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Intraoperative thoracic epidural anaesthesia attenuates stress-induced immunosuppression in patients undergoing major abdominal surgery†

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Background. Intraoperative stress may suppress the adaptive immune system. Abolished proinflammatory lymphocyte function is associated with higher risk of infection and postoperative complications. We hypothesized that thoracic epidural anaesthesia (TEA) reduces intraoperative stress and thus attenuates lymphocyte decrease and impairment of proinflammatory lymphocyte function.

Methods. Fifty-four patients undergoing major abdominal surgery who had a thoracic epidural catheter inserted were studied. In the TEA-I group, this catheter was used for intraoperative analgesia, whereas the TEA-P group received systemic opioids during surgery. In both groups, patient-controlled epidural analgesia was used for postoperative pain management. Blood samples for immune analyses were obtained before induction of anaesthesia, 2 h after skin incision, and at days 1 and 4 after surgery. Lymphocyte subpopulations, expression of human leucocyte antigen (HLA)-DR on monocytes, plasma concentrations of interleukin (IL)-10, interferon-γ (IFN-γ), and IL-12, and concanavalin-A-stimulated concentrations of IFN-γ and IL-10 were measured. Intraoperative data including bispectral index and plasma concentrations of epinephrine/cortisol were analysed; APACHE-II, SAPS II, and additional postoperative data were documented.

Results. Plasma concentrations of epinephrine and cortisol were significantly lower in the TEA-I patients during surgery. IFN-γ/IL-10 ratio was significantly higher in the TEA-I group from 2 h after skin incision until day 1. Lymphocyte numbers and T-helper cells were significantly higher in the TEA-I group at day 1, whereas no significant differences were detected among IL-12, HLA-DR, and postoperative clinical course.

Conclusions. Intraoperative use of thoracic epidural catheter reduced stress response and prevented stress-induced perioperative impairment of proinflammatory lymphocyte function.

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Major surgery and associated acute stress response cause extensive immunological changes.[1–3] Stress hormones epinephrine and cortisol play a key role in stress-induced suppression of the adaptive (acquired) immune system.[4 5] Attenuation of stress response by postoperative epidural anaesthesia (EA) has shown beneficial effects such as lower pain scores and less immunological alterations.[6–9]

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Therefore, additional reduction of perioperative stress by combined general anaesthesia and EA during surgery may lead to further beneficial effects.

Some recently published trials investigated the effects of intraoperative use of additional EA on cytokines of the innate immune system and on circulating lymphocyte subpopulations.[10–14] To the best of our knowledge, proinflammatory lymphocyte function, playing a crucial role in immune defence,[15–17] has not been evaluated in this context so far. In addition, lymphocyte subpopulations and human leucocyte antigen (HLA)-DR expression on monocytes have been monitored only after operation, but not intraoperatively.

The aim of this randomized, controlled pilot trial was to examine the effects of additional intraoperative thoracic EA on the release of stress hormones, HLA-DR expression on monocytes, circulating lymphocyte subpopulations, and associated pro- (interferon-γ/IFN-γ, interleukin-12/IL-12) and anti-inflammatory (IL-10) cytokines during surgery, and in the early postoperative phase.

Methods

The study was approved by the local institutional ethics committee, and it has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all patients.

Sixty adult patients, ASA I–II, undergoing major abdominal surgery, were enrolled. Exclusion criteria were contraindications for receiving EA, pre-existing cardiovascular diseases, preoperative treatment with opioids, non-steroidal anti-inflammatory drugs, or other immunomodulatory substances.

All patients received midazolam 7.5 mg orally 1 h before surgery. Before induction of anaesthesia, an epidural catheter was inserted between segments Th7/8 and Th12/L1 (depending on the surgical procedure) using the midline approach and loss-of-resistance technique. General anaesthesia was induced by thiopental 3–5 mg kg^{-1} and fentanyl 1.5–2.0 μg kg^{-1}. Cisatracurium 0.1–0.2 mg kg^{-1} or succinylcholine 1.0–1.5 mg kg^{-1} was given to facilitate orotracheal intubation.

Patients were then assigned to two groups by closed-envelope randomization. In both groups, anaesthesia was maintained with isoflurane in oxygen/air mixture. Patients were normoventilated, depth of anaesthesia was controlled by Bispectral Index (BIS, Aspect Medical Systems, Natick, MA, USA), and isoflurane concentration was adjusted to keep BIS between 40 and 50.

