Orthostatic function and the cardiovascular response to early mobilization after breast cancer surgery

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Background. Early postoperative mobilization is essential for an enhanced recovery, but it can be hindered by orthostatic intolerance, characterized by signs of cerebral hypoperfusion, such as dizziness, nausea, vomiting, and ultimately syncope. Orthostatic intolerance is frequent after major surgical procedures, because of an attenuated cardiovascular response, but the cardiovascular response and the incidence of orthostatic intolerance after minor procedures have not been clarified. We investigated the cardiovascular response and the incidence of orthostatic intolerance during early mobilization after breast cancer surgery.

Methods. Twenty-four women undergoing breast cancer surgery performed a mobilization procedure before and 30 min after surgery, with measurement of arterial pressure, stroke volume (SV), cardiac output (CO), and total peripheral resistance (TPR) (Modelflow), besides evaluation of cerebral and muscle oxygenation (near-infrared spectroscopy) and recording of symptoms of orthostatic intolerance.

Results. There were no differences in the cardiovascular response and tissue oxygenation before and 30 min after surgery (P>0.05). Upon mobilization, systolic arterial pressure, SV, CO, and cerebral and muscle oxygenation decreased (P<0.05), whereas heart rate increased without change in TPR. After surgery, one patient (4%) experienced orthostatic intolerance, and one patient could not complete the mobilization procedure after surgery because of sedation.

Conclusions. With the used regimen of anaesthesia, pain treatment, and fluid therapy, orthostatic intolerance is infrequent 30 min after breast cancer surgery, apparently because the cardiovascular response and tissue oxygenation are preserved. Future studies assessing orthostatic intolerance should focus on larger surgical procedures and apply interventions that potentially maintain the cardiovascular response to mobilization.

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Early mobilization after surgery is essential for enhanced recovery and is a cornerstone of a multimodal intervention strategy to reduce morbidity and hospital stay. The ability to mobilize after surgery may, however, be hindered by factors such as pain and orthostatic intolerance. Orthostatic intolerance represents an inability to uphold an upright posture because of signs of cerebral hypoperfusion, including symptoms such as dizziness, nausea, feeling of heat, blurred vision, and eventually syncope. Although improved pain management may facilitate earlier mobilization, orthostatic intolerance remains a challenge for early mobilization after surgery and may potentially prolong hospital stay even after minor ‘ambulatory’ surgery. The cardiovascular response to head-up tilt on a tilt-table 15 min after general minor surgery and mobilization 24 h after cardiac surgery have been reported, but only one study has assessed the cardiovascular response and orthostatic intolerance to early mobilization in detail, demonstrating a 50% incidence of orthostatic intolerance related
to an attenuated cardiovascular response after radical prostatectomy.3

Since the cardiovascular response to the upright position has not been evaluated after minor surgical procedures, we assessed cardiovascular variables and tissue oxygenation during mobilization before and 30 min after breast cancer surgery.

Methods

Twenty-four women undergoing breast cancer surgery (lumpectomy or mastectomy) were included consecutively in the period from February 9 to May 19, 2009, after giving informed consent. Mean age was 55 (range 27–78) yr, weight 67 (41–95) kg, and height 168 (158–182) cm. Exclusion criteria were history of orthostatic hypotension, use of β-blockers, ASA class II, alcohol abuse (>5 U day−1), sedative premedication, psychiatric disease, age <18 or >80 yr, and unavailability of the members of the study group (R.G.M. and M.B.). The study was approved by the regional ethics committee (H-KF-2006-7209) and registered by the Danish data protection agency (Copenhagen, Denmark) and ClinicalTrials.gov (NCT00824876).

Mobilization procedure

The mobilization procedure was performed immediately before, and 30 min after surgery (defined as the time of removal of the laryngeal mask airway). The mobilization procedure included supine rest (5 min), then sitting on the hospital bed with both feet on the floor (3 min), followed by standing (3 min), where the subjects were instructed to stand on their toes and displace their body weight from one leg to another to activate the muscular pump and thereby attenuate venous pooling in the lower extremities.7 Finally, a 5 min recovery period was registered. The procedure was terminated if the patients reported symptoms of orthostatic intolerance or upon a decrease in systolic arterial pressure (SAP) of ≥30 mm Hg.

