynamic Variables, Tissue Oxygenation, and Hormones when Patients Were Supine before a Standardized Mobilization Procedure

	Preoperative		6 h Postoperative	
Variable	Control	GDT	Control	GDT
Hemodynamic variables				
SAP, mmHg	144 (136 to 152)	148 (142 to 154)	120 (113 to 127)*	130 (121 to 139)*
DAP, mmHg	78 (74 to 82)	78 (76 to 81)	65 (62 to 69)*	68 (64 to 73)*
MAP, mmHg	103 (97 to 108)	104 (100 to 107)	85 (81 to 90)*	91 (85 to 97)*
HR, beats/min	67 (64 to 73)	70 (66 to 74)	72 (66 to 77)*	71 (67 to 75)*
SV, ml	84 (78 to 90)	91 (82 to 100)	94 (84 to 104)*	100 (91 to 110)
CO, l/min	5.7 (5.2 to 6.3)	6.3 (5.6 to 7.1)	6.6 (5.9 to 7.3)*	7.1 (6.4 to 7.8)
TPR, $mmHg \cdot s^{-1} \cdot ml^{-1}$	1.12 (1.00 to 1.24)	1.07 (0.91 to 1.23)	0.82 (0.72 to 0.92)*	0.83 (0.70 to 0.95)*
Tissue oxygenation				
S_MO_2, %	75 (72 to 79)	73 (67 to 78)	76 (73 to 78)	74 (71 to 77)
S_CO_2, %	72 (69 to 75)	73 (70 to 76)	68 (66 to 71)*	68 (67 to 70)*
Hormones				
Angiotensin II, pg/ml	5.5 (4.1 to 7.4)	4.7 (3.9 to 5.7)	4.9 (3.8 to 6.3)	4.3 (3.5 to 5.2)
ANP, pg/ml	116 (97 to 139)	95 (82 to 111)	114 (95 to 137)	103 (84 to 127)
Vasopressin, pg/ml	1.2 (0.9 to 1.6)	1.3 (1.0 to 1.8)	8.1 (4.1 to 15.8)*	14.6 (7.3 to 29.3)*
Epinephrine, pmol	0.4 (0.3 to 0.5)	0.6 (0.4 to 0.8)	0.3 (0.3 to 0.4)	0.4 (0.3 to 0.5)*
Norepinephrine, pmol	3.0 (2.7 to 3.3)	2.8 (2.6 to 3.1)	2.9 (2.5 to 3.3)	2.7 (2.4 to 3.1)

Data presented as mean (95% CI).

* Different from preoperative $P < 0.05$.

ANP = atrial natriuretic peptide; CO = cardiac output; DAP = diastolic arterial pressure; GDT = goal-directed therapy; HR = heart rate; MAP = mean arterial pressure; SAP = systolic arterial pressure; S_CO_2 = frontal lobe cerebral oxygenation; S_MO_2 = muscle tissue oxygenation; SV = stroke volume; TPR = total peripheral resistance.

after surgery ($P < 0.001$) and was reduced compared with orthostatic tolerant patients ($P < 0.0001$).

Discussion

The main finding of this study was that GDT did not reduce the prevalence of OI or orthostatic hypotension at 6 h after open radical prostatectomy. However, we found that OI was associated with an attenuated plasma norepinephrine response, suggesting that the pathophysiology of OI after surgery includes dysregulation of the vasopressor response. In addition, we found no difference in LOS between randomization groups, but those patients experiencing OI had a 1-day longer LOS compared with orthostatic-tolerant patients.