Group 1 (TEA-I) received additional intraoperative thoracic EA (TEA). Thirty minutes before skin incision, sufentanil 1 μg ml^{-1} in ropivacaine 0.2% was administered epidurally as a bolus of 8 ml, followed by continuous infusion of 6 ml h^{-1}. If analgesia seemed to be insufficient by clinical signs, a second bolus of 6 ml was given. In the case of persisting clinical signs for insufficient analgesia, patients were excluded from the study and received fentanyl i.v. to ensure appropriate analgesia.

Group 2 (TEA-P) received isoflurane–fentanyl anaesthesia. Fentanyl 4–6 μg kg^{-1} i.v. was injected 20 min before skin incision. Insufficient intraoperative analgesia, measured by clinical signs, was treated by additional application of fentanyl at the discretion of the anaesthetist. At the beginning of peritoneal closure, 8 ml of ropivacaine/sufentanil solution (see above) was injected as bolus into the epidural catheter, followed by continuous infusion of 6 ml h^{-1}.

Both groups received patient-controlled EA (PCEA) for postoperative pain therapy (starting with basal rate of 6 ml h^{-1}, patient-controlled bolus 4 ml, maximum number of bolus requests 3 h^{-1}) and were cared for by a dedicated 24 h Acute Pain Service. Basal rate and bolus dose were adjusted according to pain, as measured by visual analogue scale. In the case of no longer need for EA treatment, the catheter was removed—as it was in the case of suspected dislocation—and the following measurements were not performed.

Duration of surgery, concentration of end-expiratory isoflurane/BIS values/heart rates (at skin incision and 40 min after surgery), postoperative clinical data including PCEA details until day 1, APACHE-II score[18] (first 24 h at ICU), and SAPS-II score[19] (daily until one group consisted of less than five ICU patients) were documented.

Blood was drawn at baseline [before placement of epidural catheter, measurement (M) 1], 2 h after skin incision (M2, 'surgery'), and at postoperative days 1 (M3) and 4 (M4). Samples for stress hormone measurements were obtained at baseline (M1) and 40 min after skin incision (M5). Numbers of leucocytes were counted by Cell-Dyn 1600 cell counter (Abbot Diagnostics, Abbot Park, IL, USA). Samples were processed according to manufacturer's instructions for flow cytometry analyses and cell surface fluorescence was measured in a FACScan cytometer (Becton Dickinson, San Jose, CA, USA). White blood cell differential blood count was analysed by CD14 and CD45 pattern. Lymphocyte subpopulations were defined as follows. T-helper (T4) cells=positive for CD3 and positive for CD4 ($CD3^+CD4^+$), T-suppressor (T8) cells=$CD3^+CD8^+$, natural killer (NK) cells=$CD3^-CD16/56^+$, γδ-T-cells =$CD3^+TCR\gamma\delta^+$ (all antibodies from Becton Dickinson).

Blood was incubated (37°C, 5% CO_2) in RPMI 1640 plus Concanavalin-A (Con-A, both from Sigma-Aldrich, St Louis, MO, USA) 24 h for *in vitro* lymphocyte stimulation. In addition, blood was centrifuged immediately after withdrawing for measurement of *in vivo* plasma concentrations. The centrifuged supernatant was frozen until further processing. IL-10, IFN-γ, and IL-12 were analysed by enzyme-linked immunosorbent assays according to manufacturer's instructions (Pharmingen, San Diego, CA, USA) at a MR5000 photometer (Dynatech, Billingshurst, UK).

Stress hormone analyses: blood samples were centrifuged and stored frozen until further processing.

Plasma cortisol was measured with radio immunoassays (Diagnostic Products Corporation, Los Angeles, CA, USA), epinephrine was measured by a single isotope derivate method and high pressure liquid chromatography (Chromsystems, Munich, Germany).

Data were processed using the 'Statistical Package for the Social Sciences', Version 14.0 (SPSS Inc., Chicago, IL, USA). Absolute numbers of lymphocytes and lymphocyte subpopulations were derived from leucocyte counts and the per cent distribution measured by flow cytometry. Stimulated cytokines were standardized for 1000 lymphocytes and IFN-γ/IL-10 ratio was calculated. Immunological data (M2–M4) were adjusted for M1 and logarithmized because of asymmetric distribution. Intraoperative and early postoperative immunological data (M1–M3) were then analysed by general linear model (GLM) for repeated measurements. *Post hoc* analyses of M1–M3 and immunological differences at M4, concentration of stress hormones at M5, and other interval scaled data were performed by unpaired Student's *t*-test. Mann–Whitney test (corrected for repeated measurements) was used to compare ordinal scaled data; Fisher's exact test was used for analyses of nominal scaled data. A *P*-value of <0.05 was considered significant.

