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Local metabolic changes in subcutaneous adipose tissue during intravenous and epidural analgesia

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Background: This clinical study aimed at investigating the impact of postoperative thoracic epidural analgesia on extracellular glycerol concentration and glucose metabolism in subcutaneous adipose tissue, using the microdialysis technique. The sympathetic nervous activity, which can be attenuated by epidural anesthesia, influences lipolysis and the release of glycerol.
Methods: Fourteen patients who underwent major abdominal or thoraco-abdominal surgery were studied postoperatively over 3 days. For postoperative analgesia the patients were prospectively randomized to receive either thoracic epidural analgesia with a bupivacaine/morphine infusion (EPI-group, n=6) or a continuous i.v. infusion of morphine (MO-group, n=8). The concentration of glycerol, glucose and lactate in the abdominal and deltoid subcutaneous adipose tissue were measured using a microdialysis technique.
Results: The abdominal glycerol levels were equal in both groups. In the deltoid region of the EPI-group, glycerol concentrations started to increase on Day 2, and reached significantly higher levels on Day 3 compared with the MO-group. The glucose and lactate levels showed no differences between groups in the two regions.
Conclusion: The uniform glycerol levels in abdominal subcutaneous adipose tissue in conjunction with the difference in glycerol levels in the deltoid area indicate that the local lipolysis is different in the two study groups. This might be explained by a regional metabolic influence of thoracic epidural analgesia, possibly via the sympathetic nervous system.

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Key words: anesthesia epidural; analgesia epidural; autonomic nerve block; microdialysis; adipose tissue; postoperative period; lipolysis; glycerol; adult.

Previous studies on metabolic effects of epidural analgesia have focused on the quantifying metabolic markers in blood (1, 2) or urine (3) to represent whole body estimates. Some investigators have studied regional effects (4, 5), but little is known about the tissue's local metabolism within and outside the anesthetized area during long-term postoperative epidural anesthesia.

The microdialysis technique provides possibilities of monitoring interstitial chemical events in various tissues. It was originally developed to monitor the brain (6) and has become a standard experimental technique. The technique has recently been introduced in clinical practice (7, 8). With the microdialysis technique it is possible to monitor substances such as glycerol, glucose and lactate in various tissues under clinical conditions. The biochemical changes in the extracellular fluid adjacent to the microdialysis catheter can be estimated with short-time intervals for several days (9).

Previous investigations have shown that interstitial glycerol concentration in the subcutaneous adipose tissue may serve as a marker for the intracellular lipolytic rate (10). Subcutaneous lipolysis is activated by the sympathetic nervous system (11–13), and the activity in the sympathetic nerve fibers could be blocked within the area covered by epidural anesthesia (14, 15). Therefore, we hypothesized that epidural analgesia would attenuate the regional lipolysis within the area covered by the epidural analgesia, reflected as decreased glycerol concentrations as measured using the microdialysis technique. We expected the glycerol levels in areas not covered by the epidural analgesia to remain unaltered.

Thoracic epidural anesthesia has not been demonstrated to alter the glucose metabolism peri- or postoperatively during or after major surgery (16). However, little is known about the local glucose metabolism in subcutaneous adipose tissue during neural blockade in patients. Accordingly, we studied the energy metabolism (glucose and lactate) and our hypothesis was that epidural anesthesia would not affect extracellular glucose or lactate concentrations.

For 3 postoperative days, we studied patients after major non-cardiac surgery when either thoracic epidural analgesia or intravenous morphine was used to achieve similar postoperative pain relief. Interstitial fluid from the subcutaneous adipose tissue was analyzed for glycerol, glucose and lactate, and the microdialysis catheters were positioned inside and outside the area covered by the epidural blockade.

Materials and methods

Twenty-four patients (14 men and 10 women) admitted to the Department of Surgery for major abdominal (aortic surgery, gastrectomy, and BII-resection) and thoraco-abdominal surgery (esophagectomy) were included in the study. The Ethics Committee at Lund University Hospital approved the study. All patients were given detailed written and oral information regarding the study, and each patient gave their written consent.

