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Orthostatic intolerance and the cardiovascular response to early postoperative mobilization

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Background. A key element in enhanced postoperative recovery is early mobilization which, however, may be hindered by orthostatic intolerance, that is, an inability to sit or stand because of symptoms of cerebral hypoperfusion as intolerable dizziness, nausea and vomiting, feeling of heat, or blurred vision. We assessed orthostatic tolerance in relation to the postural cardiovascular responses before and shortly after open radical prostatectomy.

Methods. Orthostatic tolerance and the cardiovascular response to sitting and standing were evaluated on the day before surgery and 6 and 22 h after operation in 16 patients. Non-invasive systolic (SAP) and diastolic arterial pressure (DAP) (Finometer®), heart rate, cardiac output (CO, Modelflow®), total peripheral resistance (TPR), and central venous oxygen saturation (Scv_{O_2}) were monitored.

Results. Before surgery, no patients had symptoms of orthostatic intolerance. In contrast, 8 (50%) and 2 (12%) patients were orthostatic intolerant at 6 and ~22 h after surgery, respectively. Before surgery, SAP, DAP, and TPR increased ($P<0.05$), whereas CO did not change ($P>0.05$) and Scv_{O_2} decreased ($P<0.05$) upon mobilization. At 6 h after operation, SAP and DAP declined with mobilization ($P<0.05$) and the arterial pressure response differed from the preoperative response both upon sitting ($P<0.05$) and standing ($P<0.05$) due to both impaired TPR and CO. At ~22 h, the SAP and DAP responses to mobilization did not differ from the preoperative evaluation ($P>0.05$).

Conclusions. The early postoperative postural cardiovascular response is impaired after radical prostatectomy with a risk of orthostatic intolerance, limiting early postoperative mobilization. The pathogenic mechanisms include both impaired TPR and CO responses.

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Recovery after surgery can be enhanced by a multi-interventional strategy referred to as fast-track surgery for which early mobilization is a cornerstone.[1] Early mobilization may, however, be hindered by orthostatic intolerance characterized by an inability to maintain an upright posture because of symptoms of cerebral hypoperfusion, including dizziness, nausea, feeling of heat, blurred vision, and eventual syncope.[2]

In the upright position, gravity displaces blood to the abdominal and leg vasculature. Accordingly, the upright posture is associated with a reduced central blood volume and cardiac output (CO), but arterial pressure is maintained by reflex increase in total peripheral resistance (TPR).[3] Also, activation of the muscle pump and vasoconstriction of capacitance vessels counteract the decrease in venous return caused by gravity. The postoperative patient may be especially vulnerable upon mobilization because blood and fluid losses during surgery aggravate the postural reduction in central blood volume in the upright position. Furthermore, drugs used for premedication, anaesthesia, and postoperative analgesia, including opioids,[4 5] may contribute to orthostatic intolerance because of a reduced arterial pressure and an associated reduction in cerebral blood flow and oxygenation.[3 6]

Transient inability to ambulate is observed after ambulatory surgery and is a major cause of prolonged hospital stay,[7–9] but the incidence and duration of orthostatic intolerance in patients after major procedures is not known. Although the haemodynamic response to mobilization has been studied 24 h after cardiac surgery[10] and the frequency of orthostatic hypotension has been assessed on a tilt table after general surgery,[11] there have been no detailed studies of the haemodynamic changes on early postoperative mobilization and their relationship to orthostatic intolerance. We evaluated the incidence of orthostatic intolerance before and shortly after open radical prostatectomy and its relationship to non-invasively determined cardiovascular variables.

Methods

Sixteen patients median (range) age of 63 (46–70) yr, weight 85 (68–105) kg, and height 181 (168–188) cm undergoing open radical prostatectomy were studied. Informed consent was obtained. Exclusion criteria were the history of orthostatic hypotension, use of beta-blockers, ASA class >II, diabetes mellitus, and alcohol abuse (>5 u day^{-1}). The trial was approved by the local ethics committee (KF01 2006-7209) and registered by the Danish data protection agency and ClinicalTrials.gov under the US national library of medicine (NCT00431535).