Results

Three patients in each group were excluded because of problems during catheter placement ($n=5$) or suspected catheter dislocation during surgery ($n=1$). Thus, each group consisted of 27 patients, respectively. Seven patients in the TEA-I group (three at day 1, one at days 2 and 3, respectively, and two at day 4) and five patients in the TEA-P group (two at day 1, one at day 2, and two at day 3) had to quit the trial ahead of schedule because of removed catheters (no significant difference between the groups).

No significant differences were found concerning sex, age, height, weight, potential immunosuppressive concomitant diseases (alcohol abuse and diabetes mellitus), type, and duration of surgery (Table 1).

Intraoperative BIS values, concentration of end-expiratory isoflurane and heart rates, length of stay (LOS) on ICU, hospital LOS, readmission to ICU or redo-surgery, survival rates, PCEA consumption/pain scores during first 24 h after surgery, APACHE-II scores, SAPS-II scores at postoperative days 1–3, and rate of postoperative infections were also not significantly different (Table 2).

Forty minutes after skin incision, an increase in cortisol ($P=0.016$) and epinephrine ($P=0.036$) was significantly attenuated in the TEA-I group (Fig. 1).

In the TEA-I group, significantly higher con-A-stimulated IFN-γ/IL-10 ratio was found in GLM ($P=0.017$), in *post hoc* analyses 2 h after incision ($P=0.009$) and on day 1 ($P=0.01$). This effect was mainly a result of a significant decrease of IFN-γ in TEA-P (GLM: $P=0.003$), but not of differences of IL-10 release (Fig. 2). Standardization to 1000 lymphocytes also revealed significant differences in concentration of IFN-γ in GLM ($P=0.01$), *post hoc* analyses failed to reach level of significance at single measurements (surgery: $P=0.051$, day 1: $P=0.057$, Table 3).

Plasma (*in vivo*) IFN-γ/IL-10 ratio was also significantly higher in the TEA-I group during surgery ($P=0.01$). In contrast to stimulated cytokine analyses, this effect was a result of significantly higher concentration of IL-10 in the TEA-P patients (GLM: $P=0.012$, surgery: $P=0.056$). HLA-DR expression and plasma concentration of IL-12 decreased in all patients without significant differences between the groups (Table 3).

Number of circulating total lymphocytes and number of nearly all subpopulations (except increasing NK cell numbers in the TEA-P group during surgery) decreased in both groups without significant differences in GLM. *Post hoc* analyses revealed significantly lower numbers of T4 cells in the TEA-P group at day 1 ($P=0.036$, Table 4).

Table 1 Patient characteristics. Height and weight are presented as mean (SD), age is presented as mean (range); TEA-I, intraoperative and postoperative TEA; TEA-P, only postoperative TEA

	TEA-I	TEA-P
Age (yr)	55 (34–77)	59 (29–80)
Sex (male/female)	16/11	18/9
Height (cm)	172 (7)	171 (8)
Weight (kg)	69 (14)	71 (12)
Concomitant diseases		
Alcohol abuse (*n*)	5	4
Diabetes mellitus (*n*)	2	5
Type of surgery		
Gastrectomy (*n*)	7	3
Resection of colon (*n*)	5	4
Rectal resection (*n*)	4	5
Pancreatectomy (*n*)	6	10
Others (*n*)	5	5

Table 2 Intra- and postoperative clinical data. Data are presented as median (IQR); BIS, bispectral index; HR, heart rate; 24 h, first 24 h after surgery; VAS, visual analogue scale; PCEA, patient-controlled epidural analgesia; ICU, intensive care unit; *n*, number of patients; TEA-I, intraoperative and postoperative TEA; TEA-P, only postoperative TEA

	TEA-I	TEA-P
Surgery (min)	228 (135, 267)	236 (145, 302)
BIS (at incision)	44 (36, 58)	42 (39, 48)
BIS (40 min)	43 (36, 50)	45 (42, 49)
Isoflurane (incision) (%)	0.8 (0.6, 0.9)	0.7 (0.6, 0.8)
Isoflurane (40 min) (%)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)
HR (incision) (beats min^{-1})	72 (63, 96)	63 (57, 75)
HR (40 min) (beats min^{-1})	84 (72, 93)	79 (71, 84)
24 h max pain (VAS)	20 (10, 30)	20 (0, 30)
24 h PCEA (ml)	130 (106, 149)	143 (104, 163)
APACHE II score	8 (5, 11)	7 (6, 9)
SAPS II score day 1	14 (8, 27)	17 (9, 23)
SAPS II score day 2	16 (12, 24)	19 (12, 24)
SAPS II score day 3	19 (8, 28)	19 (15, 25)
ICU re-admission (*n*)	5	3
Redo-surgery (*n*)	3	2
Infections (*n*)	3	2
Days on ICU	2 (2, 6)	2 (2, 3)
Hospital days	14 (10, 18)	13 (11, 18)
Survivors (*n*)	25	26