The day before surgery the patients were randomized, using a closed envelope system, to receive either thoracic epidural anesthesia (EPI; n=12) or intravenous morphine (MO; n=12). In the EPI-group, five patients were excluded on Day 2 because of epidural catheter failure (n=2), atrial fibrillation requiring cardioversion, respiratory failure, and postoperative confusion, respectively. One patient was excluded on Day 3 because of protocol violation. In the MO-group, four patients were excluded: two patients were excluded perioperatively because of technical errors, one patient was excluded on Day 2 because of a surgical complication, and another patient wished to be excluded on Day 3. Thus, eight patients in the MO-group and six patients in the EPI-group participated during the study period.

Preoperatively, patients in the EPI-group had an epidural catheter inserted via a vertebral interspace between T_7 and T_{10} while under local anesthesia. In all patients general anesthesia was induced with thiopental, N_2O/O_2 and isoflurane or desflurane. The EPI-group subsequently received an epidural bolus of 6–10 ml mepivacaine (Carbocain 2%, Astra®, Sweden) followed by a continuous infusion of 5–8 $ml\,h^{-1}$ depending on age and height. Epidural morphine 3–4 mg (Morfin Special® 0.4 $mg\,ml^{-1}$, Astra, Sweden) was administered simultaneously with the bolus infusion, and repeated after 8 h if surgery continued. The MO-group received an i.v. infusion of fentanyl (2 $\mu g\,kg^{-1}h^{-1}$), which was gradually reduced and terminated at the end of surgery.

Patients in the EPI-group received an epidural infusion of bupivacaine (2.5 $mg\,ml^{-1}$) and morphine (0.05 $mg\,ml^{-1}$) before the termination of general anesthesia. The infusion rate was initially 3–5 $ml\,h^{-1}$ depending on age and height. The MO-group received an intravenous infusion of morphine (1 $mg\,ml^{-1}$) at 1–3 $mg\,h^{-1}$ with a patient-controlled analgesia option of 1 mg with a lockout interval of 10 min. For all patients the analgesic agents dosage was adjusted during the study to score a visual analog scale (VAS 0–10) of below four. All patients received paracetamol 1 g×4 rectally four times daily during the study.

The patients spent the first postoperative night in a postoperative care unit, and the amount of analgesics administered was continuously adjusted to individual demands. On the first postoperative day all the patients returned to the surgical ward. The efficacy of the analgesia was continuously checked via VAS scoring. During the 3-day study period the patients were monitored by the attending ward nurse who regarded the VAS at rest and during mobilization. The pain score and the dose of analgesics were evaluated daily by an anesthesiologist. Two liters of glucose 100 $mg\,ml^{-1}$ were given each day for nutritional needs. One liter was started at 09:00 and the next at approximately 16:00. In addition, one patient in the EPI-group started oral nutrition on day one and one patient in the MO-group on day two. All patients were encouraged to mobilize as early as possible with the help of a physiotherapist.

Microdialysis

After the induction of the general anesthesia two microdialysis catheters (CMA 60®, CMA, Solna, Sweden; membrane length 30 mm with a molecular cut-off at 20 kDa) were inserted into the subcutaneous adipose tissue. One catheter was placed on the left side of the abdominal wall in the region representing the T_{10} dermatome, approximately 10–12 cm from the midline. The second catheter was inserted into the adipose tissue in the deltoid area of the left arm. Each catheter was connected to a microdialysis pump (CMA 106®, CMA, Solna, Sweden) and perfused with Ringer's solution at 0.3 $\mu l\,min^{-1}$. Capped microvials (Microvials, prod. no P000001, CMA, CMA, Solna, Sweden) containing the dialysate were exchanged hourly from 06:00 to 21:00 throughout the study period starting on the first postoperative day at 06:00. They were stored at −18°C for later biochemical analyses (glucose, lactate, and glycerol) with enzymatic techniques (CMA 600®, CMA, Solna, Sweden). The concentration of a compound obtained by microdialysis is influenced by various technical factors. The

Table 1

Postoperative pain scores at rest and during mobilization.