During the test, the muscle and cerebral oxygenation were assessed with intervals of 10 s by near-infrared spectroscopy (NIRS, Somanetics, INVOS®, cerebral oximeter, Troy, MI, USA) with optodes placed on the biceps brachii muscle and on the forehead, respectively. The NIRS-determined regional tissue oxygenation is based on the absorption of light in the spectra for oxygenated and deoxygenated haemoglobin and reports the percentage of light absorption by oxygenated to total haemoglobin. An emitter generates light at 733 and 808 nm and the reflection is registered by two sensors allowing for the subtraction of reflections derived from superficial tissues. Thus, values reported account predominantly for haemoglobin oxygenation in the biceps muscle and frontal lobe cortex.8 9 Arterial pressure was measured continuously using a finger cuff, applied on the middle part of the third finger. From the arterial pressure wave, an aortic flow waveform is computed by simulating a non-linear, time-varying model of the aortic input impedance (Model flow®, Finapres Medical Systems, Amsterdam, The Netherlands) and integrating the computed aortic flow waveform per beat provides stroke volume (SV). Cardiac output (CO) is calculated as SV multiplied by heart rate (HR); total peripheral resistance (TPR) is the ratio of mean arterial pressure (MAP) to CO.10 During the postoperative test, a 0–10 verbal rating scale was used to assess pain for each body position.

Orthostatic classification

Patients were classified as having orthostatic intolerance if they experienced signs of cerebral hypoperfusion, defined as having symptoms including dizziness, nausea, feeling of heat, blurred vision, or syncope. Patients were also monitored for orthostatic hypotension, defined as a decrease in SAP of ≥20 mm Hg, a decrease in diastolic arterial pressure (DAP) of ≥10 mm Hg upon standing, or both.11

Anaesthesia and surgery

Two hours before surgery, all patients received premedication comprising acetaminophen 1 g, celecoxib 400 mg, dexamethasone 8 mg, dextromethorphan 30 mg, and gabapentin 600 mg (300 mg if ≥70 yr).12 Propofol 2 mg kg−1 and fentanyl 0.15 mg were administered i.v. to induce anaesthesia, and a further dose of fentanyl 0.15 mg was administered 5 min before incision. To facilitate ventilation of the lungs, a laryngeal mask airway was placed and anaesthesia was maintained with i.v. infusion of propofol 0.15–0.2 mg kg−1 min−1. Additional fentanyl 0.05–0.1 mg or low-dose remifentanil infusion was administered if HR increased ≥20% from set point; ephedrine 5 mg was administered if MAP decreased by ≥20% from the set point. Ondansetron 4 mg was administered 10 min before the end of the procedure. Fluid therapy was standardized to Ringer’s lactate 25–30 ml kg−1.13 When surgery was completed and the patients gained consciousness and eventually were able to breathe sufficiently, the laryngeal mask airway was removed.

Data analysis

The finger arterial pressure curve was analysed using Beatscope software (Finapres Medical systems, BV). Estimates representing the rest periods were averaged over 5 min. For estimates representing the 3 min periods of sitting and standing postures, the first 20 s were excluded before averaging because of a normal initial down-swing in arterial pressure.14
Results

Perioperative management

Patients were anaesthetized for a median (IQR) of 120 (108–150) min and surgery lasted 78 (65–100) min. The amount of i.v. fluid administered during surgery was 1100 (1000–1600) ml of Ringer’s lactate and median estimated blood loss was 0 (0–100) ml. During surgery, the patients received an average (range) of 0.3 (0.2–0.5) mg fentanyl and three patients received additional remifentanil infusion during surgery (total dose 0.35–2.55 mg) to establish sufficient analgesia judged according to arterial pressure and HR.

Before surgery

At the preoperative test, none of the 24 patients experienced orthostatic intolerance, although four patients presented orthostatic hypotension. From the supine to the upright position, HR increased 15 (95% CI 13–18) beats min⁻¹ (P<0.001), whereas SV decreased 20 (15–26) ml (P<0.0001), CO 0.4 (0.1–0.8) litre min⁻¹ (P<0.01), and SAP 7 (2–12) mm Hg (P<0.01), while DAP and TPR did not change significantly. Also, from the supine to the upright position, muscle oxygenation decreased 5.0 (3.4–6.6)% (P<0.001) and cerebral oxygenation 3.3 (2.1–4.5)% (P<0.001).