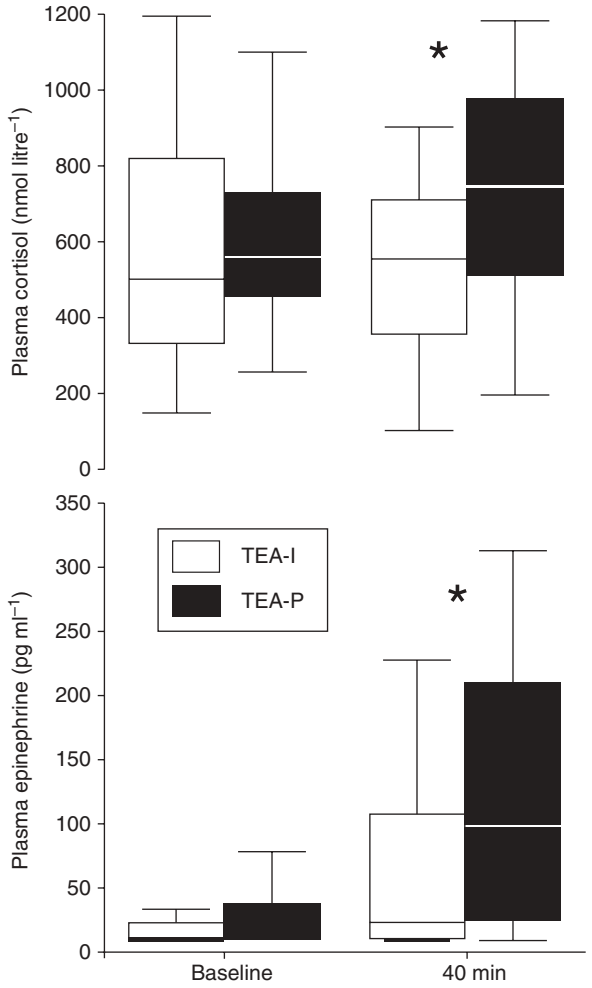

Fig 1 Plasma concentration of epinephrine and cortisol at baseline and 40 min after skin incision; data are presented as box plots (median with quartiles); TEA-I, intraoperative and postoperative TEA; TEA-P, only postoperative TEA. *Significant differences between the treatment groups.

Numbers of total lymphocytes (P=0.097, Table 4), T8- (P=0.098), and γδ-T-cells (P=0.087) were also slightly lower in the TEA-P group at day 1, but failed to reach the level of significance (data not shown). Analyses of lymphocyte fractions revealed significantly increased percentages of NK cells in the TEA-P group during surgery (P=0.009, Table 4).

Discussion

It is well established that the normal response to stress is immunosuppressive, which is on the first glance protective, but can be harmful in the perioperative setting if prolonged and severe.[1] Therefore, reduction of perioperative stress is one of the most important goals for patient care. The presented data show that additional intraoperative use of TEA reduces plasma concentrations of stress hormones