		VAS Day 1	Day 2	Day 3
EPI-group	Rest	2.3±0.3	1.6±0.3	2.2±0.6
	Mobilization	5.1±0.6	3.2±0.5	3.9±0.6
MO-group	Rest	1.8±0.4*	0.8±0.2*	0.7±0.2*
	Mobilization	3.8±0.5	4.0±0.5	3.4±0.5

Postoperative pain scoring according to the visual analog scale (VAS; 0–10 cm), mean±SEM, measured daily at rest and during mobilization in the postoperative patients with thoracic epidural analgesia (EPI) or intravenous morphine (MO).
*Significantly lower ($P<0.05$) VAS values at rest in the MO-group compared with the EPI-group.
There were no differences between the groups during mobilization.

relative recovery of extracellular substances with the microdialysis technique represents the concentration in the outgoing dialysate divided by the true concentration in the extracellular space×100 (17). With the microdialysis membrane used in the present study and a perfusion rate of 0.3 μl min^{-1} the relative recovery for glycerol is almost 100%, for lactate 100%, and for glucose 79–90% (18).

Statistical methods

For statistical comparisons between the groups the daily area under the curve (AUC) was calculated for glucose, lactate and glycerol levels. Analysis of variance (ANOVA) was performed, and thereafter Student's unpaired and paired *t*-tests were used for specific comparisons if the ANOVA indicated a difference between or within the groups. Visual analog scale data are presented as mean±SEM.

Results

There were no differences between the groups regarding gender, age, weight, or height. The distribution of surgical procedures, duration of surgery and intraoperative blood loss did not differ between the groups. The amount of glucose given per patient day^{-1} did not differ between the groups during the 3 postoperative days. The mean VAS scores at rest were below four during the whole study period in both groups (Table 1) in accordance with the intentions in the study protocol. However, the VAS scores at rest were lower in the MO-group ($P<0.05$). The mean dose of bupivacaine 2.5 mg ml^{-1} and morphine 0.05 mg ml^{-1} given epidurally was 4.7±0.14 ml h^{-1} (mean±SEM), 4.2±0.12 ml h^{-1}, and 3.8±0.12 ml h^{-1} on the first, second, and third postoperative day, respectively. On the first postoperative day, two patients in the EPI-group received one dose each of 2.0 and 2.5 mg IV ketobemidone, respectively. Thereafter no parenteral opioids were given to patients in the EPI-group. The mean dose of IV morphine in the MO group was 2.0±0.11 mg h^{-1}, 1.5±0.10 mg h^{-1}, and 1.4±0.15 mg h^{-1} on the first, second, and third postoperative day, respectively.