Orthostatic challenge

A central venous catheter was inserted under ultrasound guidance in the right internal jugular vein on the day before surgery and central placement was confirmed by X-ray.[12] A mobilization procedure was performed before and after operation: in the afternoon on the day before surgery, and 6 h, and ~22 h after operation defined as time from tracheal extubation. The evaluation 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 standing while the patient was verbally encouraged to stand up onto the toes and move body weight from one leg to the other in order to activate the muscle pump (3 min).[13] Nasal oxygen was supplied at 2 litre min^{-1} and a finger cuff was applied on the middle part of the third finger (Finometer®, FMS, Finapres Medical Systems BV, Amsterdam, The Netherlands) with arterial pressure referred to heart level. Using a non-linear three-component model of the arterial impedance (Modelflow®), continuous stroke volume (SV), CO, and TPR were calculated.[14] During the mobilization procedure, the patients graded pain on a 0–10 point verbal rating scale. The mobilization procedure was discontinued, if the patient experienced orthostatic intolerance defined as intolerable dizziness, nausea and vomiting, feeling of heat or blurred vision, but the patient was allowed to continue the mobilization procedure, if such symptoms were felt to be minor or transient. Blood samples for central venous oxygen saturation (Scv_{O_2}) were obtained anaerobically in heparinized syringes at the end of the defined periods or at the onset of symptoms of orthostatic intolerance. Blood samples were stored at room temperature for <30 min before analysis (ABL-700, Radiometer Medical, Copenhagen, Denmark).

Orthostatic response

Orthostatic intolerance was defined as intolerable dizziness, nausea and vomiting, feeling of heat, or blurred vision upon mobilization.[2] In addition, patients were categorized as having orthostatic hypotension, if they displayed ≥20 mm Hg decrease in systolic arterial pressure (SAP), a 10 mm Hg decrease in diastolic arterial pressure (DAP), or both upon mobilization.[15] Since orthostatic hypotension is a large deviation from the normal response, which includes a maintained SAP and an increase in DAP of ~10 mm Hg,[16] we also evaluated whether the postoperative cardiovascular response differed from that obtained in the preoperative evaluation.

Anaesthesia and surgery

Premedication included acetaminophen 1 g and oxycodone 20 mg. Regional anaesthesia was not used. For induction of anaesthesia, fentanyl 0.25 mg and propofol 2 mg kg^{-1} were administered. Cisatracurium 0.1 mg kg^{-1} was used to facilitate tracheal intubation in all patients except for two for whom gastro-oesophageal reflux symptoms were considered to require rapid sequence induction including the use of suxamethonium. Anaesthesia was maintained with propofol and fentanyl or remifentanil. To cover basal fluid losses, a fixed volume regimen of 12.5 ml $kg\ h^{-1}$ Ringer's lactate (RL) was administered during the first hour and 6.25 ml $kg\ h^{-1}$ was provided for the following hours until surgery was completed. Blood loss was replaced 1:1 with 6% hydroxy ethyl starch (HES) (130/0.4, Fresenius Kabi AB, Uppsala, Sweden); no blood products were used. Surgery was performed with a midline incision. Morphine 0.1–0.15 mg kg^{-1} was administered 40 min before termination of surgery and 40 ml of bupivacaine 2.5 mg ml^{-1} was infiltrated in the incision at the end of surgery.[17] Tracheal extubation was carried out as soon as the patient gained consciousness and was able to breathe sufficiently.

Postoperative care

Postoperative pain treatment included oral oxycodone 20 mg 12 h^{-1}, acetaminophen 1 g 6 h^{-1}, and ibuprofen 600 mg 8 h^{-1}.[17] In the post-anaesthetic care unit (PACU), supplemental morphine was administered when the pain score was >3 at rest and >5 during movement. Nausea and vomiting were treated with i.v. ondansetron

Table 1 Intra- and postoperative fluid administration and losses. Values are shown as median with IQR. PACU, post-anaesthetic care unit; RL, Ringer's lactate; HES, hydroxy ethyl starch 130/0.4; 6 h, orthostatic test 6 h after operation; ~22 h, orthostatic test ~22 h after operation