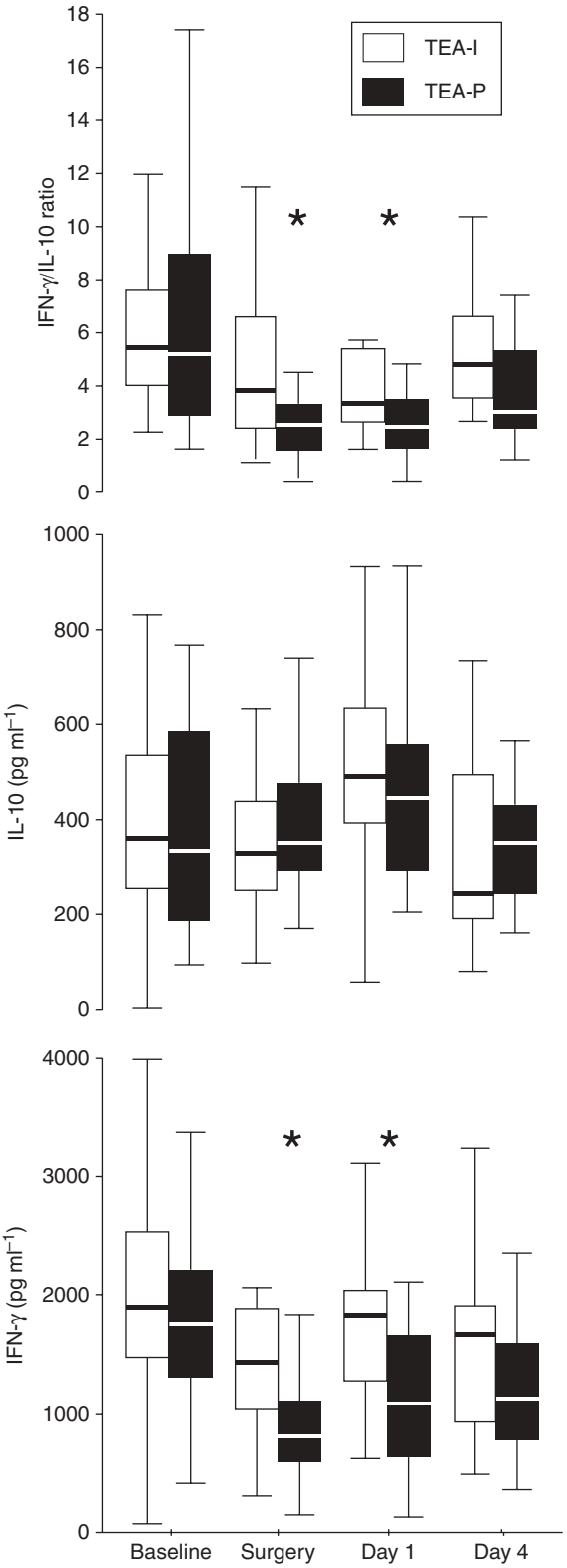

Fig 2 Concanavalin-A-stimulated concentration of IFN-γ and IL-10 and ratio of both values at baseline, during surgery, at postoperative days 1 and 4; data are presented as box plots (median with quartiles); TEA-I, intraoperative and postoperative TEA; TEA-P, only postoperative TEA. *Significant differences between the treatment groups.

Table 3 Con-A-stimulated cytokines (standardized for 1000 lymphocytes), HLA-DR expression on monocytes and *in vivo* plasma cytokines. Data are presented as median (IQR); Con-A, concanavalin-A; IFN-γ, interferon-γ; IL-10, interleukin-10; HLA-DR, human leucocyte antigen-DR; IL-12, interleukin-12; TEA-I, intraoperative and postoperative TEA; TEA-P, only postoperative TEA. $^{**}P<0.05$ in GLM, $^{*}P<0.05$ in *post hoc* analysis, $^{\dagger}P<0.06$ in *post hoc* analysis

	TEA-I				TEA-P			
	Baseline	**Surgery**	**Day 1**	**Day 4**	**Baseline**	**Surgery**	**Day 1**	**Day 4**
IFN-γ Con-A (pg 1000 cells^{-1})**	1.4 (0.9, 2.2)	1.3† (1.0, 1.9)	1.7† (1.3, 2.5)	1.5 (1.3, 3.0)	1.4 (1.0, 2.3)	0.9† (0.6, 1.3)	1.4† (0.7, 2.1)	1.6 (1.0, 2.6)
IL-10 Con-A (pg 1000 cells^{-1})	0.3 (0.2, 0.4)	0.4 (0.2, 0.5)	0.4 (0.3, 1.0)	0.3 (0.2, 0.9)	0.3 (0.2, 0.5)	0.4 (0.3, 0.5)	0.6 (0.4, 1.0)	0.5 (0.4, 0.9)
HLA-DR on monocytes (mean)	405 (329, 644)	147 (94, 244)	95 (42, 141)	141 (83, 194)	482 (256, 648)	168 (103, 303)	110 (67, 161)	134 (75, 221)
IL-12 (plasma) (pg ml^{-1})	302 (185, 486)	291 (154, 391)	207 (133, 470)	234 (153, 430)	292 (200, 421)	233 (162, 384)	180 (116, 308)	169 (128, 281)
IFN-γ (plasma) (pg ml^{-1})	32 (19, 42)	27 (14, 36)	24 (14, 39)	26 (19, 44)	22 (15, 38)	18 (9, 34)	19 (10, 29)	21 (15, 27)
IL-10 (plasma) (pg ml^{-1})**	12.5 (3.9, 18.9)	11.5† (3.9, 21.6)	15.3 (4.9, 20.7)	15.7 (8.5, 27.0)	3.9 (3.9, 18.4)	15.4† (9.6, 30.6)	10.7 (3.9, 15.7)	9.3 (3.9, 20.2)
IFN-γ/IL-10 ratio (plasma)	2.7 (1.7, 4.2)	2.2* (1.2, 3.8)	1.6 (0.9, 4.5)	2.0 (1.2, 5.1)	3.5 (1.3, 5.4)	1.1* (0.5, 1.7)	2.5 (1.0, 4.3)	2.9 (1.7, 4.7)