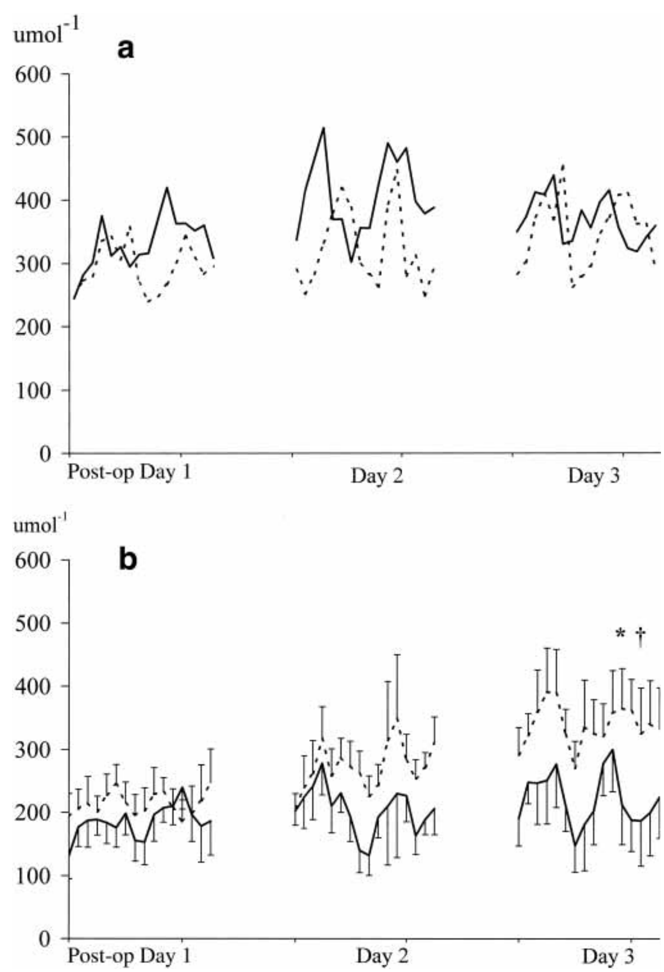

*Fig. 1. Hourly concentrations from 06:00–21:00 of glycerol measured with microdialysis in the abdominal (a) and the deltoid (b) subcutaneous adipose tissue for 3 postoperative days after major non-cardiac surgery in the thoracic epidural analgesia group (EPI-group, broken line) and the intravenous morphine group (MO-group, solid line). EPI- vs. MO-group on postoperative Day 3, *P<0.05. Postoperative Day 3 vs. Day 1 in the EPI-group, †P<0.05.*

Table 2

Max.–min. area under the curve per hour of glycerol in subcutaneous adipose tissue.

	Deltoid EPI	MO	Abdominal EPI	MO
Day 1	112–312	83–289	141–423	187–518
Day 2	151–388	129–271	101–512	220–574
Day 3	151–501	107–325	114–635	235–574

Max.–min. values for glycerol area under the curve per hour (μmol l^{-1} h) measured with microdialysis in the abdominal and the deltoid subcutaneous adipose tissue for 3 postoperative days in the patients treated with either thoracic epidural analgesia (EPI) or intravenous morphine infusion (MO).

Figure 1 shows the abdominal and deltoid subcutaneous glycerol concentrations in the EPI- and MO-group. In the abdominal region there was no significant difference between the EPI- and MO-groups during any of the 3 study days. In the deltoid region the glycerol concentration was similar in both groups on Day 1. On Day 2 the levels in the EPI-group started to increase, and on Day 3 there was a significant difference ($P<0.05$) between the groups with higher deltoid glycerol levels in the EPI-group compared with the MO-group (Fig. 1b). The glycerol levels in the deltoid region within the EPI-group were also significantly higher on Day 3 than on Day 1 ($P<0.05$). The max.–min. values regarding glycerol AUC h^{-1} are presented by groups, sites and days in Table 2.

There were no significant differences between the MO- and EPI-groups regarding the glucose concentrations in subcutaneous adipose tissue neither in the abdominal region nor in the deltoid region (Fig. 2). During the study period the interstitial mean glucose values ranged between 5.2 and 11.0 mmol l^{-1} in the MO-group and between 5.1 and 11.6 mmol l^{-1} in the EPI-group. A difference in the daily variations in glucose concentration was observed between Day 1 and the following 2 days. Glucose levels remained almost constant on the first postoperative day, and were low in the morning with a nadir of approximately 5 mmol l^{-1} at 08:00–09:00 on Day 2 and 3. Thereafter, a steep increase in glucose concentration reached a peak value of approximately 10 mmol l^{-1} in the afternoon. This pattern was similar between the groups and also between the studied regions.

There were no significant differences between the MO- and EPI-groups regarding the lactate concentration in the subcutaneous adipose tissue (Fig. 3). The mean lactate levels ranged between 1.1 and 3.2 mmol l^{-1} in the MO-group and between 1.2 and 3.2 mmol l^{-1} in the EPI-group.

