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1. The capillary permeability reducing effect of prostacyclin compared with terbutaline and theophyllamine in cat skeletal mucle

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An increase in capillary permeabilty is a common pathophysiological state in critical illness such as SIRS, capillary leak syndrome and after trauma. Terbutaline and theophyllamine have been used to reduce the capillary leakage without convincing effects. It has been shown in this laboratory and by others that the endothelial produced substance prostacyclin reduces capillary permeability. Prostacyclin is also an inhibitor of platelet aggregation, a vasodilator and has cytoprotective effects. The aim of this study was to compare the permeability reducing effect of prostacyclin with terbutaline and theophyllamine.

The observations were made on an autoperfused, denervated cat gastrocnemius muscle enclosed in a plethysmograph with continuous recording of volume changes, arterial and venous blood pressures and flow. Twelve cats, anaesthetized with ketamine were used. The capillary filtration coefficient (CFC), reflecting the capillary surface area for fluid exchange, was determined by the rate of a steady-state increase in tissue volume per min after an increase in venous pressure of 5 mmHg. A change in CFC reflects a change in capillary permeability but the number of open capillaries is also of importance. CFC determinations were carried out using *intravenous* infusion of different doses of each drug alone. Further, the three drugs were given separately during simultaneous *local intra-arterial* infusion of TNFα (0.75 μg 100 g^{-1} muscle min^{-1}) or histamine (50 μg 100 g^{-1} muscle min^{-1}), respectively.

Prostacyclin in doses of 2, 5, 10, 20, 40 and 60 ng kg^{-1} min^{-1} reduced CFC from a control value of 0.012 ± 0.001 (SEM) ml (min mmHg 100 g^{-1}) reaching maximum reduction of 28% at 20 ng kg^{-1} min^{-1} (P<0.001), 2 ng kg^{-1} reduced CFC by 16% and 5 ng kg^{-1} min^{-1} by 18% (P<0.01). TNFα and histamine significantly increased CFC by 57 and 72% respectively. Infusion of prostacyclin 2 ng kg^{-1} min^{-1} reduced the TNFα induced increase in CFC to 17% below the initial control value with maximal reduction of 23% obtained at 20 ng kg^{-1} min^{-1}. During histamine infusion, the same reduction of 23% was obtained but at the dose of 10 ng kg^{-1} min^{-1} of prostacyclin. Terbutaline in doses of 3.5, 7 and 14 μg kg^{-1} bw h^{-1} and theophyllamine in doses of 12.5, 25 and 50 mg kg^{-1} h did not reduce CFC from the control value. Both terbutaline and theophyllamine had some, though non-significant, reducing effect on the increased CFC values during the TNFα and histamine infusions. However, terbutaline and theophyllamine caused vasodilation, which by increasing the number of open capillaries could mask some permeability reducing effects measured by this CFC method. Prostacyclin, at doses up to 20 ng kg^{-1} min^{-1}, just slightly reduced vascular tone indicating that these doses are indeed low for the cat. This also indicates that the reduction in CFC must be as a result of decreased capillary permeability as the number of open capillaries must be roughly unchanged.

Prostacyclin in this model is far superior to terbutaline and theophyllamine in reducing capillary permeability and especially when considering the differences in their vasodilator effects. All these drugs are known to act by increasing intracellular cAMP which relaxes endothelial cells, decreasing capillary permeability. Prostacyclin is also thought to reduce

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permeability through an influence on leukocytes and platelets which could explain its more powerful permeability effect. This study indicates that low dose prostacyclin may be useful in pathophysiological states with increased capillary permeability. The effects of prostacyclin are under further evaluation in this intensive care unit.

2. Epidural clonidine does not attenuate hypoxic pulmonary vasoconstriction in anaesthetized swine

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Clonidine has been shown *in vitro* to vasodilate precontracted porcine pulmonary artery ringlets [1]. Hypoxic pulmonary vasoconstriction (HPV) *in vivo* is a predominantly local response to hypoxia reducing ventilation-perfusion mismatch and shunt. During one lung ventilation in dogs, inhalational agents have been shown to increase the shunt fraction by attenuating HPV, whereas induction agents have no effect on HPV [2]. This study was designed to investigate the effects of epidural clonidine on HPV *in vivo* in the intact anaesthetized pig. It was also performed under a licence obtained under the Cruelty to Animals Act and EC Directive 86/609.

General anaeshesia was induced in five pigs (20–25 kg) with intramuscular ketamine and halothane and maintained solely with continuous intravenous propofol infusion of 10 mg kg^{-1} h^{-1}. The lungs were ventilated with oxygen and air to normocapnia. Halothane washout after induction resulted in an end-tidal halothane concentration which did not exceed 0.2%, a concentration previously shown to have an insigificant effect on HPV [3]. Arterial pressure (SBP), central venous (CVP), pulmonary artery (PAS) and pulmonary artery occlusion pressures (PAOP) and cardiac output (CO) were monitored via the femoral vessels using an intraarterial 20-G cannula and a 7-F pulmonary artery catheter. An 18-G lumbar epidural catheter was sited. Measurements were made at baseline and 30 min after an epidural bolus of 2 μg mL^{-1} clonidine. After 5 min of ventilation with a hypoxic mixture, F_1O_2 0.1–0.15, arterial and mixed venous partial pressures of oxygen (PaO2, PvO2) were obtained and HPV was measured indirectly by calculating pulmonary vascular resistance (PVR). Statistical analysis was by paired Student's *t*-test.

Table 1. (abstract 2).

Hypoxic ventilation (mean, standard deviation)			
	Base-line	Epidural clonidine	*P*
PVR (mmHg L^{-1} min^{-1})	510, 236	565, 219	NS
HR (b.p.m.)	126, 20	112, 11	NS
SBP (mmHg)	133, 13	121, 7	NS
CO (L min^{-1})	4.4, 0.7	3.9, 0.8	NS
PAOP (mmHg)	6, 2.4	6.2, 0.9	NS
PAS (mmHg)	42, 12.4	41, 11.5	NS
SVR (mmHg L^{-1} min^{-1})	1872, 573	1957, 407	NS
CVP (mmHg)	6, 1	6, 0.7	NS
PaO_2 (KPa)	5.8, 0.5	5.8, 0.9	NS
$P\bar{v}O_2$ (KPa)	3.8, 0.6, 4.0	3.3, 1.0	NS
pH	7.5, 0.04	7.52, 0.03	NS

Epidural clonidine does not result in a decrease in PVR. It is concluded from this study that epidural clonidine does not attenuate HPV in the intact pig. It is therefore suggested that the adjunctive use of epidural clonidine in surgery requiring one lung ventilation will not result in deleterious effects on oxygen transfer because of an increased shunt.

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3. Effects of alveolar hypoxia and reoxygenation on pulmonary capillary pressure and lung fluid balance in dogs

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Pulmonary oedema formation during alveolar hypoxia and reoxygenation is considered to be the result of increased capillary pressure and/or increased capilllary permeability because of endothelial cell damage. To test this hypothesis pulmonal arterial pressure (PAP), pulmonary capillary pressure (P_c), extravascular

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lung water (EVLW) and pulmonary capillary permeability-surface area (PS) were measured for urea in *in vivo* dog lungs during constant blood flow during prolonged alveolar hypoxia and reoxygenation.

Twenty dogs (nine time controls and 11 test animals) were investigated *in vivo* during constant blood flow. P_c and segmental vascular resistance was determined by analysis of pulmonal arterial occlusion pressure-profiles. The multiple indicator-dilution technique was used to study EVLW and PS-urea.

During hypoxic pulmonary vasoconstriction, PAP increased with time in a biphasic fashion. P_c remained unchanged because of a predominant precapillary constriction. During reoxygenation, PAP, P_c and segmental vascular resistance were similar to base-line values. EVLW increased significantly during hypoxia and reoxygenation, whereas PS-urea remained unchanged.

Table 2. (abstract 3).
Table of median values (95% confidence interval)

	PAP (mmHg)	P_c (mmHg)	EVLW (mL)	PS-urea (mL s^{-1})
Normoxia	8.9 (1.6)	3.6 (0.4)	85 (7)	9 (2.4)
Hypoxia	14.3 (1.8)*	5.1 (0.8)	103 (7)*	8 (1.3)
Reoxygenation	11.7 (1.3)	5.1 (0.6)	110 (10)*	8 (1.6)

* Indicates $P<0.05$ for normoxia vs. hypoxia/reoxygenation.

Pulmonary oedema formation during hypoxia and reoxygenation is not because of increased capillary filtration nor to increased capillary permeability, but rather is a consequence of increased water flow through hydraulic pathways in capillary endothelial cells.

4. A simple method for evaluating the efficiency of ultrasonic nebulizers when used to deliver drugs to intubated, ventilated patients

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Little is known about the performance of ultrasonic nebulizers when used in breathing circuits under different ventilation patterns. The effect of variations in inspiratory flow has been described, as has the effect of changes of minute volume although this did not take into account changes in flow rate [1]. The aim of this present study was to devise a method to evaluate the performance of an ultrasonic nebulizer at different rates of nebulization and under changing conditions of positive end-expiratory pressure (PEEP), flow rate and minute volume, prior to use of the nebulizer as a drug delivery system in an ITU setting.

A Hamilton Amadeus ventilator connected to a 2-L Ohmeda reservoir bag formed an *in vitro* model of intermittent positive pressure ventilation. The De Vilbiss 'Ultra-Neb 2000' ultrasonic nebulizer, filled with 30 mL of 0.9% saline, was incorporated into the inspiratory limb of the breathing circuit. Performance was assessed by measuring the residual volume of saline after 5 min of nebulization. Each measurement was repeated until a variability of less than 10% was obtained for three residual volumes. Observations were made at three different nebulizer settings, during changing levels of PEEP. (0, 5 and 10 cmH_2O), inspiratory flow (8.6 vs. 34.3 L min^{-1}) and minute volume (3.6 vs. 2.2 L). During assessment of the effect of the two different minute volumes, the inspiratory: expiratory ratio was altered to maintain a constant flow rate of 10.6 L min^{-1}. Results were analysed by one-way analysis of variance.

Increasing the amount of PEEP from 0 to 10 cmH_2O had no significant effect on the volume of saline nebulized at any of nebulizer settings ($P>0.05$). Increasing the inspiratory flow rate decreased the volume of saline nebulized at the two higher nebulizer settings ($P<0.01$), but had no significant effect at the lowest setting ($P>0.05$). Increasing the minute volume resulted in a significant increase in the volume of saline nebulized at low and medium nebulizer setting ($P<0.05$) and caused a decrease in the volume nebulized at the high setting ($P<0.01$).

Ultrasonic nebulizers are affected by different patterns of ventilation, and therefore, without prior assessment, may be an unreliable method of drug delivery. This study revealed that ventilator flow rate and minute volume independently affect ultrasonic nebulizer function while positive end expiratory pressure does not. This method for assessing the effect of changing patterns of ventilation is simple to perform

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and allows for more informed use of an ultrasonic nebulizer as a drug delivery system in the ITU setting.

Reference

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5. Nitric oxide and oxygen free radical production during orthotopic liver transplantation. An experimental study

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Nitric oxide (NO) and oxygen free radicals (OFR) are involved in many pathophysiological processes during orthoptic liver transplantation (OLT). Their role in respiratory, haemodynamic and metabolic aspects of post-reperfusion sydrome remains unclear. In order to contribute in elucidating this problem an experimental study with OLT in pigs was undertaken.

Forty-two adult pigs of 25 Kg mean weight were divided in 4 groups as follows: Group A: 18 pigs served as donor group. Group B: 6 pigs served as control group. Group C: 6 healthy pigs underwent OLT. Group D: 12 pigs with surgically induced fulminant hepatic failure following liver devascularization were divided into 2 subgroups: Subgroup D1: Half (6 pigs) underwent OLT with whole liver graft. Subgroup D2: The other half underwent OLT with split liver graft. Standard anaesthetic and surgical procedures were used. NO, S-nitrosothiols and serum total antioxidant capacity (STAC) were measured in blood serum obtained from the animals at specific stages during OLT: before laparotomy, before IVC/PV clamping, before reperfusion, 30 and 60 min post-reperfusion.