Table 4 Lymphoctes per nanolitre and lymphocyte subpopulations. Data are presented as median (IQR); TEA-I, intraoperative and postoperative TEA; TEA-P, only postoperative TEA. $^{*}P<0.05$ in *post hoc* analysis

	TEA-I				TEA-P			
	Baseline	**Surgery**	**Day 1**	**Day 4**	**Baseline**	**Surgery**	**Day 1**	**Day 4**
Total lymphocytes (1 nl^{-1})	1.2 (1.1, 1.6)	1.0 (0.8, 1.3)	1.0 (0.6, 1.5)	0.7 (0.5, 1.3)	1.3 (0.8, 1.5)	0.9 (0.7, 1.2)	0.8 (0.5, 0.9)	0.7 (0.5, 1.1)
T4-lymphocytes (1 nl^{-1})	0.6 (0.4, 0.9)	0.5 (0.3, 0.7)	0.4* (0.3, 0.7)	0.3 (0.2, 0.6)	0.6 (0.3, 0.7)	0.4 (0.3, 0.6)	0.3* (0.2, 0.4)	0.4 (0.2, 0.5)
T4-lymphocytes (% of lymphocytes)	45 (37, 57)	47 (41, 56)	44 (38, 50)	44 (36, 56)	46 (30, 53)	43 (37, 50)	41 (33, 50)	47 (38, 55)
T8-lymphocytes (% of lymphocytes)	22 (18, 29)	21 (16, 25)	26 (19, 32)	21 (16, 27)	25 (18, 29)	23 (18, 32)	23 (16, 30)	23 (15, 27)
γδ-T-lymphocytes (% of lymphocytes)	2.2 (1.4, 3.9)	1.5 (1.0, 3.1)	2.5 (1.5, 3.8)	2.0 (1.0, 2.6)	2.4 (1.1, 4.5)	1.9 (0.8, 5.2)	1.8 (0.8, 3.7)	1.6 (0.7, 3.2)
Natural killer cells (% of lymphocytes)	13 (6, 18)	14* (9, 19)	11 (8, 15)	11 (7, 13)	12 (9, 18)	18* (13, 25)	13 (9, 20)	10 (5, 14)
T4/T8 ratio	2.2 (1.5, 3.1)	2.4 (1.7, 3.3)	1.9 (1.4, 2.5)	2.5 (1.3, 3.2)	1.8 (1.3, 3.2)	1.6 (1.2, 2.9)	1.7 (1.0, 3.4)	2.1 (1.5, 3.7)

epinephrine and cortisol. Moreover, intraoperative TEA resulted in altered innate and adaptive immune responses, characterized by less depressed T4 cell numbers, maintained capacity of T-cells to produce IFN-γ, lower circulating plasma concentration of IL-10, higher ratio of IFN-γ/IL-10, and lower percentages of circulating NK-cells. Intra- and postoperative decrease of monocyte HLA-DR expression was not influenced by intraoperative TEA, whereas the decrease of IL-12 plasma concentration was slightly attenuated.

Attenuated postoperative decline of total lymphocytes[8 11 13] and T4-cells[8 13] by the use of intraoperative, postoperative, or both EA has been described in patients undergoing major surgery. In contrast, reduced postoperative HLA-DR expression on monocytes was not attenuated by intraoperative EA.[12 14] These postoperative findings are concordant with our results. Intraoperative measurement of lymphocyte subpopulations and HLA-DR-expression with or without intraoperative TEA has not been performed so far.