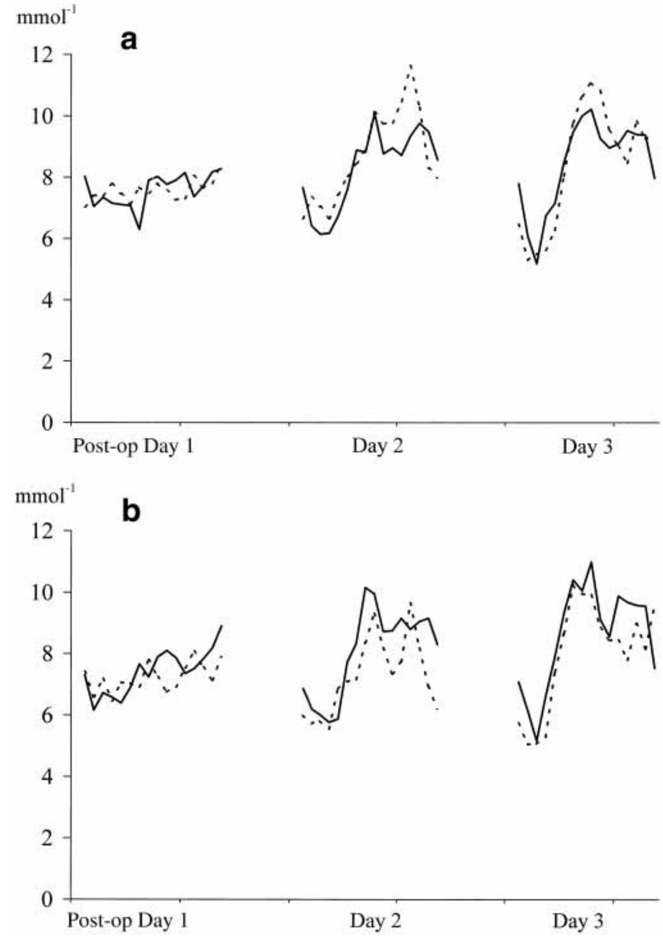

Fig. 2. Hourly concentrations from 06:00–21:00 of glucose measured with microdialysis in the abdominal (a) and the deltoid (b) subcutaneous adipose tissue for 3 postoperative days after major non-cardiac surgery in the thoracic epidural analgesia group (EPI-group, broken line) and the intravenous morphine group (MO-group, solid line).

Discussion

The main observation in the present study was the uniform glycerol levels in the abdominal subcutaneous adipose tissue together with the difference in the glycerol levels in the deltoid area for patients treated with postoperative epidural and intravenous analgesia.

These observations indicate that regional lipolysis differs according to the postoperative analgesic regimen, but the results should be interpreted with caution. An increased concentration of a compound in the interstitial fluid might depend on several factors, e.g. increased transport from the cells or from the blood, or a decreased uptake by the cells or a decreased clearance via the blood. It might also be a result of changes in the relative recovery of the compound.

The relative recovery for glycerol was nearly 100% using the present microdialysis technique (18). As we did not determine the relative recovery in this study there is the possibility of variation in this parameter, and hence microdialysis is only semiquantitative. If a change in relative recovery should occur over time, a decrease would be the most logical development resulting from, e.g. a tissue reaction around the membrane (19), causing a decrease in glycerol over time at a constant extracellular concentration.

Regional differences in glycerol concentration can occur (20), but there are no previous studies on glycerol comparing the subcutaneous adipose tissue in the deltoid and abdominal regions. In resting healthy volunteers the abdominal tissue glycerol concentration ranges from 185 to 350 μM (18). In the present study a considerable variation was obtained with values mainly in the upper normal range or above. As normal values for glycerol concentrations in the deltoid region are not available, we do not know if the MO-group or the EPI-group in our study represents the normal physiologic concentrations. We can only conclude that there is a difference, and that we should compare the concentrations in the corresponding sites between the groups and not the deltoid vs. the abdominal concentrations between or within the groups. Microdialysis glycerol values from subcutaneous adipose tissue should not be compared to mixed venous glycerol levels because the plasma glycerol concentration represents a whole-body mean value. However, the obtained plasma level is a regional value, the more peripherally the sample is drawn, as demonstrated by Landau *et al*. (21). They found that the plasma glycerol concentration in a superficial forearm vein was 140% of the arterial concentration, which was interpreted as a regional glycerol release from the subcutaneous adipose tissue.