A considerable decrease in NO and S-nitrosothiols levels by approximately 70% with an additional decrease in STAC of approximately 50% were observed following reperfusion. This drop was found to be statistically significant (ANOVA, $P<0.05$). The decreased levels of NO may be increased as a result of OFR production, which reacts with NO resulting in peroxinitrite ($ONNO^-$) formation. It may thus be assumed that pulmonary hypertension occuring following clinical OLT can be attributed to neutralization of NO by superoxide (O_2^-) produced during ischaemia. It is concluded that metabolic and haemodynamic disturbances observed during and after transplantation may be the result of increased OFR production. The use of scavengers may have significant value in maintaining the integrity of the hepatic graft.

6. Renal effects of nitric oxide scavenging during hyperdynamic sepsis

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Nitric oxide (NO) synthase inhibition aggravates renal failure in non-septic rats [1]. In a previous study it has been shown, that NO scavenging with modified haemoglobin reverses the haemodynamic changes seen with hyperdynamic sepsis [2]. Infusion of free haemoglobin can also effect renal function [3]. Therefore the effects of modified haemoglobin on renal function during ovine sepsis by measuring creatinine clearance and regional blood-flow in the kidney were investigated.

Four days after surgical preparation for chronic study, sheep ($n=14$) received an infusion of live Ps. aeruginosa bacteria for 48 h. After 24 h of sepsis the animals were assigned to either a control ($n=7$, saline), or a treatment group ($n=7$, 100 mg Pyridoxalated Haemoglobin Polyoxyethylene Conjugate (PHP) kg^{-1}). Creatinine clearance was determined every 12 h during the experiment. Regional blood flow to the kidney was measured with fluorescent microspheres. Statistic: Fisher's LSD with Bonferroni correction. Data are given as percent of base-line (mean $\pm$ SEM).

After 24 h all sheep had developed a hyperdynamic sepsis. PHP-infusion normalized the haemodynamic parameters. Effects of PHP-infusion on renal function and blood-flow are shown in Fig. 1.

PHP-infusion during hyperdynamic sepsis caused a significant increase in creatinine clearance and no

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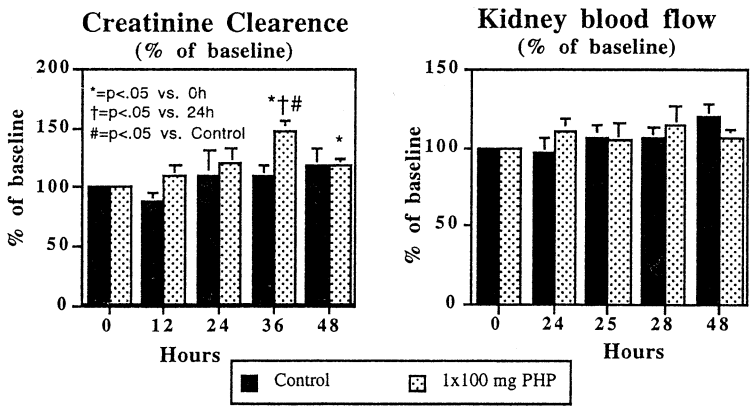

Fig. 1. (abstract 6).

change in blood-flow to the kidney was observed after PHP-infusion. Renal side effects do not limit the use of modified haemoglobin in the treatment of septic shock.

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7. Effects of sympathetic nerve blockade by thoracic epidural anaesthesia on nitric oxide synthase inhibition in sheep

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Nitric oxide (NO) is produced by nitric oxide synthase (NOS) and stimulates the soluble guanylate cyclase, thus causing an increase in intracellular cyclic guanosin monophosphate, which in turn produces relaxation of the vascular smooth muscle cell [1]. Inhibition of NOS thus causes intense vasoconstriction (for review see [2]). NO is also synthesized by NOS in sympathetic nerves [3] and inhibits sympathetic nerve activity (SNA) in the central nervous system [4] as well as in peripheral sympathetic nerve fibres [5]. Inhibition of NOS is thus hypothesized to cause uninhibited SNA and thereby vasoconstriction. Recently it was suggested that NOS inhibition in subjects with abolished SNA does not cause vasoconstriction [6]. We investigated the effects of NOS inhibition in sheep with reversible sympathetic block, rendered possible by epidural anaesthesia (EA).

In chronically instrumented sheep ($n=9$) a sympathetic block was established by administration of bupivicaine 0.5% through a catheter previously positioned into the thoracic epidural space. Efficacy of EA was judged by complete paralysis of all extremities. L-NAME was given at two doses (2.5 mg kg^{-1} and 5.0 mg kg^{-1} to sheep during control conditions and during EA.

L-NAME caused significant, dose-related vasoconstriction, during control conditions and during EA, as reflected by the increase in systemic vascular resistance index (SVRI see Table 3). A significant increase in left ventricular stroke work index (LVSWI) was only observed during SB. Furthermore, heart rate (HR) fell significantly more during SB compared with control conditions.

EA causes a reversible sympathetic block [7]. NOS inhibition with L-NAME caused vasoconstriction independent of SNA. The more pronounced reduction in HR was mainly responsible for the significant increase in LVSWI.

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Table 3. (abstract 7).

	Control			SB		
	Base-line	L-NAME 2.5 mg	L-NAME 5.0 mg	Base-line	L-NAAME 2.5 mg	L-NAME 5.0 mg
SVRI	1260±57	1567±93*	1852±121*	1114±58	1619±145*	1965±163*
HR	95±5	89±6	81±3	69±3*†	59±3*†	
LVSWI	67±7	71±6	71±4	73±3	92±6*†	106±9*†

SVRI in dyn s cm^{-5} m^2; HR in 1 min^{-1}; LVSWI in g m/m^2
* = P<0.5 vs. base-line; † = P0.05 vs. corresponding control value.

8. Thoracic epidural anaesthesia does not affect recovery from myocardial stunning during propofol anaesthesia in chronically instrumented dogs

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Thoracic epidural anaesthesia (TEA) improves myocardial perfusion and increases the subendocardial to subepicardial blood flow ratio in non-ischaemic myocardium [1]. The effects of TEA on myocardial stunning during propofol anaesthesia (PROP) have not yet been examined.

Five dogs were chronically instrumented for measurement of aortic blood pressure (ABP), left ventricular pressure (LVP), LVdP/dt, left atrial pressure (LAP), and myocardial wall thickening fraction (WTF). LAD-ischaemia was induced with an occluder around the LAD. TEA was performed with lignocaine at TgN 2. After recovery two experiments were performed in random order: (1) 10 min of LAD-ischaemia during PROP (30 mg kg^{-1} h^{-1}) without TEA, and (2) with TEA. PROP was discontinued upon reperfusion. WTF was measured until complete recovery from ischaemic dysfunction occurred. Comparisons were made by ANOVA for repeated measures followed by paired t-test with Bonferroni correction.

PROP caused a significant reduction in LAD-WTF (−16.5±4.1%). LAD-ischaemia led to a further significant decrease in LAD-WTF (−140±6.3% with TEA and −128±5.1% without TEA) (Fig. 2). There were no significant differences in LAD-WTF between the two experiments at the time points measured (Fig. 2). No significant differences between the experiments were observed for the other parameters.

During PROP, TEA does not alter affects of stunning in chronically instrumented dogs. Recovery from stunning during high dose PROP is compared with data observed in awake animals [2].

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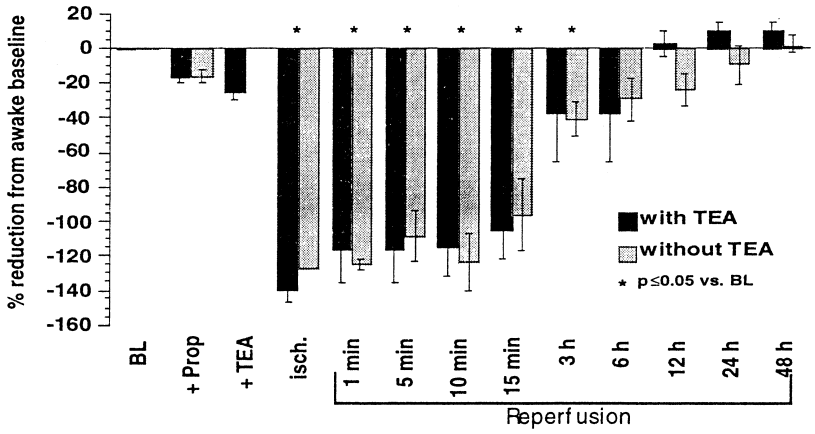

Fig. 2. (abstract 8).

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9. Permanent vascular access – incidence of complications

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Modern chemotherapy requires a safe vascular access, primarily because of the risk of drug extravasation, with subsequent necrosis and ulceration. Implantable port catheter systems are commonly used in patients with solid tumors, whereas the Hickman-type tunneled catheters are used in patients with malignant haematological diseases. The incidence of infections per device-day is greater with catheters than with ports [1]. The department of Anaesthesiology has taken care of the activity since May 1995 in this hospital. The aim of this presentation is to present our first year experience.

All insertions were made by four specialists in anaesthesiology using a classical percutaneous approach to the subclavian vein with peroperative X-ray to verify catheter placement and location. Until May 1995 no systematic assessment of the implanted ports and catheters was available. From January 1996 we have initiated recording, which is retrospective (back to May 1995) and prospective from January on. Based on patient records and continuous recordings, the complication rate is presented. The reasons for removal of the systems are presented for PAC and Hickman separately. Results are given as mean with 2.5 percentiles in the PAC group and with quartiles in the Hickman group. Age of the patients and time used for insertion are presented. Only infections necessitating removal are recorded.

A total of 148 central venous access devices were inserted as: 42 Hickman catheters and 106 Port-á-Cath (PAC) systems. Four of the Hickman catheters were double lumen catheters.

The implanted ports used for venous access were operational for an average of 148 days (quartiles 61 and 224 days and a total of 15 732 days), 13 catheters were removed before the end of treatment, 2 were misplaced, 2 had tunnel infections and one septicaemia, 4 were malfunctioning, and of 4 ports were lost due to spontaneous perforation of the skin. The age of the patients was 29.7–55.0–70.0 (mean and range) years. The time consumption is 30–70–157 min. The incidence of infections with PAC was 0.19:1.000 catheter days.

The Hickman catheters were operational for 37.5–72–102.8 days with a total of 3284 days. Nineteen catheters were removed due to: Tunnel infection 6, sepsis 3, bleeding 1, thrombosis 1, occlusion of catheter 1. Finally, one catheter was accidentally lost. Mean age of the patients was 48.4 years (range 15–83) and time consumption was 30–35–70 min. *The incidence of infections with single lumen Hickman catheters were 2.74:1,000 catheter days*.

The registered incidence of infections necessitating catheter removal is low. The incidence of infections also shows that the infection risk is 14 times higher in the haematological patient with a Hickman catheter as compared with the oncological patient with PAC.

The registered incidence of infections necessitating catheter removal compares well with results from other centres [2–5].

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10. Dramatic effect of treatment in the prone position on oxygen saturation in patients, with severe acute lung insufficiency treated prone

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The purpose of this clinical follow up-study was to confirm the positive effect of the prone position on gas exchange in patients with impaired lung function. In this series, 13 patients, younger than seventy years of age, who had severe acute lung insufficiency and of whom 11 fulfilled proposed criteria for ECMO treatment, were studied supine and prone.

The lungs of all patients were mechanically ventilated via endotracheal Portex tubes using a Servo 300 ventilator. They had all been through testing using different ventilatory settings in order to reach the most

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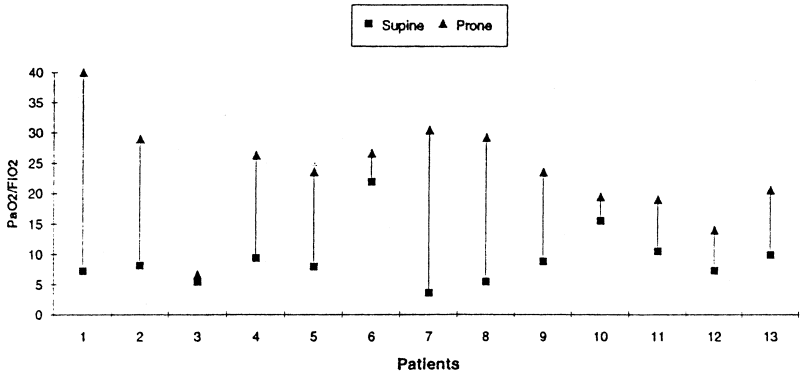

Fig. 3. (abstract 10).

efficient for each patient. All patients had arterial and central venous lines for monitoring. Haemoglobin oxygen saturation was continuously followed by a pulse-oximeter. In some of the cases mixed venous haemoglobin oxygen saturation was also monitored via a Swan-Ganz catheter. Oxygen index (PaO_2/FiO_2, OI,kPa) as well as alveolo-arterial oxygen differences were recorded.