	Intraoperative	**PACU**	**Ward**	
			6 h	**~22 h**
RL (ml)	1700 (1500–2000)	700 (400–1000)	0 (0–600)	0 (0–200)
HES (ml)	1000 (500–1000)	0 (0–500)	0	0
Glucose (ml)	—	—	—	0 (0–800)
Oral (ml)	—	175 (100–300)	0 (0–100)	750 (300–1025)
Bleeding (ml)	800 (450–1100)	0 (0–35)	0	33 (15–55)
Diuresis (ml)	100 (75–150)	360 (225–620)	110 (0–375)	1395 (1190–1630)

4 mg. During the PACU stay, standard care included infusion of up to 1000 ml of RL and 500 ml of colloid (HES 130/0.4). If MAP decreased to <60 mm Hg or urine output was <0.5 ml h^{-1}, patients were allowed to exceed these limits (Table 1). Patients were discharged from the PACU according to the modified Aldrete criteria.[18]

Data analysis

The finger arterial pressure curve was analysed using Beatscope software (Finapres Medical Systems BV) and artifacts were removed using MATLAB 7.4 analysis software (MathWorks, Natick, MA, USA). At rest, variables were averaged over 5 min. For estimates representing the periods of sitting and standing postures, the first 20 s was excluded before averaging because there is a normal initial swing in arterial pressure.[19] For patients with orthostatic intolerance, variables were averaged over the 5 s preceding appearance of symptoms.

Statistical analysis

A formal power analysis could not be performed, since no similar observations are available. Since an unpaired *t*-test comparison with 16 patients in each group is sufficient to detect a difference of 1 SD with a power of 80%, we chose that number. One-way ANOVA for repeated measurements was used to analyse differences within and between the three mobilization sessions. The TPR and CO were included as covariates in order to explain differences between sessions. Additionally, one-way ANOVA was used to compare orthostatic tolerant and intolerant patients with the preoperative session and the *t*-test was used to compare orthostatic intolerance patients with patients completing the mobilization procedure. Finally, a multiple regression analysis was performed to assess any correlation between opioid administration and the occurrence of orthostatic intolerance. Data analysis was conducted with SAS 9.1 (SAS Institute Inc., Cary, NC, USA) with a *P*-value of <0.05 considered to represent a statistical significant difference.

Results

Perioperative management

The patients were anaesthetized for a median (inter-quartile range, IQR) of 190 (125–205) min with surgery lasting 125 (110–145) min. Intra- and postoperative fluid administration and losses are shown in Table 1. In four patients, the administered amount of fluid differed from the standard regimen during the PACU stay (three patients received 1100 and one patient 1350 ml of RL). The median (IQR) time in PACU was 180 (75–240) min. The haemoglobin concentration was mean (SD) 14.0 (1.1) g dl^{-1} at the preoperative test, 10.5 (1.3) g dl^{-1} at the end of surgery, and 11.9 (1.6) and 11.3 (1.3) g dl^{-1} at 6 and 22 h, respectively. The first postoperative mobilization test was performed after 6 h and carried out 165 (70–190) min after arrival on the surgical ward. The second postoperative mobilization test was performed at a median (IQR) time of 1345 (1320–1370) min after tracheal extubation.

Pain and opioids

Pain scores at 6 h were median (IQR) 3 (1.5–4), 3.5 (2–5.5), and 4 (3–5) at rest, sitting, and standing, respectively and the corresponding pain scores at 22 h were 1 (0–2), 1.5 (1–3), and 2 (1.5–4). There was no difference in the pain scores on sitting (P=0.59) and standing (P=0.68) between patients discontinuing and completing the mobilization procedure and the amount of supplemental fentanyl (P=0.27) or morphine (P=0.62) was not related to orthostatic intolerance in a multiple regression analysis.