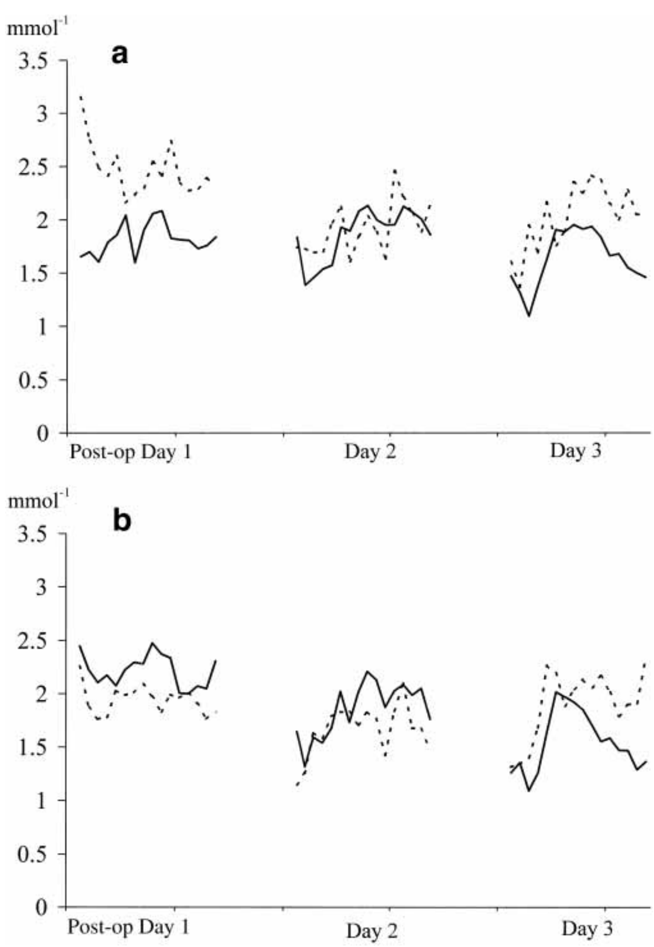

Fig. 3. Hourly concentrations from 06:00–21:00 of lactate measured with microdialysis in the abdominal (a) and the deltoid (b) subcutaneous adipose tissue for 3 postoperative days after major non-cardiac surgery in the thoracic epidural analgesia group (EPI-group, broken line) and the intravenous morphine group (MO-group, solid line).

Variations in local blood flow around the microdialysis membrane may influence the metabolite levels obtained. For a substance produced in the tissue, such as glycerol, an increase in local blood flow will increase the transport away from the adipose tissue and decrease the extracellular concentration during constant lipolysis (22), and vice versa. Also, the extracellular glucose concentration is partly dependent on local blood flow (23), but in the opposite way, as glucose is mainly transported to the adipose tissue. If the higher deltoid glycerol levels in the EPI-group were a result of an altered local blood flow, a lower deltoid blood flow (lower glycerol clearance from the adipose tissue) in the EPI-group than in the MO-group would be the cause. If so, a lower deltoid glucose level in the EPI-group would have been logical. Although less likely, the role of a decreased local blood flow as a cause for the increased deltoid glycerol levels in the EPI-group cannot be ruled out.

The metabolism of glycerol is closely related to glucose metabolism via α-glycerophosphate and dihydroxyacetone phosphate. Theoretically, an alteration in the glucose metabolism could result in a decreased consumption of glycerol, resulting in increased intracellular glycerol concentrations, and thus increased concentrations in the extracellular compartment. Alternatively, increased synthesis of glycerol from the glucose metabolism could occur. To what degree glucose metabolism affects intracellular glycerol concentrations in subcutaneous adipose tissue is difficult to estimate. But, as postoperative patients have an increased lipolysis (24), it seems unlikely that carbohydrate metabolism is the major cause of the increased deltoid glycerol concentration in the EPI-group.