The best improvements in OI for each of the 13 patients are presented in Fig. 3. Nine of the patients had an OI of 13 or less where 13 represents the proposed criterion for ECMO treatment. Only one patient did not respond to the treatment in the prone position – patient no 3. She suffered from an alcohol addiction with a severe liver disease and ascites. Her gas exchange responded well, however, to NO treatment. In spite of the improved saturation she died from a gram negative septicaemia. Altogether 9 patients (69%) survived and none died from an impaired gas exchange.

Treatment in the prone position has a dramatic effect on the gravely impaired gas exchange seen with acute lung insufficiency. Our previous results, using ECMO, showed a survival rate of 35% compared with 69% using the prone position in this study. The prone position is a first line treatment and must be used prior to more complex treatment modalities such as NO and ECMO.

11. Modulation of cardiac arrhythmias by opioid antagonists: A peripheral mechanism

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Ventricular arrhythmias are an important cause of death following acute myocardial ischaemia. Endo-

Table 4. (abstract 11).
Effects of naltrexone and methylnaltrexone on cardiac arrhythmias and survival during coronary occlusion and reperfusion

	Occlusion (40 min)					Reperfusion (40 min)					
	N	VF	VT	Other	AS	N	VF	VT	Other	AS	SV
Control	8	4	6	8	4.8±1.7	6	0	2	6	2.3±0.8	6
Ntx 2 mg kg^{-1}	6	0*	1*	5	2.0±1.2†	6	0	2	6	2.2±1.3	6
Mntx 2 mg kg^{-1}	6	0*	1*	4	1.7±0.5†	6	0	2	6	2.3±1.5	6

Ntx-Naltrexone; Mntx-Methylnaltrexone.
Figures represent number of animals; VF- ventricular fibrillation; VT- ventricular tachycardia; AS- Arrhythmia Score; Others include Premature atrial contractions, atrial fibrillation, A-V block, premature ventricular contractions, ventricular bigemini, Sv- Survival *- Statistical difference from control values at the level of $P<0.05$ by χ^2 test, by *t*-tests. AS- mean±SD.

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genous opioid peptides (EOP) modulate cardiac arrhythmogenesis and opiate receptor antagonists possess antiarrhythmic activity. Whether this is a central or peripheral effect remains unclear. The importance of peripheral opioid antagonism in prevention of post ischaemia and reperfusion arrhythmias was evaluated using Methylnaltrexone (Mntx) a quaternary derivative of Naltrexone (Ntx) which does not cross the blood brain barrier.

Healthy Sandy Lop rabbits (2.8–4.2 Kg) were anaesthetized with intravenous sodium pentobarbitone and artificially ventilated. The heart was exposed through a left thoracotomy incision in the 3rd intercostal space. A 3-0 silk suture with a short polyethylene tube thread around it was placed under the circumflex artery. After 15 min of equilibration Ntx, Mntx or saline was administered intravenously over a 10-min period. Five min post infusion the circumflex artery was occluded by applying tension on the suture and clamping immediately above it. Occlusion was maintained for 40 min followed by a 40-min period of reperfusion. Arrhythmias were assessed by recording the incidence of ventricular fibrillation, ventricular tachycardia and other arrhythmias (PVC, AF etc) and summarized as an arrhythmia score (AS).

Ntx or Mntx had no significant effect on heart rate or blood pressure. Arrhythmia results are summarized in Table 4.

The data suggest that the antiarrhythmic actions of opioid antagonists may be mediated via a peripheral mechanism.

Neither Ntx nor Mntx had a significant effect on reperfusion arrhythmias.

Reference

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12. Noninvasive assessment of cardiac autonomic function after passive tilt: the influence of ageing

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Spontaneous heart rate variability (HRV), a frequency domain analysis, and induced heart rate peak (HRP) changes after passive head-up tilt, a time domain analysis, have been widely used for exploring the interactions between the autonomic nervous system and the heart [1] Decreases in both HRV and HRP have been demonstrated with increasing age as well as in autonomic failure. Autonomic reflex dysfunction is associated with an increased incidence of hypotension after induction of anaesthesia [2]. The combined analysis of both methods as well as their relations to ageing has never been reported.

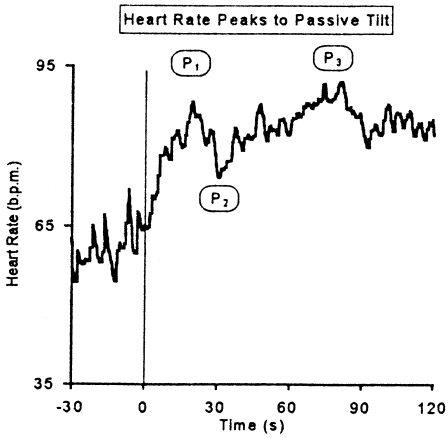

Fig. 4. (abstract 12).

In order to assess the ageing effect on the autonomic modulation of heart rate (HR), the ECG recordings in 32 healthy volunteers (ages 24–71 years) were analysed. The HR was quantified in the time-domain measuring the three consecutive HRP (defined as P1, P2 and P3, see Fig. 4) induced by passive 70° head-up tilt. The HRV was quantified by means of the fast Fourier transform algorithm in both supine and upright positions, the frequency bands were ranged as medium (MF 0.04–0.15 Hz) and high (HF 0.15–0.4 Hz)

Table 5. (abstract 12).

	Younger	Elderly	*P*<
MF supine (mS^2Hz)	1428 ±228	459 ±66	10^{-3}
MF upright (mS^2Hz)	1982 ±400	569 ±97	10^{-2}
MF/HF^{-1} up.	2.24 ±0.2	1.19 ±0.18	10^{-3}
P1 (b.p.m.)	23.2 ±3.1	11.1 ±1.6	10^{-3}
P2 (b.p.m.)	−17.1 ±2.3	−7.4 ±0.9	10^{-3}
P3 (b.p.m.)	22.9 ±2.1	7.5 ±1.0	10^{-3}

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frequencies. The population sample was split into two groups of 16: youngsters (<40 years, age: 32 ± 1.4) and elderly (>40 years, age: 57 ± 2.4). Unpaired *t*-test and cross-correlation were applied for statistical analysis.

Significant differences were found between both groups (see Table 5). Significant positive cross-correlation were found between the HRP and the HRV and both parameters decreased with ageing. The amplitude of HRP showed a positive correlation with MF spectral bands of HRV, supine and upright ($r = 0.66$ and 0.63, $P < 10^{-4}$ and 10^{-3} respectively, for $n = 32$). These data suggest that changes in HRV as well as in HRP induced by passive tilt is at least partially controlled by a common physiological mechanism. The best variables to assess cardiovascular autonomic dysfunction in elderly patients were: 1. in the time domain analysis, the amplitude of the third peak; 2. In the frequency domain analysis, the MF band, considered as an index of cardiac sympathetic modulation.

The simultaneous analysis of HR on time- and frequency-domain is particularly useful in quantifying cardiovascular system ageing and could be considered as an alternative test in the assessment of autonomic failure.

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2 *Anesthesiology* 1994; **80**: 326–337.

13. Haemodynamic effects of NO-synthase-inhibition and dopexamine in healthy and septic sheep

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The purpose of this study was to evaluate the effects of N-Nitro-L-Arginin-Methyl-Ester (L-NAME) during dopexamine (DP) administration. Dopexamine is a synthetic catecholamine, that stimulates β1, β2 and dopamine-receptors.

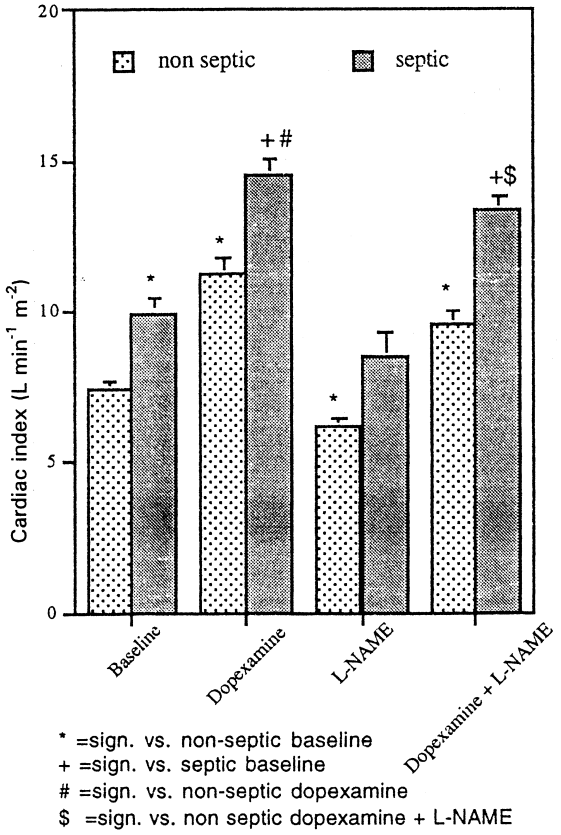

Fig. 5. (abstract 13). Effect of dopexamine on cardiac index in healthy and septic sheep with and without NO-sythase-inhibition.

Sheep ($n = 6$) were surgically prepared for a chronic study. After at least 3 days recovery, the non-septic part was started and base-line measurements were performed. DP was given intravenously ($10\ \mu g\ kg^{-1}\ min^{-1}$). Half an hour after discontinuation of DP, L-NAME was given (bolus $2.5\ mg\ kg^{-1}$, $0.5\ mg\ kg^{-1}\ h^{-1}$), followed by an DP-infusion. Three days later, sepsis was induced by continuous infusion of endotoxin (*S. typhosa*, $10\ ng\ kg^{-1}\ min^{-1}$). After 24 h of sepsis, DP and L-NAME were administered again, doses and sequence were the same as in the non-septic state. Haemodynamic measurements were performed at all time points.

The graph shows changes in cardiac index ($L\ min^{-1}\ m^{-2}$) induced by DP during the four study phases. Sepsis resulted in a hyperdynamic circulation. DP increased the cardiac index in healthy and septic sheep. L-NAME had no influence on the effects of DP, neither in the normal nor in the septic circulation.

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Student's *t*-test with Bonferroni correction. Significance was set at $P<0.05$.

NO-synthase-inhibition does not modify the haemodynamic effects of DP as far as the cardiac index is concerned.

14. A modified valsalva manoeuvre to study cardiovascular reflex control: DIBEX manoeuvre

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To evaluate the influence of drugs, e.g., spinal anaesthesia, or diseases on baroreflex blood pressure control one would like to have a test which causes a step wise change in blood pressure (BP) which persists for long enough to allow dynamic properties to be studied. The Valsalva manoeuvre evokes large changes in BP, but it can be maintained only relatively briefly, while it induces multiple effects caused by the active straining. It also involves certain risks for patients with retinopathy. In this study a modified Valsalva manoeuvre is proposed, which induces a large step wise BP decrease and increase without these disadvantages.

With informed consent and approved by the ethical committee of the Vrije Universiteit Ziekenhuis Amsterdam, 10 control subjects performed the new manoeuvre in the sitting position. The manoeuvre is called *DIBEX* manoeuvre: *D*eep *I*nspiration, *B*reath-holding against a closed glottis while relaxing thoracic and abdominal muscles, no straining, and after 40 s *EX*piration. Beat-to-beat BP was measured noninvasively with the Finapres™, as the heart rate (HR) was recorded. The DIBEX manoeuvre was expected to provoke a large instant reduction in venous return, due to a positive intrathoracic pressure, 40 s later followed by an inverse step wise increase in venous return.