Before surgery

Upon leg elevation, cardiovascular variables did not change, apart from a minor increase in SAP (Table 2). However, from the supine to the standing position, there was a mean (95% CI) increase in SAP of 17 (10–24) mm Hg (P<0.0001), DAP increased 11 (7–15) mm Hg (P<0.0001), and HR increased 7.5 (5.8–9.2) beats min^{-1} (P<0.0001). Moreover, TPR increased by 0.24 (0.14–0.33) mm Hg s ml^{-1} (P<0.0001), whereas Scv_{O_2}

Table 2 Cardiovascular variables during mobilization procedure presented as mean (SD). 6 h, 6 h after tracheal extubation; ~22 h, ~22 h after tracheal extubation. *Different from supine, resting position (supine) ($P<0.05$); †different from preoperative ($P<0.05$); Legs up, legs 30° elevated; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; Scv_{O_2}, central venous oxygenation

	Preoperative				6 h				~22 h			
	Supine	Legs up	Sit	Stand	Supine	Legs up	Sit	Stand	Supine	Legs up	Sit	Stand
SAP (mm Hg)	151 (21)	157 (19)*	159 (19)*	168 (25)*	142 (19)	149 (19)	128 (22)*†	121 (26)*†	125 (15)†	130 (17)†	134 (22)†	133 (21)†
DAP (mm Hg)	72 (8)	76 (9)	80 (10)*	83 (12)*	69 (11)	73 (11)	68 (9)†	64 (11)†	62 (9)†	64 (9)†	67 (10)†	67 (8)†
HR (beats min^{-1})	70 (10)	70 (10)	72 (9)*	77 (9)*	71 (12)	72 (13)	73 (15)	81 (15)*	72 (10)	71 (9)	80 (11)*,†	85 (13)*,†
SV (ml)	121 (35)	119 (38)	102 (31)*	100 (33)*	121 (37)	118 (35)	102 (31)*	94 (21)*	113 (27)	118 (32)	106 (26)	104 (33)
CO (litre)	8.4 (2.9)	8.4 (3.1)	7.2 (2.2)*	7.7 (2.7)	8.5 (2.5)	8.3 (2.2)	7.4 (2.6)*	7.5 (1.7)*	8.2 (2.1)	8.4 (2.3)	8.4 (2.0)	8.8 (2.8)
TPR (mm Hg s ml^{-1})	0.83 (0.30)	0.88 (0.36)	1.03 (0.34)*	1.06 (0.39)*	0.74 (0.23)	0.79 (0.22)	0.79 (0.15)†	0.70 (0.13)†	0.68 (0.25)†	0.69 (0.23)†	0.70 (0.24)†	0.78 (0.59)
Scv_{O_2} (%)	74.8 (5.1)	75.4 (4.4)	63.5 (4.6)*	60.1 (6.0)*	73.4 (4.4)	74.2 (4.7)	59.0 (7.4)*,†	53.3 (9.4)*,†	71.8 (3.8)	73.0 (3.5)	59.9 (4.8)*,†	53.6 (7.1)*,†

decreased by 15 (13–17)% ($P<0.0001$) and SV decreased by 20 (9–30) ml ($P<0.0001$). CO tended to decrease, −0.73 (−1.48 to 0.02) litre min^{-1} ($P=0.06$) from the supine to standing. One patient demonstrated orthostatic hypotension but experienced no symptoms of orthostatic intolerance at mobilization.