This is the first trial, which evaluated con-A-stimulated IFN-γ and IL-10 release and plasma concentrations of IL-12 and IFN-γ as a measure of adaptive immunity in patients undergoing intraoperative EA. Three studies described different influences of intraoperative EA on plasma concentration of IL-10.[12–14] In one study, intra- and postoperative increase of IL-10 was attenuated by the use of intraoperative EA[14] in patients undergoing cardiac surgery. In contrast, no effect of EA on postoperative IL-10 was found in two studies with patients undergoing gastrectomy or radical oesophagectomy.[12 13] Two of the aforementioned studies also showed conflicting results with regard to cortisol and epinephrine release: Volk and colleagues[14] described attenuated increase of cortisol and epinephrine, which is consistent with the presented data. In contrast, cortisol increase of patients undergoing radical oesophagectomy was not altered by the use of two epidural catheters to ensure a block from dermatomes C3–L4.[13]

The presented results are in accordance with described other stress-induced immune responses. Stress-induced transient increase of NK cells and decrease of T4-cells, total lymphocytes, IFN-γ/IL-10 ratio, and IL-12 has been described in patients undergoing therapeutic whole body hyperthermia.[4] Increase of NK cells was also found in rats during swim stress[20] and in healthy volunteers during aerobic exercise.[21] In addition, psychological stress caused reversible decrease of T4-cells and plasma IFN-γ/IL-10 ratio.[22 23]

Interactions of cortisol and epinephrine with the adaptive immune system are well known. Lymphocyte migration out of the blood flow towards skin, bone marrow, lung, and gut is caused by cortisol, whereas stimulation of β_2-receptors on lymphocytes by epinephrine leads to mobilization of lymphocytes from endothelial cells into the blood flow.[24 25] As density of β_2-receptors is high on NK cells, and low on T4-cells,[26] NK cells may be able to compensate number of migrating cells transiently. In addition, apoptosis of T-lymphocytes (but not of NK cells) is increased by cortisol, whereas T4-cell proliferation is decreased by epinephrine.[27 28] The change towards an anti-inflammatory pattern of cytokines in our patients is also similar to known effects of stress hormones. Epinephrine and cortisol suppress plasma concentrations of IL-12 and IFN-γ and reduce IL-12 receptors on pro-inflammatory T4 (TH1)-cells, while production of IL-10 is increased and TH2-proliferation is stimulated.[5 26 29]

As IFN-γ plays a crucial role in proinflammatory adaptive immune defence, lack of IFN-γ may lead to an increased risk of infection.[15 17] In addition, reduced plasma concentration of IFN-γ and direct stimulation by catecholamines and cortisol have been described to cause impairment of NK cell activity—in spite of transiently increased NK cell numbers during stress.[26 30] Animal experiments indicate that stress-induced immunosuppression after stroke, which led to spontaneous occurrence of pneumonia, is mainly due to impairment of IFN-γ release. IFN-γ secretion was restored and occurrence of pneumonia decreased only by beta-blocking agents but not glucocorticoid receptor antagonists.[15] It is therefore reasonable that the preserved capacity of T4-cells to produce IFN-γ by intraoperative EA was mainly due to attenuation of sympathetic activation and less due to inhibition of cortisol. One might speculate that preservation of IFN-γ production by T4-cells may be favourable with regard to postoperative risk of infections. However, one limitation of the presented pilot study is the small sample size, which does not allow definite conclusions on differences in postoperative course of patients with regard to the described immunosuppression.

Intraoperative BIS values, concentration of end-expiratory isoflurane, and heart rates were not different between both groups—at the same time, when the stress hormones were significantly higher in the TEA-P patients, heart rates were even slightly lower in this group. This may indicate that patients underwent severe stress reactions with the described resulting immunosuppression, which were not noticeable by standard monitoring during general anaesthesia.

In summary, intraoperative use of TEA diminishes stress reactions and thus attenuates perioperative suppression of the adaptive immune system.

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References

1 Munford RS, Pugin J. Normal responses to injury prevent systemic inflammation and can be immunosuppressive. *Am J Respir Crit Care Med* 2001; **163**: 316–21

2 Isitmangil G, Isitmangil T, Balkanli K, *et al*. Detection of thoracotomy-induced alterations in cell- and humoral-mediated immune response. *Eur J Cardiothorac Surg* 2002; **21**: 497–501

3 O'Sullivan ST, Lederer JA, Horgan AF, *et al*. Major injury leads to predominance of the T helper-2 lymphocyte phenotype and diminished interleukin-12 production associated with decreased resistance to infection (see comments). *Ann Surg* 1995; **222**: 482–90

4 Ahlers O, Hildebrandt B, Dieing A, *et al*. Stress induced changes in lymphocyte subpopulations and associated cytokines during whole body hyperthermia of 41.8–42.2 degrees C. *Eur J Appl Physiol* 2005; **95**: 298–306

5 Elenkov IJ. Glucocorticoids and the Th1/Th2 balance. *Ann N Y Acad Sci* 2004; **1024**: 138–46

6 Akural EI, Salomaki TE, Tekay AH, *et al*. Pre-emptive effect of epidural sufentanil in abdominal hysterectomy. *Br J Anaesth* 2002; **88**: 803–8