Systolic BP, within 6–8 beats, dropped by 40–60 mmHg, but within 10–20 s a steady state was reached just below control level, due to baroreflex control. After breath release BP showed a large overshoot due to pooled venous blood now pumped into the constricted arterial system. Note the large reduction in pulse-pressure (at time 60 s) Fig. 6, indicating a small stroke volume, caused by a depressed venous return. HR showed a vagal and sympathetic mediated tachycardia, with a slight overshoot during breath holding; after breath release a strong vagus mediated bradycardia follows within one beat.

The DIBEX manoeuver, in contrast with the Valsalva, requires no straining, thus, no exercise reflexes. It evokes a clear, almost step wise stimulus long enough to study dynamic as well as steady-state control aspects of BP control. This manoeuvre is a promising test for cardiovascular and autonomic nerve functioning under physiological conditions, as well as under influence of diseases or drugs.

15. Cardiovascular response to the DIBEX manoeuvre: Practical applications

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We developed the DIBEX manoeuvre to study vasoconstriction performance in man. *DIBEX* stands for:

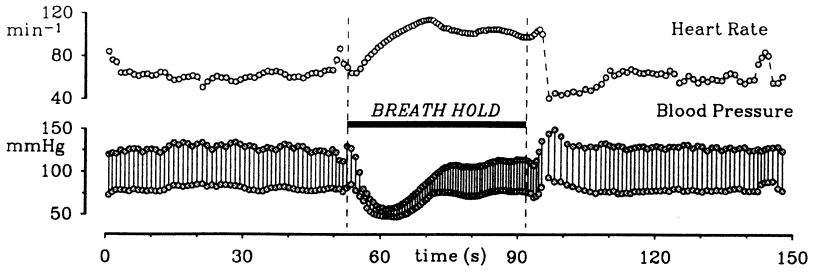

Fig. 6. (abstract 14). Pulse and blood pressure responses to breath hold.

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Deep Inspiration, Breath-holding against a closed glottis while relaxing thoracic and abdominal muscles, no straining, and after 40 s Expiration. This manoeuvre provokes an instant reduction in venous return and consequently a large drop in arterial pressure, 40 s later followed by an inverse step wise increase in venous return. We evaluated in two separate studies the extent by the DIBEX manoeuvre which reveals vasoconstriction performance: (1) under the influence of ketanserin, (2) in the presence of a high spinal cord lesion.

With informed consent and approval by the ethical committee of the Vrije Universiteit Ziekenhuis Amsterdam two studies were performed. Study (1) 2×5 mg of ketanserin was administered i.v. to seven healthy volunteer subjects with a time interval of 5 min. The DIBEX manoeuvre was performed in the standing position before and 30 min after the administration of ketanserin. Study (2) 10 quadriplegic subjects performed the DIBEX manoeuvre in sitting position. In both studies beat-to-beat blood pressure (BP) was measured noninvasively with the Finapres™, the heart rate (HR) was also recorded.

Study (1) In agreement with previous data ketanserin did not affect HR. Thirty min after the administration of ketanserin there was no significant difference in BP. Before ketanserin during the DIBEX manoeuvre, systolic BP dropped within 6–8 beats by 40–60 mmHg. After 10–20 s BP reached a new steady state just below control level, due to the intact baroflex control. After breath release, the control group showed a large BP overshoot, due to pooled venous blood now pumped into the constricted arterial system. An immediate and strong reflex bradycardia compensated the BP rise. After the administration of ketanserin, BP also showed the initial step wise fall, but BP remained low. Three volunteers even fainted at the end of the DIBEX manoeuvre. After breath release there was no BP overshoot. Study (2) In the quadriplegic group BP also showed the initial step wise fall, and BP remained low. After breath release, BP and HR returned to the base levels without overshoots, due to an absence of vasoconstriction.

Ketanserin does not affect the cardiac baroreflex and has no effects on basal haemodynamic responses in normal people under static conditions. However, in the case of a strong enough and prolonged BP decreasing stimulus, the vasoconstriction inhibiting effect of ketanserin could be demonstrated even in normal man. The DIBEX manoeuvre proves to be such a strong BP stimulus that a suppressed vasoconstriction leads to abnormal responses, and in some cases to (near) fainting. It also showed that in quadriplegic subjects the response to the DIBEX manoeuvre was very different when compared with control subjects, emphasizing the manoeuvres capability for testing sympathetic vasomotor control. These two practical applications of the DIBEX manoeuvre confirm that this manoeuvre is a very powerful test of vasoconstriction capacity in man.

16. Continuous infusion of dopamine to maintain stable arterial pressure during spinal anaesthesia for caesarean section

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To maintain stable maternal arterial blood pressure during spinal anaesthesia for caesarean section is a major concern for anaesthesiologists. Volume preloading, uterine displacement to the left and preventive administration of vasopressors are manoeuvres used by anaesthesiologists to prevent hypotension. In this study, the effects of continuous infusion of dopamine on maternal haemodynamic responses have been studied.

Healthy women undergoing elective ceasarean section under spinal anaesthesia at term were allocated randomly to receive a continuous infusion of dopamine ($5\ \mu g\ kg^{-1}\ min^{-1}$: $n = 15$, D-group) or non-dopamine infusion ($n = 15$, non-D-group). After preloading with 1000 mL Ringer lactate solution, maternal arterial blood pressure (ABP), heart rate (HR) and pulse oxymetry were recorded. Spinal anaesthesia with 0.3% dibucaine (1.6–2.0 mL) at L2-3 or L3-4 was performed. The indication for bolus ephedrine was a reduction in ABP to $\leqslant 90\%$ of base-line values.

During spinal anaesthesia no significant difference in fluctuation of ABP and HR was detected between the D-group and the E-group. Only in the non-D-group, 10 of 15 patients, was the fall in ABP to a level for which bolus ephedrine was indicated. All neonates had 1-min Apgar scores of 8 or more. There were no

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significant differences in Apgar scores between the two groups.

Continuous infusion of dopamine is effective for the prevention and management of maternal hypotension during spinal anaesthesia for caesarean section.

17. Influence of artificial plasma expanders on molecular haemostatic parameters

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Artificial colloid plasma expanders such as dextran (D), gelatine (G) and HES (H) are increasingly used in preoperative haemodilution or in treating (intravascular) volume depletion. Besides anaphylactoid reactions, the influence of these substances on haemostasis has been controversially discussed in recent years.

In this trial we studied the effects of the above-mentioned substances on total cell count in whole blood as well as on plasmatic coagulation and fibrinolysis. Fourteen healthy young volunteers without any history of allergy or haemorrhagic diathesis received 9 ml kg^{-1} body weight of each substance and Ringer's solution (R) as a control at intervals of 3 weeks each. Blood samples were drawn immediately before (P_0) directly after (P_1) and 2 h after the end of the infusion (P_2). The volunteers were continuously resting in a supine position throughout the procedure.

As expected, with all four solutions (D, G, H, and R) we observed a dilutional decrease in haematocrit, haemoglobin, thrombocytes and leukocytes directly after the infusion. These changes had largely been compensated for 2 h later. For G, H and D, we neither observed an activation of the procoagulatory system nor did fibrinolytic factors increase.

However in controls, who had only received Ringer's solution, we observed a continuous increase in fibrinogen concentration and also in the procoagulatory markers TAT-complex, prothrombin fragments F_{1+2} also a significantly decreased aPTT which is possibly a sign of increased factor-VIII activity from P_0 over P_1 to P_2. Fibrinolytic parameters, fibrin monomers and D-dimers show a significant increase whereas values for PAI-I (plasminogen activator inhibitor) decreased respectively. PA (total plasminogen activator) and t-PA (tissue plasminogen activator) showed only slight dilutional changes which were detected in all 4 groups to a similar extent.

In conclusion all three colloid plasma expanders D, G and H can be administered safely for treatment of acute volume depletion or preoperative haemodilution when diagnosis and indication are diligently made and intra- as well as extracellular volume load are carefully evaluated. This is also true for a possibly unknown derangement of haemostasis caused by excessive volume depletion haemodilution or a possible preexisting subclinical coagulation disorder. It is extremely interesting to note that Ringer's solution which is essentially 0.9% normal saline, showed hitherto unexplained changes in coagulation, as these are usually seen in certain thrombotic states, such as during and after surgical operations. We can only speculate so far that this is a sequela of increased intravascular volume. This, on the other hand, means that plasma expanders suppress a procoagulatory volume effect (see results of Ringer's) which seems to be accompanied by increased fibrolytic activity. Preoperatively this may not be a desired effect, since it may be vital for the patient to maintain blood clotting ability. So far this finding has not resulted in any fatal sequelae in clinical practice and is possibly compensated for by a simultaneous inhibition of fibrinolysis. The procoagulatory and fibrinolytic systems may thus be compensated for at a lower level.

18. Routine autotransfusion maintains the transfusion sparing effect observed in a preceding controlled trial

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In a recent prospective, randomized, controlled study of patients undergoing coronary artery bypass grafting (CABG) [1], autotransfusion of shed mediastinal blood in the first 18 h after the operation halved the number of patients needing transfusion of allogenic blood, i.e. from 55% to 28% of the patients.

In the present study we assessed (a) whether the

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Table 6. (abstract 18).

	Group I ($n=56$)	Group II ($n=50$)	Group III ($n=53$)	Group IV ($n=56$)
The number of patients receiving allogenic blood	14 (25%)	15 (28%)	24 (48%)	31 (55%)
Units of blood transfusion	33	26	60	78

transfusion sparing effect of autotransfusion would be proved true 10 months after including this procedure in the standard regime after CABG and (b) whether the conduction of the prospective study *per se* led to a more strict adherence to the departments criteria for transfusion of allogenic blood.

We retrospectively reviewed the charts of two groups of CABG patients. Group I: 60 consecutive patients who were operated on 10 months after autotransfusion had become the standard procedure. Group III: 60 consecutive patients who were operated immediately before the start of the prospective study and who did not receive autotransfusion. Data on these groups of patients were compared with data on the 60 patients of the autotransfusion group (group II) and the 60 patients comprising the control (group IV) in the prospective study, respectively. The criteria for blood transfusion in our institution are: Haemoglobin concentration <5.0 mmol L^{-1} in the ICU and haemoglobin concentration <5.5 mmol L^{-1} during stay in the surgical ward.

A total of 25 patients were excluded due to re-operation or inotropic therapy. The number of patients excluded did not differ among the groups. The groups were comparable with respect to age, duration of cardiopulmonary bypass, number of grafts and post-operative mediastinal bleeding. There were no differences in post-operative haemoglobin concentration between the groups.

The blood conservation effect of autotransfusion of shed mediastinal blood was still demonstrated 10 months after this procedure was included in the standard regime after CABG. Transfusion of allogenic blood was given in strict accordance with the departments criteria both before, during and after the prospective, randomized study.

Reference

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19. Value of autologous blood for intra-operative massive bleeding

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We studied 108 patients I-IV ASA classification randomly selected for elective or emergency orthopaedic and abdominal surgery with massive bleeding. They were allocated to two groups. In group A′ (55 patients) the patients were transfused with stored blood from the blood bank and in group B′ (53 patients) with autologous blood from the autotransfusion device (red cell saver). Pre-operatively and post-operatively haemoglobin (Hb), haematocrit (Ht), prothrombin time, bilirubin level, the number of platelets, mean arterial pressure (MAP), heart rate (HR), the values of blood gases, potassium (K^+) and sodium (Na^+) were evaluated. Intra-operatively the blood loss, the amount of transfused blood, MAP, HR, Hb, Ht, the number of platelets, the values of blood gases, K^+ and Na^+ in the stored blood and in the bags of saved red cells were measured.

Our statistics showed a significant increase in Hb, Ht, PaO_2, $PaCO_2$ and SaO_2 values in group B′ (saved red cells – $P<0.05$). In this group the values of pH, K^+, Na^+ and SBE were approximately at normal levels but the statistical comparison of the two groups gave significantly higher results for group B′ (the group given saved red cells) in this study ($P<0.001$).