The most probable cause of the increased deltoid glycerol levels in the EPI-group is, in our view, lipolysis. The reason for an increased lipolysis remains speculative, but it is known that lipolysis is stimulated by sympathetic nervous activity (11–13). A parallel change in plasma catecholamines and interstitial glycerol levels has also been demonstrated during surgery (25). The lipolysis rate is accelerated during general anesthesia and abdominal surgery because of increased catecholamine production (26). Lumbar, but not thoracic, epidural anesthesia, is demonstrated to decrease whole body lipolysis in lower, but not upper, abdominal surgery, probably because of insufficient afferent sympathetic blockade during thoracic epidural anesthesia (16, 27, 28). Therefore, we would not anticipate any difference in whole body lipolysis between the groups in our study.

When local anesthetics are administered epidurally there is an attenuation of the sympathetic activity in the anesthetized area. This has been demonstrated by Lundin *et al*. in humans, where a total blockade of sympathetic nerve activity in the skin and muscle of the leg could be obtained during lumbar epidural anesthesia (14, 15). Postoperative analgesia with a thoracic epidural technique aims at a low dose of local anesthetics epidurally to avoid systemic effects, e.g. orthostatic hypotension. Accordingly, the attenuation of the sympathetic tone in the area covered by the epidural analgesia is most likely less profound than in Lundin's studies. Besides, thoracic epidural anesthesia gives a different regional attenuation of the sympathetic activity, allowing unaffected sympathetic impulses to the legs (29). We have not found any study of sympathetic activity cranial to epidural segments (e.g. deltoid area) during a postoperative period. Taken together, we expected a low attenuation of the sympathetic activity within the area covered by the thoracic epidural analgesia and no influence outside this area.

We did not measure the extent of epidural anesthesia in our study. A VAS score below four and a patient satisfied with the analgesia were our endpoints. We have earlier examined the extension of the epidural anesthesia (30, 31) in the same type of patients and found a constant level of epidural anesthesia for several days. The same bupivacaine concentration was used but the morphine content was higher ($0.125\,mg\,ml^{-1}$ vs. 0,05 $mg\,ml^{-1}$) than in the present study. This does not guarantee a stable sensory blockade in our study, but taken together with satisfying pain relief, it increases the probability of a stable neural blockade.

Unexpectedly, the patients in the MO-group had lower VAS scores at rest than those in the EPI-group, which might be an effect of a small size study population. In another study performed at our department 1670 patients received a postoperative epidural and 1026 patients an intravenous morphine analgesia in a similar way to the present study (Flisberg *et al*. unpublished observation). The EPI-group had overall lower VAS scores, except on the fourth postoperative day. Also, it could be debated if the statistically significant difference in the present study is clinically relevant because the VAS scores at rest in both groups were low.

In contrast to our hypothesis, we found similar abdominal glycerol levels in the groups but higher deltoid glycerol concentrations in the EPI-group compared with the MO-group. With our study design we can only speculate about the explanations. Our main theory is that the increased deltoid glycerol levels in the EPI-group reflect an increased lipolysis, which, in turn, is a result of an increased deltoid sympathetic activity. The reason for similar abdominal sympathetic activity in the groups but higher deltoid sympathetic activity in the EPI-group might be a regional attenuation of the sympathetic activity within, but not outside, the anesthetized area. Several possible explanations for an increased sympathetic activity in the EPI-group exist; for example the difference in VAS score does reflect a higher level of pain in the EPI-group, which increases the sympathetic activity (32), or a different degree of mobilization between the groups (33, 34). Another hypothetical explanation might be a compensatory increased sympathetic excitation of unblocked segments, as demonstrated by Taniguchi *et al*. (35). The same phenomenon might have a parallel in compensatory sweating in other locations after sympathectomy for palmar hyperhidrosis (36). The difference in deltoid glycerol levels appeared on day three only. Obviously, there is a time factor of importance involved and the microdialysis technique is well suited to this type of long-term study.

Conclusion

As evaluated with the microdialysis of the subcutaneous adipose tissue, local glycerol concentrations, but not glucose and lactate, were altered by the postoperative epidural analgesia, but not until the third postoperative day. We interpret the increased deltoid glycerol concentration as an increased local lipolysis, and speculate that an increased lipolysis is the result of increased sympathetic activity.

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