Six hours after surgery

Eight patients terminated the procedure (three during sitting and four patients during standing, because of nausea/vomiting, dizziness, or feeling of heat). One patient could not be mobilized because of pain and the haemodynamic variables from this patient were excluded from the 6 h test. Six of the seven remaining orthostatic intolerant patients displayed orthostatic hypotension. In two of these patients, the decrease in both SAP (29 and 68 mm Hg) and DAP (30 and 31 mm Hg) manifested 10–30 s after they experienced symptoms of orthostatic intolerance, and orthostatic intolerance appeared to be related to a decrease in CO of 3.4 and 1.6 litre min^{-1}, respectively. Four of the eight patients without orthostatic intolerance demonstrated orthostatic hypotension. Figure 1 illustrates changes in arterial pressure in a patient with orthostatic intolerance during sitting. Upon 30° leg elevation neither SV nor CO increased significantly in orthostatic intolerance or non-orthostatic intolerance patients (Fig. 2). Upon standing, SAP declined by a mean (95% CI) of 22 (8–36) mm Hg ($P<0.003$) whereas DAP did not change ($P=0.13$) (Table 2). The SAP response was 24 ($P=0.0008$) and 39 mm Hg ($P<0.0001$) smaller upon sitting and standing, respectively, compared with the preoperative evaluation. Equally, the change upon sitting and standing in DAP was 11 ($P=0.004$) and 17 mm Hg ($P<0.0001$) smaller, respectively, compared with before operation. DAP decreased more in patients demonstrating orthostatic intolerance, mean (95% CI), 14 (4–25) mm Hg ($P=0.01$), than that in patients completing the mobilization procedure, but there was only a trend for a larger decline in SAP, 21 (9–52) mm Hg ($P=0.15$). Also, CO declined by a mean of 1.4 litre min^{-1} and SV declined by a mean of 31 ml upon standing, but this was not significantly different from the preoperative response. In patients with orthostatic intolerance, the mean change in TPR upon standing was 0.34 mm Hg s ml^{-1} smaller than that seen in the preoperative evaluation ($P<0.01$), whereas in the patients without orthostatic intolerance, the response in TPR was only 0.19 mm Hg s ml^{-1} smaller ($P=0.05$). Neither CO nor TPR alone could explain the difference in SAP and DAP responses to standing before surgery and 6 h after operation. However, when including CO and TPR as covariates in the statistical model, they explained the differences in the arterial pressure responses. Scv_{O_2} was reduced by a mean (95% CI) of 21 (18–23)%, ($P<0.001$) on standing compared with the supine and the reduction was 6 (3–10)% ($P=0.002$) larger than observed at the preoperative evaluation.

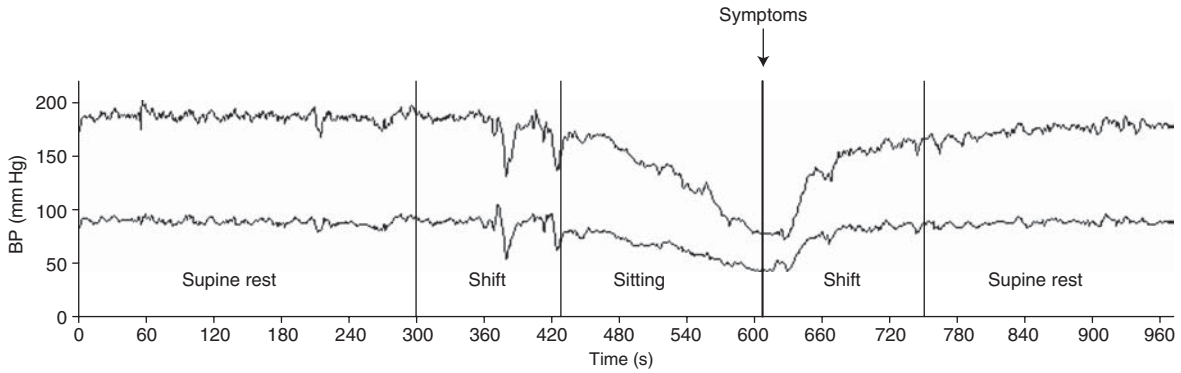

Fig 1 Continuous arterial systolic (upper curve) and diastolic (lower curve) pressure 6 h after operation in a patient who experienced symptoms of orthostatic intolerance. Shift indicates changing from the previous position.

Twenty-two hours after surgery

Only two patients experienced orthostatic intolerance during standing and another two patients showed orthostatic hypotension without orthostatic intolerance. In all evaluable subjects, SAP and DAP was significantly lower at all times compared with the preoperative evaluation and TPR was also lower except when standing (Table 2). However, the changes in SAP, DAP, and TPR upon mobilization were not significantly different compared with the preoperative evaluation, although these variables did not show the normal increase upon standing. The Scv_{O_2} declined by a mean of 21% upon standing ($P<0.001$) and this was similar to the preoperative decline ($P=0.10$).

Discussion

Mobilization is a key element in facilitating recovery after surgery.[1] The main finding of this study is that orthostatic intolerance impeded early postoperative mobilization in 50% of the patients 6 h after operation and that SAP and DAP responses in general were impaired upon mobilization, when compared with the preoperative evaluation. This postoperative functional haemodynamic impairment could be ascribed to a combination of attenuated responses in the main determinants of arterial pressure, that is, TPR and CO, but not by either of these variables alone. At 22 h after operation, the extent of orthostatic haemodynamic changes was reduced and only two of 16 patients experienced orthostatic intolerance.