In conclusion the rapid and effective restoration of an adequate circulating blood volume is crucial in the early management of major haemorrhage, as mortality increases with the duration and severity of shock. This study supports our experience that autologous blood transfusion is safe for the patient and offers rapid restoration of circulating blood volume with

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reduction of the workload and conserves blood bank stocks.

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20. The comparison of oral or rectal midazolam for a paediatric premedication

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Preanaesthetic sedation is one of the most important steps in paediatric anaesthesia. Fear of painful and unpleasant procedures, separation from parents and an unwillingness to breathe through an anaesthesia face mask may lead to an intolerable anaesthetic induction in unpremedicated children. The aim of this study is to investigate and compare the effects of orally or rectally administered midazolam, an anxiolitic with sedative properties.

Sixty paediatric patients ASA I, 0–10 years of age were studied after obtaining approval from the hospital Ethics Committee. Children were randomly allocated to two groups (*n*: 30 each). Thirty min prior to the operation 1st group received oral midazolam 0.5 mg kg^{-1}, in 5 mL orange juice and 2nd group received rectal midazolam 1 mg kg^{-1}. Anxiety scores, heart rates, blood pressures, respiratory rates and O_2 saturations were monitored. And the results were recorded before premedication, at 10th and 20th min after premedication, after induction, end of the operation and during the recovery period. Student's *t*-test and Mann–Whitney *U*-tests were used for statistical analysis.

In both groups the anxiety scores were decreased significantly ten minutes after administering the drug. But these decreases were only significant in the 2nd group ($P<0.05$). The decrease in mean arterial blood pressure was statistically significant in the 2nd group ($P<0.05$). No significant changes were seen among other variables.

We conclude that rectal midazolam is more effective in decreasing the anxiety score, its onset of effect is rapid and it facilitates a smooth anaesthetic induction period and therefore it may be the choice for preanaesthetic medication.

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21. Comparison of oral midazolam and fentanyl in paediatric preanaesthetic medication

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Oral premedication is easy to administer and more tolerable in the paediatric age group. The aim of this study is to minimize the psychological trauma of anaesthetic induction in children after applying oral midazolam and fentanyl.

Sixty children scheduled for ENT, urological, orthopaedic elective surgery were randomly allocated to two groups (*n*: 30 each) after obtaining approval from the hospital Ethics Committee. 1st group received 0.5 mg kg^{-1} midazolam, 2nd group 10 μg kg^{-1} fentanyl 40 min before surgery, all mixed with 10 mL orange juice. Induction of anaesthesia was with thiopentone sodium (4–6 mg kg^{-1}), 50% O_2-N_2O and halothane 1–1.5% were used for maintenance. Anxiety scores, heart rates, blood pressures, respiratory rates and SaO_2 were monitored and recorded from the beginning of the procedure until the end (just before premedication, at 10th, 20th, 30th min after premedication, during induction, at the end of the operation and during the recovery period). Student's *t*-test and Mann–Whitney *U*-tests were used for statistical analysis.

Anxiety scores showed a more significant decrease in the 1st group ($P<0.05$). Heart rates were also higher in the 1st group. There were no statistically significant differences between the two groups in respect of the other parameters. We found that oral midazolam administered for paediatric preanaesthetic medication is more effective than fentanyl in decreasing the

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anxiety scores. Fentanyl seemed to have more adverse effects such as respiratory depression, bradycardia and arterial desaturation than midazolam.

We conclude that midazolam can be preferred to fentanyl because of its lower adverse effects incidence and the profound sedation which results.

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22. Oral transmucosal administration of alfentanil and midazolam for premedication of paediatric patients

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The goals of perfect premedication in paediatric patients are anxiolysis, sedation, facilitation of induction of anaesthesia and anticholinergic effects. Since children dislike needles intensely, a non-painful route should be used if possible. The oral route is widely used and is quite satisfactory for the average child having minor surgery. This study compared the effects of oral transmucosal alfentanil and midazolam on preanaesthetic sedation and anaesthetic recovery scores.

Forty children (ASA1, 2–12 years) scheduled for ENT surgery were randomly allocated into two groups. Group A ($n=20$) received oral transmucosal alfentanil 0.01 mg kg^{-1} group M ($n=20$) received oral transmucosal midazolam 0.1 mg kg^{-1} as drops on a cube of sugar. All patients were anaesthetized with O_2, N_2O, propofol, halothane and atracurium; and evaluated for oral irritation, preinduction anxiety, ease of induction, recovery scores, pulse rate and SpO_2 changes. All results were statistically analyzed.

The sedation scores, response to separation from parents and mask toleration or insertion of needle for anaesthetic induction were good in two groups. The bad taste was the main problem in the midazolam group. There were no differences between the two study groups in the discharge time from the recovery room, pulse rate and SpO_2 changes. (Table 7). We have found that oral transmucosal alfentanil and midazolam provide satisfactory anxiolysis, and sedation for preanaesthetic medication in paediatric patients. No oral irritation occurred following alfentanil administration. Oral transmucosal alfentanil is as effective as, and better accepted than, midazolam for preanaesthetic sedation in children.

Table 7. (abstract 22)
All data

	Group A ($n=20$)	Group M ($n=20$)
Bad taste (%)	0	50*
Satisfactory sedation score (%)	100	80
Mask toleration or insertion of needle (%)	90	90
Preinduction pulse rate (beats min^{-1} ± SD)	110 ± 22	128 ± 16
Time until recovery room discharge (min ± SD)	11.5 ± 3.3	11 ± 4.5
Pulse rate at recovery discharge (beats min^{-1} ± SD)	105.3 ± 15	115 ± 21
SpO_2 changes at recovery discharge (% ± SD)	95.4 ± 1.2	96.2 ± 2
Excessive oral secretion (%)	60	60
Vomiting (%)	20	30

*Significant difference from group A ($P<0.01$, χ^2 test).

23. Effect of diltiazem on midazolam and alfentanil disposition in CABG patients

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Midazolam and alfentanil are desirable anaesthetic adjuncts for cardiac anaesthesia. They are metabolized by cytochrome P450 3A (CYP3A) enzymes. These isoenzymes are inhibited by concurrent medication including the calcium antagonist diltiazem which may have an impact on the recovery from anaesthesia.

After obtaining institutional approval and written consent, 30 patients undergoing elective CABG were randomly assigned to receive either diltiazem (60 mg orally and an infusion of 0.1 mg kg^{-1} hr^{-1} for 23 h) or

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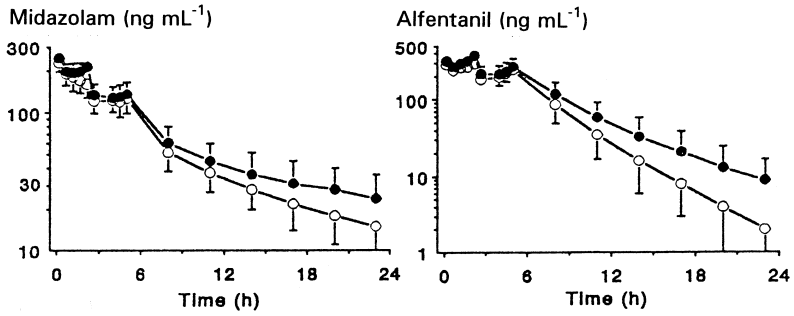

Fig. 7. (abstract 23). Drug plasma concentrations (mean ± SD) in patients receiving placebo (○) and diltiazem.

placebo in a double-blind manner. Anaesthesia was induced with midazolam 0.1 mg kg^{-1}, alfentanil 50 μg kg^{-1}, and propofol 20–80 mg and maintained with an infusion of 1.0 μg kg^{-1} min^{-1} of both midazolam and alfentanil supplemented with isoflurane. Midazolam and alfentanil plasma concentrations and areas under the plasma concentration-time curves from the end of anaesthesia until the first postoperative morning (AUC) were determined. The terminal half-life ($t_{\frac{1}{2}}$) and the context-sensitive half-time (t_{50}) for midazolam and alfentanil were calculated. Weaning from mechanical ventilation and the endotracheal extubation were performed according to the study protocol.

Diltiazem increased the AUC of midazolam by 25% (P<0.05) and that of alfentanil by 40% (P<0.05). The $t_{\frac{1}{2}}$ of midazolam was 40% and that of alfentanil 50% longer in patients receiving diltiazem. The t_{50} of midzolam was prolonged by 25% and that of alfentanil by 40% (Fig. 7, Table 8). The patients receiving diltiazem were extubated on the average 2.5 h later (P=0.054) than those receiving placebo.

Diltiazem may inadvertently prolong extubation after high doses of midazolem and alfentanil. CYP3A mediated drug interactions should be considered as confounders when recovery from anaesthesia with midazolam and alfentanil infusions is assessed.

Table 8. (abstract 23).
Pharmacokinetic variables (mean ± SD) of midazolam and alfentanil in CABG patients

	Midazolam		Alfentanil	
Variable	Placebo	Diltiazem	Placebo	Diltiazem
$t_{\frac{1}{2}}$ (min)	493 ± 130	704 ± 214*	169 ± 32	254 ± 70*
t_{50}	148 ± 49	185 ± 94	107 ± 26	153 ± 70*

*Significantly different from placebo P<0.05.

24. Studies on the mechanism of action of etomidate

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We have previously shown that propofol, thiopentone and ketamine inhibit K^+ evoked [^{3}H]noradrenaline ([^{3}H]NA) release from SH-SY5Y human neuroblastoma cells with thiopentone also inhibiting carbachol (CCh) evoked release [1,2]. As K^+ evoked release is entirely extracellular Ca^{2+} dependent [3] these data suggest that anaesthetic agents may block Ca^{2+} entry through voltage sensitive Ca^{2+} channels. In this study we have examined the effects of etomidate on K^+ and CCh evoked [^{3}H]NA release and the associated increase in extracellular Ca^{2+} ($[Ca^{2+}]_i$).

[^{3}H]NA release was measured in monolayers of SH-SY5Y cells preloaded with [^{3}H]NA (~50 nM) in Krebs/HEPES, pH 7.4 for 60 min, rinsed for 3 × 20 min periods then stimulatd with K^+ (100 mM, Na^+ adjusted) or 1 mM CCh [3]. $[Ca^{2+}]_i$ was measured in suspensions of Fura2 loaded SH-SY5Y cells [2] challenged with K^+ (80 mM, Na^+ adjusted) or 1 mM CCh. Binding of [^{3}H]PN200-110 to L-type voltage sensitive Ca^{2+} channels on SH-SY5Y cell membranes was performed in 1 ml volumes of 50 mM Tris buffer, pH 7.4 for 90 min. Where appropriate data are mean ± SEM and from at least 5 experiments.

After subtraction of basal, K^+ (100 mM) and CCh

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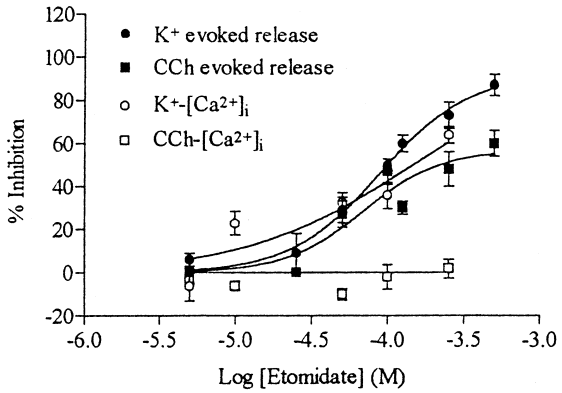

Fig. 8. (abstract 24). Etomidate inhibits K^+ and carbachol evoked [^{3}H]NA release and K^+ stimulated increased $[Ca^{2+}]_i$

(1 mM) stimulated [^{3}H]NA release from SH-SY5Y cells amounted to 5.5 ± 0.7 and 2.9 ± 0.2% respectively. K^+ and CCh evoked release were inhibited dose-dependently by etomidate. The concentration of etomidate that produced 50% inhibition (IC_{50}) was 88 μM and 69 μM for K^+ and CCh respectively, Fig. 8. Only K^+ stimulated increase in $[Ca^{2+}]_i$ was inhibited by etomidate with an estimated IC_{50} of 146 μM. In addition etomidate displaced [^{3}H]PN200-110 binding with an affinity, K_i of 48 μM.