7 Schenk MR, Putzier M, Kugler B, *et al*. Postoperative analgesia after major spine surgery: patient-controlled epidural analgesia versus patient-controlled intravenous analgesia. *Anesth Analg* 2006; **103**: 1311–7

8 Volk T, Schenk M, Voigt K, *et al*. Postoperative epidural anesthesia preserves lymphocyte, but not monocyte, immune function after major spine surgery. *Anesth Analg* 2004; **98**: 1086–92

9 Beilin B, Shavit Y, Trabekin E, *et al*. The effects of postoperative pain management on immune response to surgery. *Anesth Analg* 2003; **97**: 822–7

10 Kuo CP, Jao SW, Chen KM, *et al*. Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. *Br J Anaesth* 2006; **97**: 640–6

11 Hong JY, Lim KT. Effect of preemptive epidural analgesia on cytokine response and postoperative pain in laparoscopic radical hysterectomy for cervical cancer. *Reg Anesth Pain Med* 2008; **33**: 44–51

12 Kawasaki T, Ogata M, Kawasaki C, *et al*. Effects of epidural anaesthesia on surgical stress-induced immunosuppression during upper abdominal surgery. *Br J Anaesth* 2007; **98**: 196–203

13 Yokoyama M, Itano Y, Katayama H, *et al*. The effects of continuous epidural anesthesia and analgesia on stress response and immune function in patients undergoing radical esophagectomy. *Anesth Analg* 2005; **101**: 1521–7

14 Volk T, Dopfmer UR, Schmutzler M, *et al*. Stress induced IL-10 does not seem to be essential for early monocyte deactivation following cardiac surgery. *Cytokine* 2003; **24**: 237–43

15 Prass K, Meisel C, Hoflich C, *et al*. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1-like immunostimulation. *J Exp Med* 2003; **198**: 725–36

16 Dong C, Flavell RA. Th1 and Th2 cells. *Curr Opin Hematol* 2001; **8**: 47–51

17 Schinkel C. The role of IFN-gamma in surgical patients. *J Interferon Cytokine Res* 2003; **23**: 341–9

18 Knaus WA, Draper EA, Wagner DP, *et al*. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818–29

19 Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. *J Am Med Assoc* 1993; **270**: 2957–63

20 Ben Eliyahu S, Page GG, Yirmiya R, *et al*. Evidence that stress and surgical interventions promote tumor development by suppressing natural killer cell activity. *Int J Cancer* 1999; **80**: 880–8

21 Gannon GA, Rhind S, Shek PN, *et al*. Naive and memory T cell subsets are differentially mobilized during physical stress. *Int J Sports Med* 2002; **23**: 223–9

22 Breznitz S, Ben Zur H, Berzon Y, *et al*. Experimental induction and termination of acute psychological stress in human volunteers: effects on immunological, neuroendocrine, cardiovascular, and psychological parameters. *Brain Behav Immun* 1998; **12**: 34–52

23 Marshall GD, Agarwal SA, Lloyd C, *et al*. Cytokine dysregulation associated with exam stress in healthy medical students. *Brain Behav Immun* 1998; **98**: 297–307

24 Dhabhar FS, Miller AH, McEwen BS, *et al*. Effects of stress on immune cell distribution. Dynamics and hormonal mechanisms. *J Immunol* 1995; **154**: 5511–27

25 Carlson SL, Fox S, Abell KM. Catecholamine modulation of lymphocyte homing to lymphoid tissues. *Brain Behav Immun* 1997; **11**: 307–20

26 Madden KS, Sanders VM, Felten DL. Catecholamine influences and sympathetic neural modulation of immune responsiveness. *Annu Rev Pharmacol Toxicol* 1995; **35**: 417–48

27 Dieing A, Ahlers O, Kerner T, *et al*. Whole body hyperthermia induces apoptosis in subpopulations of blood lymphocytes. *Immunobiology* 2003; **207**: 265–73

28 Steensberg A, Morrow J, Toft AD, *et al*. Prolonged exercise, lymphocyte apoptosis and F2-isoprostanes. *Eur J Appl Physiol* 2002; **87**: 38–42

29 Iwakabe K, Shimada M, Ohta A, *et al*. The restraint stress drives a shift in Th1/Th2 balance toward Th2-dominant immunity in mice. *Immunol Lett* 1998; **62**: 39–43

30 Robertson MJ, Ritz J. Biology and clinical relevance of human natural killer cells. *Blood* 1990; **76**: 2421–38