Orthostatic hypotension is defined as a reduction of 20 mm Hg in SAP or >10 mm Hg DAP during 3 min of standing,[15 20] which is very different from the normal response with a maintained SAP and an increase of DAP by about 10 mm Hg,[16] as we observed in the preoperative evaluation. Cerebral perfusion may therefore be affected, causing symptoms of orthostatic intolerance before the criteria of orthostatic hypotension are fulfilled.[21] Consequently, we focused on patients' symptoms together with cardiovascular responses to mobilization. Importantly, the patients with orthostatic intolerance demonstrated large deviations from the normal preoperative cardiovascular response and only one of the orthostatic intolerance patients did not demonstrate orthostatic hypotension with only a minor deviation from the preoperative evaluation. However, half of the patients who completed the mobilization procedure at 6 h also demonstrated orthostatic hypotension suggesting that these patients, despite the impaired cardiovascular response, maintained their cerebral perfusion. Consequently, when comparing patients completing the mobilization procedure with those who did not, the lack of significant differences in other cardiovascular variables than DAP may be due to individual different thresholds for discontinuing the mobilization procedure, since patients were allowed to continue the mobilization where only minor or transient symptoms occurred which is a subjective assessment. Furthermore, patients may have different thresholds in arterial pressure for the lower limit of cerebral autoregulation and cerebral hypoperfusion and orthostatic intolerance may be elicited over a range of arterial pressures. It has been suggested that the curve for cerebral autoregulation is dynamic, that is, the lower limit of pressure maintaining cerebral perfusion is not fixed.[22] It is, therefore, possible that anaesthesia and surgery change the lower limit of cerebral autoregulation. Accordingly, this study suggests that cerebral perfusion, oxygenation, or both should be evaluated in future trials assessing postoperative mobilization and orthostatic intolerance. In addition, patients may experience symptoms before measurable circulatory manifestations due to autonomic reflexes. Thus, a marked decrease in arterial pressure was demonstrated in two patients immediately after the onset of symptoms. Finally, medication and pain may affect symptoms associated with orthostatic intolerance. To comply with this, the pain treatment regimen was standardized and the pain scores did not suggest that pain, even at mobilization, was a significant postoperative problem. Also, multiple logistic regression analyses did not find any significant association between the use of supplemental opioids and orthostatic