These data suggest that etomidate may block Ca^{2+} entry through voltage sensitive Ca^{2+} channels and that the voltage sensitive Ca^{2+} channel may be a target site for anaesthetic agents.

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25. Propofol attenuates the contractile response induced by release of cellularly sequestered calcium isolated from human omental arteries and veins

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A side effect of the intravenous propofol is hypotension. The underlying mechanism has been suggested to be a decrease in sympathetic activity and/or a direct effect on vascular smooth muscle. In the present study, the direct effect of propofol on human vascular smooth muscle was investigated, especially concerning the modulation of propofol on muscle contraction involving extra- or intracellular calcium.

Isolated human omental arteries and veins were obtained from patients undergoing abdominal surgery and mounted in organ baths containing aerated modified Krebs–Ringer buffer solution.

Changes in circular isometric smooth muscle tension in response to the administration of propofol were measured. Contractile responses induced by the stable thromboxane A_2 analogue U46619, caffeine and KCl in the presence or absence of propofol were also measured. U46619 elicits its contractile response via IP_3-mediated release of cellularly sequestered calcium and caffeine elicits its contractile response predominantly via ryanodine receptor-mediated release of cellularly sequestered calcium. On the other hand, KCl elicits via influx of extracellular calcium through voltage-dependent calcium channels. A Ca^{2+}-free buffer solution was used for the experiments with U46619 and caffeine, whereas a normal buffer solution was used for the experiments with KCl.

Propofol (10^{-3} M) induced a contraction in both arteries and veins. Conversely, propofol concentration-dependently attenuated the contraction elicited by U46619 and caffeine in the absence of extracellular calcium and the contraction elicited by KCl in the presence of extracellular calcium. The threshold concentration for the effect of propofol was lower for the U46619-induced contraction (10^{-5} M) and the caffeine-induced contraction (10^{-5} M and $10^{-4.5}$ for artery and vein respectively) than for the KCl-induced contraction (10^{-4} M).

The present results suggest that propofol, at concentrations likely to occur clinically, attenuates contraction involving release of cellularly sequestered

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calcium. At higher concentrations of propofol, a contraction-attenuating effect of a different nature appears, which seems not solely to involve effects on intracellular calcium fluxes.

26. A new *in vitro* perfusion test system for leukocyte migration studies under shear stress effects of thiopentone and propofol

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The influence of thiopentone and propofol on leukocyte function is well documented. In these studies, however, the leukocyte migration was tested under static conditions using microporous membranes or agarose gels. *In vivo*, leukocytes have to extravasate through the endothelial cell monolayer (ECM) in order to reach an extravascular infectious focus. This process is influenced by the intravascular bloodflow and the resulting shear stress. Therefore a new approach has been used to test the effects of anaesthetic drugs under more physiological conditions.

Human umbilical vein endothelial cells (HUVEC) were isolated and cultured on microporous membrane filters (Becton Dickinson, USA). Polymorph neutrophil leukocytes (PMNL) were isolated from healthy female and male volunteers and separated by standard procedures. ECM and PMNL were preincubated with a clinically relevant concentration of thiopentone (10^{-5} M), propofol (4 μg ml^{-1}) and the lipid solvent of propofol. The migration of treated PMNL through untreated ECM was measured in a special double-chamber perfusion device (Aigner, Vienna). After a perfusion time of 3 h the migrated PMNL in the lower chamber were measured in a fluorimeter with Calcein-AM. For control measurements untreated PMNL and untreated ECM were used. Results are the means of 5 independent experiments and expressed as a percentage of the control values (Table 9). Statistical analysis was performed with Student's *t*-test and Wilcoxon signed-rank test (*P<0.05).

We could show a significant suppressive effect of thiopentone and propofol on transendothelial migration. Exclusive treatment of leukocytes resulted in a reduction in transendothelial migration that was similar to the results obtained with other test systems. However, treatment of both leukocytes and endothelial cell monolayers showed an additive effect which was not detectable by the other assays used in previous studies.

27. *In vitro* effects of the serotonin receptor agonist DOI on skeletal muscles from malignant hyperthermia susceptible patients are attenuated by dantrolene

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In susceptible pigs malignant hyperthermia (MH) is triggered by the administration of serotonin agonists which stimulate the serotonin$_{2A}$ receptor [1]. Addition of dantrolene completely abolished MH induced by serotonin$_2$ receptor agonists [1] *In vitro* studies with human skeletal muscles showed that the serotonin$_2$

Table 9. (abstract 26). Effect of propofol and thiopentone on transendothelial migration.

	untr. PMNL- untr. ECM	*treat* PMNL- untr. ECM	untr. PMNL- *treat* ECM	*treat* PMNL- *treat ECM*
Thiopentone	100%	88%*	79%*	72%*
Propofol	100%	96%	87%*	78%*
Lipofundine	100%	not done	not done	97%

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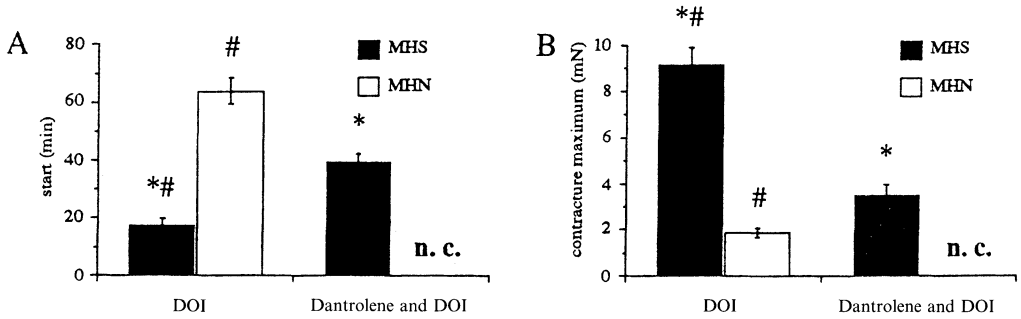

Fig. 9. (abstract 27) Start of muscle contracture (A); contracture maximum (B). n.c. = no contractures *P<0.05 vs. MHN; #P<0.05 vs. Dantrolene + DOI.

receptor agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) induced contractures in specimens from MH susceptible (MHS) but not in specimens from nonsusceptible (MHN) patients [2]. The purpose of this study was to investigate the *in vitro* effects of DOI in skeletal muscles of MHS and MHN patients following pretreatment with dantrolene.

After institutional approval and informed consent, 18 patients aged 8–58 years (26.9 ± 13.7) with clinical suspicion for MH participated in this study. The patients were first classified as MHS and MHN by the caffeine halothane contracture test (CHCT) according to the European MH protocol [3]. Surplus muscle specimens of 10 MHS and 8 MHN patients were used in this study. In the first experiment, DOI was added to the bath in a concentration of 0.002 mM. In the second part of the study, muscle specimens were preincubated with dantrolene 1.0 μM for 10 min and subsequently DOI10.02 mM was added to the organ bath. The *in vitro* effects on contracture development and muscle twitch were observed for 90 min. Data are presented as mean ± SEM. Statistical significance (P<0.05) was evaluated using the Wilcoxon and Mann–Whitney U-tests.

Muscle specimens of all patients developed contractures after administration of DOI 0.02 mM (Fig. 9). Contracture development started significantly earlier in MHS than in MHN muscles. In MHS muscles the maximum of contracture was significantly greater than in MHN. The muscle twitch decreased significantly in both groups following administration of DOI. After pretreatment with dantrolene the start of contractures was significantly delayed in MHS muscles. In MHN muscles no contracture development was observed. The maximum of contracture was significantly reduced in MHS. Muscle twitch decreased in both groups.

The development of DOI-induced contractures in skeletal muscle specimens from MHS individuals indicates, that an altered serotonin system might be involved in MH-induction in humans. Dantrolene was shown to be effective in prevention of serotonin-induced contracture development of skeletal muscles from MHS patients. Further investigations are needed to determine, whether serotonin$_2$ receptors of skeletal muscles from MHS subjects are disordered in function or structure.

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28. Preoperative creatine kinase blood levels and myopathological changes in malignant hyperthermia

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In malignant hyperthermia (MH) the fundamental lesion is located in skeletal muscle fibres. The underlying

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cause of MH is suggested to be an increase in myoplasmic calcium, which is released from the sarcoplasmic reticulum. Although MH is believed to represent myopathy, patients susceptible to MH (MHS) rarely have clinical evidence of muscle diseases [1]. Creatine kinase (CK) as muscle cell enzyme is reported to predict MH disposition when blood levels at rest are raised [2]. The purpose of this study was to determine, whether any clinical prediction could be made of abnormal pre-operative CK blood levels or whether there is a correlation between raised CK values and histological abnormalities.

After institutional approval and written informed consent, 196 patients aged 3–71 years with clinical suspicion for MH were enrolled in this prospective study. The patients were first classified as MHS or MHN (MH non susceptible) by the caffeine halothane contracture test (CHCT) according to the European MH protocol [3]. Patients tested equivocal (MHE) were excluded from this study. Additionally, small muscle specimens (approximately $3 \times 3 \times 10$ mm) were excised from each patient for histological and morphometric investigation. Preoperative levels of CK in blood were measured and compared both with the CHCT and the histological results. Data are expressed as mean $\pm$ SEM or percentages, respectively. Statistical analysis was performed using the Mann–Whitney *U*-test. $P<0.05$ was considered significant.

80 from the 196 patients in this study (40.8%) were diagnosed MHS and 116 (59.2%) MHN. In the MHS patients 26 from 80 (32.5%) had elevated CK values compared to 13 from 116 (11.2%) in the MHN group. 52 (65%) of the MHS patients showed myopathological changes (9 specific, 43 unspecific), whereas only 49 (42.2%) of the MHN patients had any myopathological abnormalities (3 specific, 46 unspecific). Preoperative CK blood levels were increased in 39 patients (19.9%) and two thirds of these were classified MHS. While 88 of all patients were female (44.9%) the distribution was a little different in the two diagnostic groups with 26 (32.5%) female MHS and 62 (53.4%) female MHN patients. It was noticed that only 7 of the 39 patients with raised CK were female (17.9%) and all of them showed myopathological abnormalities both in the MHS group (4 female) and in the MHN group (3 female). In contrast only 50% of the male patients with preoperative elevated CK values showed myopathological changes with no differences between MHS and MHN.

The results demonstrate that it is not possible to distinguish MHS from MHN individuals by determining the CK blood levels at rest or using histological techniques. At present, the CHCT remains the only reliable test method for the diagnosis of MH susceptibility. There were significantly more male than female patients with elevated CK values. A further significant difference was that 100% of the females but only 50% of the male patients with elevated CK values showed myopathological abnormalities. We recommend that all patients with increased CK levels at rest should have muscle biopsy both for MH diagnostic and histological investigation.

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29. Morphological changes in malignant hyperthermia (MH) susceptible individuals

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Numerous studies investigated histological and histochemical alterations in MH susceptible patients and in their relatives [1]. Many, but not all patients, exhibit minor nonspecific skeletal pathologies. We performed detailed morphological and biochemical examinations of muscle specimens taken from individuals undergoing common *in vitro* contracture tests (IVCT) for MH clarification.

Biopsies of 75 MH suspicious individuals underwent diagnostic halothane and caffeine IVCT's according to the European MH Group protocol [2]. All biopsies were examined by detailed light- and electron microscopy (serial transverse cryostat sections: 18 histological, histochemical, enzyme- and immunohistochemical methods). Muscle dystrophy suspicious biopsies were

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referred to dystrophin Western Blot analysis. All examinations were carried out by an experienced investigator blind to the IVCT results.

58/75 specimens revealed myopathological alterations: 8 primarily myopathic changes, 9 neuropathic findings (peripheral neuropathological diseases). The majority (41) had morphological alterations (metabolic disorders) 4/41 a deficiency of myoadenylate-deaminase (MAD), 14/41 a striking lipid and glycogen increase in muscle fibres, 6/41 morphological changes (mitochondrial myopathies), 18/41 uncharacteristic nonspecific alterations (minimal change myopathies). 43/58 myopathological specimens were shown by IVCT to be MH suspicious: 20/58 MH susceptible (MHS), 22/58 equivocal to halothane (Mheh) and 1/58 equivocal to caffeine (MHec).