With regard to postoperative orthostatic competence, trials have emphasized lack of cardiovascular control by demonstrating a high prevalence of postoperative orthostatic hypotension assessed on a tilt-table and by evaluating the cardiovascular effects of mobilization after cardiac surgery.[21,22] In addition, recent trials have related these findings to the occurrence of OI and shown that OI is a hindrance to postoperative mobilization after major surgery.[5,6] The current interventional study is the first directed to reduce postoperative OI. We hypothesized that GDT would reduce the prevalence of OI by reducing functional hypovolemia. The improvement in postoperative recovery by GDT, including reduced morbidity and LOS, may include enhanced blood flow to vital organs and especially to the gut[23] mediated by correction of perioperative hypovolemia with maximization of SV with colloid.[24–26] Because hypovolemia and an attenuated response of CO may be involved in OI, we hypothesized GDT to be beneficial, but that was not demonstrated in the current trial. The explanation hereto may be that orthostatic competence depends on both sufficient cardiac preload and intact regulation of vasomotor tone and that SV optimization with GDT addresses only preload to the heart. Our findings do not exclude that hypovolemia may be involved in the pathophysiology of OI but they demonstrate that addressing hypovolemia by GDT is not sufficient to prevent OI.

A strength of this study was that fluid administration in the control group was standardized and optimized according to international recommendations.[27] Consequently, the control group received standardized crystalloid infusion accompanied by precise substitution of blood loss with artificial colloid.[9] Studies on GDT have not used such a precise and strict treatment for the control group. Importantly, GDT translated into a larger infused colloid volume and a higher SV comparable with other GDT studies.[11] We continued GDT during the PACU stay, but this resulted only in limited fluid administration and with no difference between randomization groups, suggesting that the early postoperative volume need is sparse with regard to SV maximization.

This study confirmed previous findings of impaired hemodynamic orthostatic response to early postoperative mobilization.[5–6] In contrast to previous evaluations of postoperative