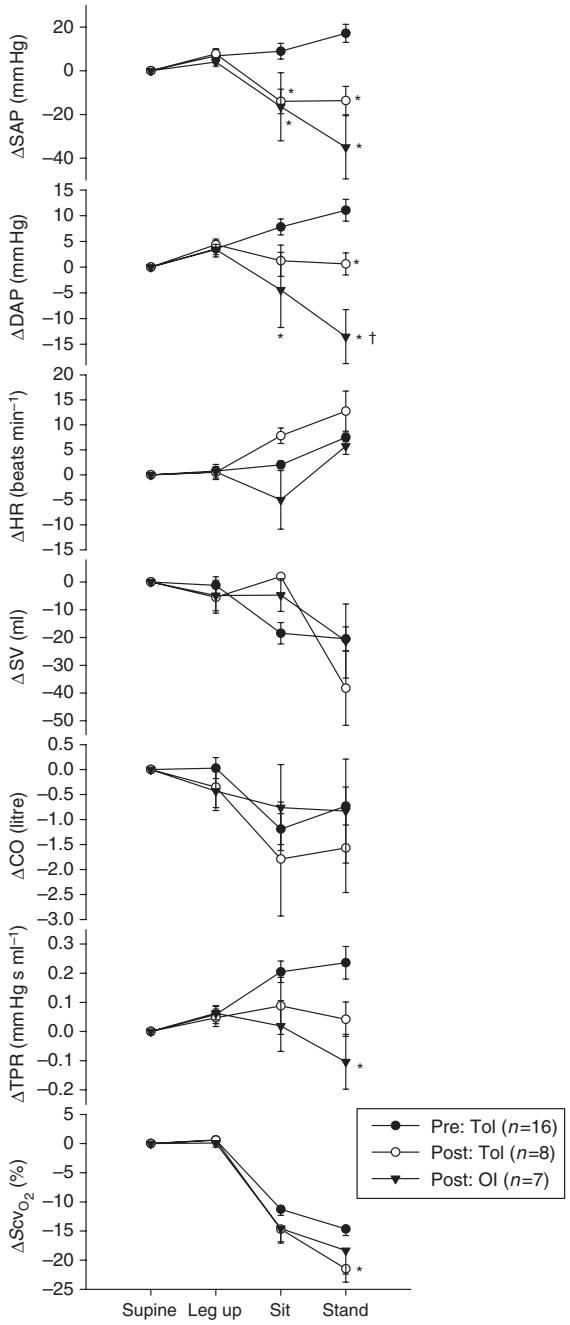

Fig 2 Changes in cardiovascular variables before operation (Pre) and 6 h after operation (Post) in orthostatic tolerant (Tol) and intolerant (OI) patients during a standardized mobilization procedure. One patient is not included after operation due to failure to mobilize because of pain. Leg up, 30° leg elevation; *$P<0.05$ compared with before operation; †$P<0.05$ compared with orthostatic tolerant patients 6 h after operation.

intolerance. However, the limited number of patients in this study hinders definitive conclusions regarding the role of opioids on orthostatic intolerance. Pain is an important restricting factor for mobilization, but pain treatment with opioids may induce orthostatic intolerance. Thus, opioid-sparing regimens with multi-modal non-opioid analgesia should be assessed in future evaluations of early post-operative orthostatic intolerance.[4 5]

It remains difficult to categorize patients in terms of having a CO or TPR problem in relation to orthostatic intolerance, because the two variables are interrelated. CO is reduced in the upright posture as a consequence of venous pooling by gravity. The reduction in CO may be larger after surgery due to a reduced blood volume, but none of the patients responded with an increase in SV or CO upon elevation of the legs. Impaired reflex vasoconstriction, vasoconstrictor control, or baroreflex dysfunction may hinder sufficient tonus of capacitance vessel to provide an adequate preload to the heart. Additionally, a reduced arterial pressure upon mobilization may be caused by the absence of a relevant increase in resistance vessels mediating increased TPR. The interplay between these mechanisms is demonstrated by the observations in the two patients who decreased in arterial pressure after onset of symptoms but decreased in CO before symptoms. Also, the patient illustrated (Fig. 1) showed an arterial pressure reduction due to decreased CO since TPR was maintained. Although patients were not fluid responsive 6 h after operation, as assessed with the raised leg test, it is unknown whether optimized fluid therapy such as goal-directed fluid therapy, which improves postoperative outcome,[23] may also reduce the frequency of orthostatic intolerance.

At 6 h after tracheal extubation, Scv_{O_2} was reduced by 21% during standing, which was 6% lower compared with the preoperative evaluation. The postoperative reduction in Scv_{O_2} is comparable with that seen on the day after aortic valve surgery.[24] In contrast to our findings, the reduction in mixed venous oxygenation (Sv_{O_2}) upon mobilization after coronary artery bypass grafting was not larger than before surgery.[25] However, the postoperative mobilization for the cardiac patients was performed the day after surgery and we also evaluated the ability to ambulate 6 h after operation.

We used Modelflow® (Finometer®) to measure arterial pressure and calculate haemodynamic variables. Modelflow®-derived CO has been shown to correlate well to a thermodilution-based assessment.[26] Moreover, Modelflow® has been widely used for determination of pathology of orthostatic intolerant patients.[14] We did not use a pulmonary artery catheter to measure the Sv_{O_2} because changes in Scv_{O_2} correspond well with those in Sv_{O_2}.[27–29]

In conclusion, this study showed that orthostatic intolerance occurs frequently in the early postoperative phase and is caused by impaired TPR and CO responses. Future studies assessing orthostatic intolerance during early post-operative mobilization should evaluate cerebral perfusion/oxygenation in relation to cardiovascular responses, fluid management, and type and duration of anaesthesia.

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