58/75 MHS or MHE classified individuals revealed morphological references to NMD's. According to other authors [3] most patients were primarily unaware of anaesthesia-related complications and/or NMD's in their families and did not report symptoms such as exertional muscle weakness, pain or cramps. However, after detailed questioning slight symptoms were discovered in the majority of the patients with clear myopathological alterations and we recommended them to undergo detailed neurological examination. The results of this study underline the importance of morphological and biochemical examinations with an experienced investigator in order to reveal underlying muscle diseases.

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30. Malignant hyperthermia (MH) susceptibility and myoadenylate deaminase (MAD) deficiency

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To date a clear association between MH susceptibility and underlying muscle disease has been shown for three clinical myopathies: King Denborough syndrome, central core disease and Evans myopathy. However, other more common myopathies such as Myoadenylate-deaminase (MAD) deficiency have also been thought to be associated with an increased risk of MH [1]. Thus we investigated in this study the occurrence of MAD deficiency in individuals who proved MH susceptible in the *in vitro* contracture test (IVCT).

Muscle specimens from 50 individuals clinically suspicious for MH were used for diagnostic IVCTs using halothane and caffeine. Specimens of all biopsies were referred to detailed light and electron microscopic examination, additionally molecular biological techniques were used. These examinations were undertaken by a blinded investigator, who did not know the result of the IVCT.

According to the protocol of the European MH Study Group 18 out of 50 individuals were diagnosed MH susceptible (MHS) and 17 out of 50 halothane equivocal (MHEh). Fourteen out of these MHS/MHEh individuals showed morphological signs of metabolic disorders. Two MHS and 3 MHEh individuals revealed a MAD deficiency that was proved by negative enzymatic biochemical and histochemical reaction. Two of the MHEh individuals were siblings. None of these individuals was aware of his enzyme deficiency, but all were suffering from subtile clinical symptoms (i.e. recurrent episodes of muscle pain and muscle weakness). None of the MHN individuals was MAD deficient.

Our data show that patients with MAD deficiency have an increased risk of MH as revealed by IVCT. Because MAD deficiency is one of the most frequent muscle diseases [2] it has to be taken into serious consideration in MH suspicious individuals with symptoms of muscle weakness and/or pain. In conclusion, our results strongly suggest that additionally to IVCT the muscle biopsies obtained from such patients should be examined by histological and biochemical methods.

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31. A comparison of the effects of tramadol and morphine on gastric emptying in man

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The major cause of delayed gastric emptying in the post-operative period is the administration of opioid

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analgesic drugs [1]. Impaired gastric emptying is associated with erratic absorption of orally administered medications.

Tramadol is an opioid analgesic agent with a potency comparable with pethidine used in the treatment of post-operative pain. Whether tramadol delays gastric emptying is unknown.

In a previous study we demonstrated that morphine 0.09 mg kg^{-1} delayed gastric emptying measured by a bioimpedance technique [2] in man. Using the same subjects and technique as previously described [2] we evaluated the effect of tramadol on gastric emptying.

In a randomized, double-blinded, cross-over placebo controlled study 10 healthy human volunteers were administered either placebo (saline) or tramadol 1 mg kg^{-1}. The rate of gastric emptying was measured using a non invasive epigastric bioimpedance technique. After the ingestion of 500 mLs of deionized water, the resultant changes in impedance can be used to follow gastric emptying of a liquid meal. The time to empty half the meal (T0.5) was calculated.

Previous data evaluating the effect of morphine 0.09 mg kg^{-1} on gastric emptying in the same subjects using the same technique allowed for comparative analysis [2].

The epigastric bio impedance technique was sufficiently sensitive to detect opioid induced changes in the rate of gastric emptying. The mean $\pm$ SEM time taken for gastric volume to decrease to 50% (T0.5) following placebo was 7.7 $\pm$ 1.2 mins.

No difference in gastric emptying rates (T0.5) between placebo and tramadol (9.5 $\pm$ 1.6 min) was noted. Morphine induced a prolongation of gastric emptying, to a T0.5 of 21 $\pm$ 2.9 min (P<0.05).

We conclude that tramadol does not delay gastric emptying in man.

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32. Timing of administration of dolasetron affects dose necessary to prevent post-operative nausea and vomiting (PONV)

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Administration of a 5-HT_3 receptor antagonist before induction of anaesthesia is based on the hypothesis that blocking the receptors is necessary prior to the emetogenic stimuli of anaesthesia and surgery. To test this hypothesis, we pooled eight clinical trials of oral or i.v. dolestron mesilate (DM) administered at four different intervals, pre- and post-surgery. DM is a new 5-HT_3 receptor antagonist, shown to prevent and treat PONV [1,2].

The eight pooled trials were designed identically (double-blind, placebo-controlled, randomized), had similar enrolment criteria (ASA physical status 1–3

Table 10. (abstract 32).

Percentage of patients with complete response

	Timing of DM Admin	No of trials	Placebo	Dolasetron Doses (mg) 12.5	25	50	100	OND 4 mg
IV Prevention	at induction	1	(n=128) 49%		(n=127) 51%	(n=129) 71%		(n=130) 64%†
Oral Prevention	1–2 h preinduction	2	(n=231) 33%		(n=234) 42%	(n=240) 52%†	(n=228) 52%	
IV Prevention	end of anaesthesia	3	(n=419) 41%	(n=419) 55%†	(n=420) 57%†	(n=421) 57%†	(n=267) 58%†	
IV Treatment	onset of PONV	2	(n=192) 11%	(n=196) 32%†	(n=184) 28%†	(n=191) 32%†	(n=194) 28%†	

† Statistically significant compared to placebo, P<0.05.

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patients), and used general balanced anaesthesia. Six trials (four i.v. and two oral) studied doses of DM for prevention of PONV. (One of the i.v. prevention trials used ondansetron (OND) as an active comparator.) Two trials assessed doses of DM for the treatment of established PONV in patients with moderate to severe nausea lasting >5 min and/or vomiting, within 2 h of awakening. The table lists number of trials, doses studied, and timing of DM or OND administration. Complete response (CR: no vomiting/retching and no rescue medication over a 24 h study period) was the primary endpoint.

When administered before or at induction of anaesthesia, the 50 mg dose was significantly more effective in preventing PONV than placebo and equivalent to OND (4 mg). The 25 mg DM dose was ineffective compared with placebo. When administered near the end of anaesthesia, the 12.5 mg DM dose produced significantly higher CR rates than placebo. CR rates with the higher doses were equivalent to the 12.5 mg dose. For treatment of established PONV, DM 12.5 mg was statistically superior to placebo for CR. Again, no increases in efficacy were recorded with higher DM doses (Table 10).

We conclude that blocking 5-HT_3 receptors prior to the emetogenic stimuli of anaesthesia and surgery is not required to prevent PONV. When dosed near the end of anaesthesia, a lower dose of dolasetron (12.5 mg) was as efficacious as 50 mg DM administered at or before induction of anaesthesia. The significant efficacy of DM 12.5 mg in treating established PONV further corroborate this finding. All doses were safely administered and well tolerated across the eight trials.

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2 *Anesthesiology* 1995; **83**: A7.

33. Dolasetron mesilate prevents and treats post-operative nausea and vomiting in female patients undergoing gynaecological surgery via laparoscopy

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Females undergoing laparoscopic gynaecological surgery experience a high incidence of post-operative nausea and vomiting (PONV) [1] DM is a 5-HT^3 receptor antagonist shown to be effective in preventing and treating PONV [2,3]. To assess the antiemetic efficacy of dolasetron mesilate (DM) in the prevention and treatment of PONV in these high-risk patients, a pooled analysis of females undergoing laparascopic gynaecological surgery across five trials was undertaken: using three PONV prevention trials and two treatments of established PONV trials.

All trials were identical in design (double-blind, placebo-controlled, randomized, multicentre). The trials had similar inclusion/exclusion criteria enrolling ASA physical status 1–3 patients. Anaesthesia regimens

Table 11. (abstract 33)

Three prevention trials	Placebo ($n=255$)	DM 12.5 mg ($n=265$)	DM 25 mg ($n=267$)	DM 50 mg ($n=268$)	DM 100 mg ($n=111$)
Complete response	91 (36%)	143 (54%)*	147 (55%)*	144 (54%)*	66 (59%)*
Median of maximum nausea scores	31 mm	11 mm*	13 mm*	16 mm*	8 mm*
Two treatment trials	($n=66$)	($n=66$)	($n=63$)	($n=71$)	($n=70$)
Complete response	8 (12%)	27 (41%)	18 (29%)*	27 (38%)*	17 (24%)
Median of maximum nausea scores	65 mm	38 mm*	40 mm*	39 mm*	48 mm*

* Statistically significant when compared to placebo, $P<0.05$.

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for all trials included N_2O, narcotic analgesic, skeletal muscle relaxant, and inhalational as needed. The three prevention trials studied placebo vs. single i.v. DM doses of 12.5, 25, and 50 mg (two of the three trials also studied a 100 mg dose), administered just prior to patient emergence from anaesthesia. The two treatment trials studied placebo and single doses of DM (12.5, 25, 50 and 100 mg) in patients with moderate to severe nausea lasting >5 min and/or vomiting within 2 h of entry into the recovery room. For all five trials, the efficacy endpoints were the same and measured for 24 h: complete response (CR = no vomiting/retching and no rescue medication) and maximum nausea self-reported by patients on a 100 mm visual analogue scale. Safety assessments used adverse event reports, labs, ECGs, and vital signs.

1166 female patients received prophylaxis for PONV and 208 female patients were treated for established PONV. Compared to placebo, all doses of DM were statistically significant in the preventing of PONV. The 12.5, 25, and 50 mg DM doses were statistically significant vs. placebo for treating established PONV. No increase in efficacy was seen with doses higher than the 12.5 mg DM dose. (Table 11). Headache was the most commonly reported adverse event with incidence similar to placebo. There were no dose-related increases in any adverse events.

Intravenous DM 12.5 mg is an effective antiemetic for females at high risk for PONV after undergoing laparoscopic/gynaecological surgery. No additional efficacy was observed with doses higher than the 12.5 mg DM i.v. dose. All treatments were safely administered and well tolerated.

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34. The influence of timing of morphine administration on post-operative pain and analgesic consumption

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To investigate whether a pre-emptive dose of morphine, given 30 min before skin incision influences post operative pain and morphine consumption after hysterectomy.

A clinically significant pre-emptive effect with opioids prior to surgery has not been established. Two studies [1,2] suggest that morphine given preoperatively, as opposed to at the end of surgery, may lead to reduced post-operative morphine consumption, but the morphine may not have been given early enough to fully pre-empt the noxious stimulus of surgery. This study was designed to see if 0.3 mg kg^{-1} of morphine given preoperatively affected pain scores and patient controlled morphine consumption, post-operatively.

In a prospective, randomized, double-blind, placebo-controlled clinical trial the primary end points were morphine consumption and pain scores in the first 24 h after surgery. Data were analysed by Mann–Whitney *U*-test and one-way ANOVA as appropriate.

Hospital ethics committee approval and written informed consent were obtained. Sixty ASA I or II patients scheduled to undergo elective abdominal hysterectony with or without salpingo-oophorectomy, through low transverse supra pubic incisions, were randomized to receive morphine (0.3 mg kg^{-1}) at either induction of anaesthesia or 30 min later at skin incision. Patients received a standardized general an-

Table 2. (abstract 34)

	Morphine at induction ($n=30$)	Morphine at incision ($n=30$)
Age (y): mean (range)	38.1 (22–56)	40.4 (29–55)
Weight (kg): mean (range)	63.5 (47–84)	64.5 (46–85)
Induction-Incision time (min)	32.5 (30–36.75)	33.5 (30–38)
Duration of surgery (min)	50 (40–64.5)	53.5 (41.5–67.75)
Morphine in recovery (mg)	0 (0–3.75)	0 (0–2)
24 h morphine use (mg)	58 (35.5–74.5)	57.5 (34.5–82.25)
VAS (AUC24 h)	1189 (709–1369)	1148 (749–1382)

Data presented as medians with interquartile ranges in brackets except age and weight.