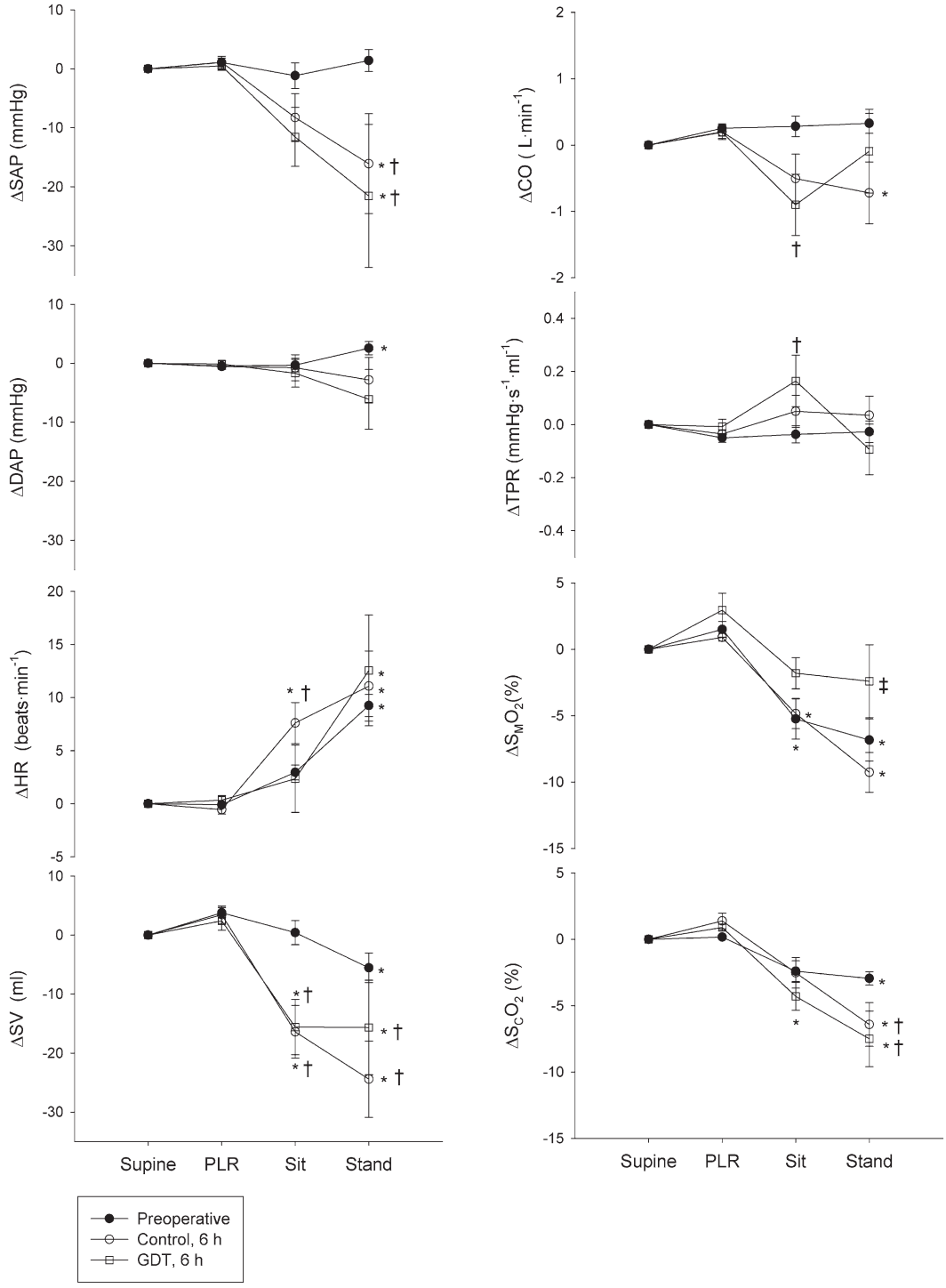

Fig. 3. Changes in cardiovascular variables before (preoperative) and 6 h after surgery in patients receiving standard therapy (control) or individualized goal-directed therapy (GDT) during a standardized mobilization procedure. Before surgery, control and GDT groups are illustrated together because there was no difference between groups in any variables (all $P > 0.05$). CO = cardiac output; DAP = diastolic arterial pressure; HR = heart rate; PLR = 30° passive leg raise test; SAP = systolic arterial pressure; S_CO_2 = frontal lobe cerebral oxygenation; S_MO_2 = muscle tissue oxygenation; SV = stroke volume; TPR = total peripheral resistance. *$P < 0.05$ compared with supine; †$P < 0.05$ compared with before surgery; ‡$P < 0.05$ compared with control.

OI, we included measures of vasoactive hormonal responses to mobilization. The postoperative response in vasopressin and epinephrine was larger in OI patients and showed trends to be larger in orthostatic tolerant patients suggesting that these hormonal responses are due to the surgical trauma *per se* rather than to a reduced intravascular volume. Conversely, in OI patients, the norepinephrine response was attenuated compared with that demonstrated in orthostatic-tolerant

patients. Because additional volume infusion to obtain SV optimization did not reduce the prevalence of OI, the results suggest that intervention with regard to impaired vasopressor response during an orthostatic challenge is of interest.

The study was powered to show a reduction in the prevalence of OI from 50 to 10%, which we consider clinically relevant because a large reduction in postoperative OI is required since GDT is both time and resource consuming. Thus, this study was not powered to detect small differences in OI occurrence between treatment groups. We designed this trial to include patients undergoing open radical prostatectomy because a study has reported a high prevalence of OI and describes the hemodynamic responses in detail to postoperative orthostasis in these patients.[6] In addition, we find open radical prostatectomy relevant for studies addressing OI and hemodynamics because the patients are typically with little comorbidity (table 1) that could affect the results and hamper evaluation of the pathophysiology of postoperative OI. Importantly, open radical prostatectomy is a relevant procedure for studies addressing fluid therapy because the blood loss may become clinically relevant,[6] as confirmed in this trial. Surprisingly, we did not find a decreased frontal lobe oxygenation with OI as estimated by NIRS. The reliability of NIRS has, however, been questioned because skin blood flow affects measurements.[28,29] In contrast to former evaluations, we did not find an attenuated TPR response in OI patients measured by Modelflow®. This can be explained by the observation that the current study found more patients experiencing OI during sitting where the attenuation in TPR and cerebral oxygenation is not as pronounced as during standing.[5,6] The results may be influenced by the technology used. The esophageal Doppler estimates SV from the velocity of blood in the descending aorta, but acceptable correlation to thermodilution measurements has been demonstrated, and the esophageal Doppler is the most frequently used technology in GDT studies showing an improvement in postoperative outcome.[11] When evaluating OI and cardiovascular variables, it is required that the measure is continuous to obtain a record of relevant variables before the appearance of OI symptoms. We used the Finometer® to measure a continuous noninvasive arterial pressure and Modelflow® to calculate hemodynamic variables during the mobilization procedure. Modelflow®-derived CO correlates well to a thermodilution-based assessment.[30] Moreover, Modelflow® has been valuable for determination of pathophysiology of OI patients.[6,7,13]