Thirty minutes after the end of surgery

Data of muscle and cerebral oxygenation from one patient were excluded because of failure in recording. Two patients could not complete the mobilization procedure, one as a result of sedation and one because of orthostatic intolerance, manifested by nausea and dizziness, accompanied by a decrease in arterial pressure and cerebral oxygenation (Fig. 1). However, this patient demonstrated only orthostatic hypotension after surgery. Three of the four patients (17%) who presented with orthostatic hypotension before surgery also displayed orthostatic hypotension after surgery but without symptoms of orthostatic intolerance. HR increased by 10 (8–12) beats min⁻¹ from the supine to the upright position (P<0.001), whereas SV and SAP declined 15 (9–22) ml beat⁻¹ and 11 (6–17) mm Hg, respectively. CO, DAP, and TPR did not change significantly from the supine to the upright position (P>0.05), whereas muscle oxygenation decreased by 6.3 (4.6–8.0)% (P<0.001) and cerebral oxygenation by 5.5 (4.2–6.8)% (P<0.001). Thus, the patient demonstrating orthostatic intolerance displayed both the lowest estimate of cerebral oxygenation during the standing period (54%) and the lowest values measured at the onset of symptoms (Fig. 1). Pain assessed by a verbal rating scale was median (IQR) 2 (1.0–3.5) during the entire mobilization procedure (P=0.99).

Changes in all cardiovascular variables were assessed for effects of time (pre vs post), position (supine, sit, stand, recovery), and their interaction, but only the effect of position was statistically significant (P<0.05). Consequently, there was no difference in the cardiovascular response or tissue oxygenation with mobilization after breast cancer surgery compared with before surgery (Fig. 2).

Discussion

The main findings of this study are that upon mobilization, cardiovascular responses and tissue oxygenation are preserved after breast cancer surgery, and orthostatic intolerance is infrequent (<5%). This is in contrast to results obtained 6 h after radical prostatectomy, where 50% of the patients displayed orthostatic intolerance upon mobilization, in conjunction with impaired cardiovascular response. The differences between the procedures in terms of stress-response, fluid shifts, and anaesthesia may, therefore, contribute to the pathophysiology of orthostatic intolerance.

An incidence of orthostatic hypotension of 49% and 41% after 15 and 45 min, respectively, has been reported after minor surgery. That study was, however, fundamentally different from the present, since procedures were not well-defined, fluid therapy and pain treatment were not standardized, and most importantly, patients’ cardiovascular responses were evaluated on a tilt-table and not with actual mobilization. In the present evaluation, only four (17%) experienced orthostatic hypotension upon mobilization 30 min after surgery and only in one of these patients, it translated into orthostatic intolerance. Consequently, cerebral perfusion/oxygenation is not necessarily compromised with orthostatic hypotension, since no symptoms emerged in these three patients. The main difference between evaluations on a tilt-table and actual mobilization is that mobilization activates the

Statistics

Data normally distributed are reported as mean (SD); data not normally distributed are reported by median (IQR). A mixed model ANOVA for repeated measurements was used to identify relations between normally distributed cardiovascular variables and body position (rest, sit, stand, and recovery), time of test (before vs after surgery), and their interactions. Pain scores were analysed with the Kruskal–Wallis test. In order to detect a minor difference of 10 mm Hg in SAP response when comparing mobilization before and after surgery, a sample size of 21 patients was needed with a power of 0.8 (1–β) and after surgery, a sample size of 21 patients was needed for effects of time (pre vs post), position (supine, sit, stand, recovery), and their interaction, but only the effect of position was statistically significant (P<0.05). Thus, the patient demonstrating orthostatic intolerance displayed both the lowest estimate of cerebral oxygenation during the standing period (54%) and the lowest values measured at the onset of symptoms (Fig. 1). Pain assessed by a verbal rating scale was median (IQR) 2 (1.0–3.5) during the entire mobilization procedure (P=0.99).