Although this study focused on symptoms during orthostatic stress, other influences may provoke the symptoms developed during OI.[8] Pain, opioid use, and central neuroaxial blockade may contribute. We used a total intravenous anesthesia regimen with short-acting opioids and avoided spinal and epidural anesthesia. For postoperative pain control, we used a standardized multimodal pain treatment regimen including wound infiltration of local anesthetics, acetaminophen, gabapentin, oxycodone, and ibuprofen and obtained an acceptable pain control with limited need for postoperative opioid supplementation. Side effects of gabapentin include sedation and dizziness that are relevant for development of OI. Nonetheless, a systematic review did not associate gabapentin use with significant sedation or dizziness,[31] and a trial in breast cancer surgery using the same regimen of gabapentin as the current trial found a low prevalence of postoperative OI.[7] Moreover, a study in open radical prostatectomy with a similar set-up, but without gabapentin use, demonstrated a comparable prevalence of OI.[6] The test procedure was stopped not only due to OI, but also if SAP decreased more than 30 mmHg to prevent syncope. However, only one patient demonstrated such a grave reduction in SAP without experiencing any symptoms. Although American Society of Anesthesiologists physical status class III was not an exclusion criterion, no patients with American Society of Anesthesiologists physical status class III were included reflecting that the population of men undergoing open radical prostatectomy is otherwise relatively healthy.

In summary, GDT did not reduce the prevalence of OI and orthostatic hypotension after open radical prostatectomy. The pathophysiology of OI includes an attenuated norepinephrine response suggesting dysregulation of vasomotor tone calling for studies involving modulation of the vasopressor response.

References

1. Harper CM, Lyles YM: Physiology and complications of bed rest. J Am Geriatr Soc 1988; 36:1047–54
2. Teasell R, Dittmer DK: Complications of immobilization and bed rest. Part 2: Other complications. Can Fam Physician 1993; 39:1440–2, 1445–6
3. Kehlet H, Wilmore DW: Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg 2008; 248:189–98
4. Grubb BP: Neurocardiogenic syncope and related disorders of orthostatic intolerance. Circulation 2005; 111:2997–6
5. Jans Ø, Bundgaard-Nielsen M, Solgaard S, Johansson PI, Kehlet H: Orthostatic intolerance during early mobilization after fast-track hip arthroplasty. Br J Anaesth 2012; 108:436–43
6. Bundgaard-Nielsen M, Jørgensen CC, Jørgensen TB, Ruhnau B, Secher NH, Kehlet H: Orthostatic intolerance and the cardiovascular response to early postoperative mobilization. Br J Anaesth 2009; 102:756–62
7. Müller RG, Bundgaard-Nielsen M, Kehlet H: Orthostatic function and the cardiovascular response to early mobilization after breast cancer surgery. Br J Anaesth 2010; 104:298–4
8. Mustafa HI, Fessel JP, Barwise J, Shannon JR, Raj SR, Diedrich A, Biaggioni I, Robertson D: Dysautonomia: Perioperative implications. Anesthesiology 2012; 116:205–15
9. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M: A rational approach to perioperative fluid management. Anesthesiology 2008; 109:723–40
10. Corcoran T, Rhodes JE, Clarke S, Myles PS, Ho KM: Perioperative fluid management strategies in major surgery: A stratified meta-analysis. Anesth Analg 2012; 114:640–51
11. Bundgaard-Nielsen M, Holte K, Secher NH, Kehlet H: Monitoring of peri-operative fluid administration by individualized goal-directed therapy. Acta Anaesthesiol Scand 2007; 51:331–40