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Fig 1 Continuous cardiovascular variables upon mobilization 30 min after operation in the patient who presented orthostatic intolerance. Periods between positions indicate shifts. SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; ScO₂, cerebral oxygenation; SmO₂, muscle oxygenation.
Fig 2 Changes in cardiovascular variables in 24 patients during a standardized mobilization procedure, before (pre) and 30 min after (post) operation presented as mean (SD). One patient is excluded from muscle- and cerebral oxygenation, because of failure in data recording. *P<0.05, compared with supine. SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; $S_{cO_2}$, cerebral oxygenation; $S_{mO_2}$, muscle oxygenation.
muscle pump, which may attenuate the reduction in central blood volume and therefore preload and CO. Whether this may affect the lower limit of cerebral perfusion remains to be evaluated.

The stress applied during surgery may initiate a profound hormonal cascade, depending on the magnitude of the surgical injury. Because of the superficial procedure of breast cancer surgery, the stress-response may be minor compared with major procedures. Similarly, fluid shifts during surgery correspond to the size of the procedure. A reduction in the central blood volume and cardiac preload may limit CO and contribute to an increased incidence of orthostatic intolerance. The present study standardized fluid administration according to results demonstrating improvement in several functional parameters after laparoscopic cholecystectomy, since similar data on different fluid regimens in breast cancer surgery are not available. Consequently, the administered fluid volume in the present evaluation was a median 1.1 litre which also is in accordance with a review of randomized studies in minor surgery showing improved outcome with the administration of >1 litre possibly because basic fluid requirements and preoperative dehydration are covered.

General anaesthesia has an impact on baroreceptor function, and may thereby influence arterial pressure regulation and the ability for early mobilization. In the present study, one patient did not complete the mobilization procedure 30 min after operation because of sedation, but the cardiovascular response in this patient was not attenuated in the period the patient was able to stand. In contrast, the only patient experiencing orthostatic intolerance demonstrated a pronounced decrease in arterial pressure and cerebral oxygenation. However, the low frequency of orthostatic intolerance suggests that the type of anaesthesia per se provided in this study does not hinder early mobilization, indicating that the pathophysiology of postoperative orthostatic intolerance may depend on other factors. This finding may be transferred to larger surgical procedures in the effort to uncover important determinants in the pathophysiology of orthostatic intolerance.

Pain has been recognized to be an important limitation to early postoperative mobilization and, consequently, optimal treatment of postoperative pain is mandatory for an enhanced recovery. However, the use of opioids may also contribute to orthostatic intolerance, and is associated with side-effects, including nausea and vomiting, ileus, and respiration depression, that all may inhibit mobilization. In the present trial, pain was not a significant clinical problem and the use of very short-acting opioids and opioid-sparing oral pain treatment regimens may enhance early mobilization as demonstrated with a low risk of orthostatic intolerance.

The patient who experienced orthostatic intolerance after surgery displayed an altered response in cardiovascular variables and tissue oxygenation upon early mobilization (Fig. 1). The lowest cerebral oxygenation recorded in this trial was in this patient when standing at the onset of symptoms. This finding suggests that a decrease in cerebral oxygenation manifests as one of the earliest signs of orthostatic intolerance, but more observations are needed on postoperative cerebral blood flow regulation. Nevertheless, NIRS appears to be valuable to assess early cerebral hypoxia. We used NIRS to estimate tissue oxygenation and although the absolute values may be difficult to interpret, changes correlate well with several measures of cerebral oxygenation and respond equally to stimuli manipulating cerebral perfusion and oxygenation. For the diagnosis and monitoring of treatment of orthostatic pathology, Modelflow® (Finometer®) has been used, and its derived SV and CO correlate well to a thermodilution-based and inert gas rebreathing determination of SV during active and passive postural stress. This study was powered to detect a minor difference of 10 mm Hg in SAP and, therefore, we cannot exclude differences in the other measured cardiovascular variables and tissue oxygenation. However, since the orthostatic intolerance was infrequent, any differences that might be detected with a larger sample size do not appear to be of clinical relevance.

In conclusion, with this regimen of anaesthesia, analgesia, and fluid therapy, orthostatic intolerance is infrequent 30 min after breast cancer surgery, apparently because the cardiovascular response and tissue oxygenation are preserved.

Future studies assessing orthostatic intolerance should focus on larger surgical procedures with opioid-sparing pain regimens and apply interventions such as optimized fluid administration or vasopressor agents that potentially can maintain the cardiovascular response to mobilization.

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