12. Kehlet H, Bundgaard-Nielsen M: Goal-directed perioperative fluid management: Why, when, and how? Anesthesiology 2009; 110:453–5
13. Harms MP, Wesseling KH, Pott F, Jenstrup M, Van Goudoever J, Secher NH, Van Lieshout JJ: Continuous stroke volume monitoring by modelling flow from non-invasive measurement of arterial pressure in humans under orthostatic stress. Clin Sci (Lond) 1999; 97:291–1
14. Murkin JM, Arango M: Near-infrared spectroscopy as an index of brain and tissue oxygenation. Br J Anaesth 2009; 103(suppl 1):i3–13
15. Simonsen JA, Rasmussen MS, Vach W, Høilund-Carlsen PF, Bie P: Exaggerated natriuresis during clamping of systemic NO supply in healthy young men. Clin Sci (Lond) 2012; 122:63–3
16. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Neurology 1996; 46:1470
17. Singer M: Oesophageal Doppler. Curr Opin Crit Care 2009; 15:244–8
18. Jørgensen CC, Bundgaard-Nielsen M, Skovgaard LT, Secher NH, Kehlet H: Stroke volume averaging for individualized goal-directed fluid therapy with oesophageal Doppler. Acta Anaesthesiol Scand 2009; 53:34–8
19. Johansson PI, Ostrowski SR, Secher NH: Management of major blood loss: An update. Acta Anaesthesiol Scand 2010; 54:1039–49
20. Aldrete JA: The post-anesthesia recovery score revisited. J Clin Anesth 1995; 7:89–1
21. Kirkeby-Garstad I, Wisløff U, Skogvoll E, Stølen T, Tjønna AE, Stenseth R, Sellevold OF: The marked reduction in mixed venous oxygen saturation during early mobilization after cardiac surgery: The effect of posture or exercise? Anesth Analg 2006; 102:1609–16
22. Cowie DA, Shoemaker JK, Gelb AW: Orthostatic hypotension occurs frequently in the first hour after anesthesia. Anesth Analg 2004; 98:40–5
23. Giglio MT, Marucci M, Testini M, Brienza N: Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: A meta-analysis of randomized controlled trials. Br J Anaesth 2009; 103:637–46
24. Grocott MP, Mythen MG, Gan TJ: Perioperative fluid management and clinical outcomes in adults. Anesth Analg 2005; 100:1093–106
25. Bundgaard-Nielsen M, Jørgensen CC, Secher NH, Kehlet H: Functional intravascular volume deficit in patients before surgery. Acta Anaesthesiol Scand 2010; 54:464–9
26. Kimberger O, Arnberger M, Brandt S, Plock J, Sigurdsson GH, Kurz A, Hiltebrand L: Goal-directed colloid administration improves the microcirculation of healthy and perianastomotic colon. Anesthesiology 2009; 110:496–4
27. Doherty M, Buggy DJ: Intraoperative fluids: How much is too much? Br J Anaesth 2012; 109:69–9
28. Davie SN, Grocott HP: Impact of extracranial contamination on regional cerebral oxygen saturation: A comparison of three cerebral oximetry technologies. Anesthesiology 2012; 116:834–40
29. Sørensen H, Secher NH, Siebenmann C, Nielsen HB, Kohl-Bareis M, Lundby C, Rasmussen P: Cutaneous vasoconstriction affects near-infrared spectroscopy determined cerebral oxygen saturation during administration of norepinephrine. Anesthesiology 2012; 117:263–70
30. de Wilde RB, Schreuder JJ, van den Berg PC, Jansen JR: An evaluation of cardiac output by five arterial pulse contour techniques during cardiac surgery. Anaesthesia 2007; 62:760–8
31. Mathiesen O, Møiniche S, Dahl JB: Gabapentin and postoperative pain: A qualitative and quantitative systematic review, with focus on procedure. BMC Anesthesiol 2007; 7:6