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aesthetic with no further analgesics. In the recovery room patients were titrated to comfort with increments of intravenous morphine and connected to a patient controlled analgesia device, set to deliver a bolus of 1 mg of morphine with a lockout time of three minutes, which was then used for the first 24 h. Verbal rating and visual analogue pain scores were collected, at rest and on movement, at 1, 2, 4 and 24 h post-operatively. Following this patients received rectal diclofenac and oral coproxamol and were reassessed at 48 h.

The two groups were similar with respect to age, weight, duration of surgery and induction to incision time. There were no significant differences in 24 h morphine consumption or pain scores throughout the post-operative period.

We have been unable to identify a pre-emptive analgesic effect. It is possible that the surgical stimulus prior to morphine administration in the control group was not of sufficient duration to allow spinal cord 'wind up' to occur.

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35. The amplitude of the evoked potential to painful stimulation may not always correlate with the perceived pain intensity

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Recently, we have shown that isoflurane in subanaesthetic concentrations induced similar reductions in the amplitude of evoked potentials elicited by painful and non-painful stimuli [1]. But isoflurane did not reduce the perceived pain to the painful stimuli. This indicates that the amplitude of the evoked potentials may not always correlate with analgesia. The aim of the present study was to investigate the effect of a sedative (propofol) and an analgesic (alfentanil) on the amplitude of evoked potentials to laser, electrical and acoustical stimuli.

Table 13. (abstract 35)

Test	Propofol	Alfentanil
Laser EP	43 (22–72)	71 (41–132)
amplitudes N1/P2	*B, *A	*B, *P
Electrical EP	42 (33–68)	79 (31–134)
amplitudes N1/P2	*B, n.s. A	*B, n.s. P
Acoustical EP	43 (22–72)	71 (41–132)
amplitudes N1/P2	*B, *A	*B, *P
Laser EP	101 (74–162)	84 (45–109)
VAS	n.s. B, n.s. A	*B, n.s. P
Electrical EP	94 (45–122)	76 (24–123)
VAS	n.s. B, *A	*B, *P
Reaction time	124 (109–236) *B, *A	113 (98–192) *B, *P

All values (median (5–95 percentile)) are expressed as percentage of baseline.
* = $P<0.05$, n.s. = $P>0.05$.
P = propofol, A = alfentanil, B = base-line.

In a randomized, double-blind, cross-over study we investigated 12 healthy volunteers. Long latency evoked vortex potentials to painful laser [2] and electrical [3] stimuli, and non-painful acoustical stimuli were recorded. The perceived pain to the painful stimulations was assessed by VAS. Sedation was assessed by the reaction time. Profofol was given in a subanaesthetic concentration (bolus dose of 1 mg kg^{-1} i.v. plus an infusion of 30 $\mu g\ kg^{-1}\ min^{-1}$), and alfentanil in an analgesic concentration (bolus dose of 15 $\mu g\ kg^{-1}$ i.v. plus an infusion of 0.3 $\mu g\ kg^{-1}$ (min).

Propofol and alfentanil induced similar reductions in the amplitudes of the evoked potentials to laser, electrical and acoustical stimulations. However, only alfentanil reduced the perceived pain to the nociceptive stimulation. Reaction time was significantly more prolonged by propofol compared with alfentanil.

The present study shows (1) that sedation can influence the amplitude of the evoked potential to painful stimuli although no changes in the perceived pain are found, and (2) that propofol in subanaesthetic doses has no analgesic effect on painful electrical and heat stimuli. It is important (a) to control for the effects of sedation, when evoked potentials are used to measure an analgesic effect, and (b) to combine elec-

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trophysiological responses with psychophysical pain ratings.

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36. Pre-emptive analgesia revisited

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The concept of pre-emptive analgesia is an attractive one, but many investigators have failed to show any value in adopting a pre-emptive technique. This may be due to a lack of the essential modalities which include opioid, non-steroidal anti-inflammatory, neural blockade, NMDA blockade, anxiolysis and, possibly, sympathetic blockade. In an attempt to study this, a combination of the above modalites were compared with standard analgesia following surgery.

Adult patients undergoing upper extremity surgery under general anaesthesia were given either a standard premedication plus immediate post-operative analgesia or following induction of anaesthesia before the start of surgery:
opioid – tramadol 400 mgs i.v.
NSAID – ketorolac 30 mgs i.v.
Supra clavicular brachial block with bupivacaine 0.5%. Plain – 20 mLs.
NMDA antagonist – ketamine 0.5 mg kg^{-1} i.v.
Anxiolysis – diazepam 3.5 mg kg^{-1} 2 hrs pre-op.
All patients received a comparable general anaesthetic and post-operative analgesic requirements were monitoried for a minimum of 48 h.

There were 10 patients in each group. In the pre-emptive group, 9/10 required no analgesia for 48 h after surgery. 1/10 required 200 mg tramadol in Recovery and none for the following 48 h. In the control group, 10/10 required analgesia in Recovery and regularly for 48 h following. The pre-emptive group showed fewer adverse events than did the controls (2/10 nausea, 1/10 dizzy to 4/10 nausea, 1/10 vomiting, 3/10 dizzy).

Pre-emptive analgesia may be effective provided the combination of agents, doses and techniques are optimized.

37. Neuraxial vs. intravenous fentanyl and their role in pre-emptive analgesia

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This study compared the efficacy and side effects of pre-incisional neuraxial fentanyl (spinal epidural) versus intravenous fentanyl for postoperative pain relief. A total of 60 patients ASA I-III were scheduled for intra-abdominal and orthopaedic surgery. The patients were randomly allocated in two equal groups of 30 patients each: Group I patients received spinal analgesia, while Group II patients received spinal analgesia. Each group was further subdivided into two equal subgroups of 15 patients each, according to the route of fentanyl administration: Subgroup IA patients received fentanyl 25 μg intrathecally, and subgroup IIA patients received fentanyl 50 μg epidurally, while subgroup IB and IIB patients received fentanyl i.v. before incision, titrated according to the patient's response, with careful recording of the total dose administered by the end of surgery.

All patients in both groups showed good cardiorespiratory stability, and side-effects were minimal in either group. However, patients who received i.v. fentanyl required a higher total dose when compared with neuraxial fentanyl.

Pain scores were lower in patients under neuraxial fentanyl, and not only did these patients require less postoperative analgesic doses of fentanyl but also their requirements for analgesia were considerably delayed when compared with patients given fentanyl parenterally.

In conclusion, neuraxial pre-emptive fentanyl proved superior to parenteral fentanyl with lower pain scores, decreased and delayed analgesic requirements, and only minimal side effects.

38. Spinal anaesthesia with pethidine: effects of added alpha-adrenergic agonists epinephrine and clonidine

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Pethidine has local anaesthetic properties, and given intrathecally provides a good operative anaesthesia for a variety of surgical procedures. The prolonged

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postoperative analgesic effect of spinal pethidine compares favourably with local anaesthetics. Assuming that pethidine acts as a local anaesthetic, drugs that alter the action of local anaesthetics might have a similar effect upon it. The present study was undertaken in order to determine whether co-administration of adrenaline or clonidine with pethidine influences the quality of spinal anaesthesia and duration and the quality of postoperative analgesia.

After institutional approval and informed consent, 45 patients were randomly allocated to one of three equal groups, scheduled for orthopaedic surgery, to receive pethidine 1mg kg^{-1} pethidine plus 200 μg adrenaline or pethidine plus 2 μg kg^{-1} clonidine. After intrathecal injection of the drug, sensory block (to pinprick) and motor block (Bromage scale) were assessed at 2-min intervals until a constant block was obtained and at 15-min intervals after operation until the regression of sensory block to the second lumbar dermatome and return of full motor function. Blood pressure and heart rate were monitored every min for first 15 min and every 5 min thereafter. After operation, time to first demand for analgesic administration was noted. The degree of sedation (Ramsay scale) and the occurrence of side effects were also recorded.

There were no statistical differences between the groups in terms of age, height, weight and duration of operation. The addition of adrenaline to pethidine prolonged the duration of sensory block (P<0.01) but did not affect its onset and extent. A similar potentiating effect was demonstrated for clonidine (P<0.001), with no differences between clonidine and adrenaline. The duration and the degree of motor paralysis were increased by the addition of both adrenaline and clonidine. Bradycardia and a decrease in mean arterial pressure was potentiated by clonidine, but not by the adrenaline. Only the addition of clonidine prolonged the post-operative analgesia (P<0.001), but was associated with an increased sedation score. The incidence of other side effects did not differ between the groups.

Addition of alpha-adrenoreceptor agonists adrenaline and clonidine to intrathecal pethidine prolongs the duration of sensory and motor blockade. The post-operative analgesia is significantly prolonged by addition of clonidine but not by adrenaline.

39. Temporal summation after spinal anaesthesia

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Weak stimuli may evoke pain if they are repeated or their duration is prolonged (temporal summation). Prolonged nociceptive input increases excitability in the spinal cord (central sensitization), which probably plays an important role in the pathophysiology of pain syndromes. [1] In a previous study we found that epidural anaesthesia inhibits poorly temporal summation of repeated electrical stimuli: pain thresholds to repeated stimuli were significantly lower than pain thresholds to single stimuli, and pain to repeated stimuli was only blocked in one of ten patients. The aim of the present study was to assess the effect of spinal anaesthesia on temporal summation, using the same methods as in the epidural study.

Eight patients (ASA I-II, age 18–55), undergoing spinal anaesthesia with plain bupivicaine 0.5% (18 mg) at L2-3, were studied before surgery. Subjective pain thresholds to single and repeated (five times at 2 Hz) electrical stimulation, delivered through surface electrodes placed distal to the lateral malleolus, were recorded. Temporal summation threshold was defined as the current intensity at which the last 1 or 2 of the five repeated stimuli were perceived as painful.

Table 14. **(abstract 39)** Pain thresholds (mA) mean values and ranges

	Basal	10 min	20 min	30 min	40 min
Single stimulus	5 (2–7)	60 (19–60)	60 (39–60)	60 (60–60)	60 (60–60)
Repeated stimuli	4 (1–7)	60 (19–60)	60 (50–60)	60 (60–60)	60 (60–60)

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Current intensity was increased in steps of 1–5 mA until pain was evoked, or a current of 60 mA was reached. Assessments were made before and 10, 20, 30 and 40 min after the administration of bupivacaine. Pain thresholds after single and repeated stimulation were compared by Wilcoxon signed rank test at each time of the experiment. $P<0.05$ was considered significant.

The table shows the median values (ranges) of pain thresholds in mA after single and repeated electrical stimuli. No statistically significant difference was found at any time. Pain to both single and repeated stimulation was blocked in all patients after 30 min.

Spinal anaesthesia inhibits temporal summation elicited by repeated electrical stimulation. Spinal anaesthesia, unlike epidural anaesthesia in our earlier study, blocked temporal summation in all patients. Spinal anaesthesia may therefore prevent central hyperexcitability to a larger extent than epidural anaesthesia.

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40. The influence of maternal supplemental oxygen on fetal oxygenation during caesarean section under spinal anaesthesia

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Despite the knowledge that the partial pressure of oxygen in umbilical venous ($UVPO_2$) and umbilical arterial ($UAPO_2$) increase both under general anaesthesia and in proportion to maternal inspiratory oxygen concentration (FiO_2), there has been little investigation of the need for supplemental oxygen during spinal anaesthesia [1]. Fetal oxygen delivery is compromised after uterine incision and thus oxygen stores are important until sustained breathing commences. This study examined the optimum maternal FiO_2 during Caesarean section under spinal anaesthesia.

With ethics committe approval and written informed consent 112 women having uncomplicated elective Caesarean section were randomly allocated to FiO_2 of 0.21, 0.40, 0.60 or 1.0 provided by appropriate masks. A base-line maternal arterial blood sample (M_1PO_2) was obtained prior to administration of a fluid preload and spinal anaesthetic using 2–2.5 mL 0.5% hyperbaric bupivicaine. At delivery umbilical venous and arterial blood samples and a further maternal arterial (M_2PO_2) sample were taken. Apgar scores were recorded at 1 and 5 min. Data were analysed using ANOVA and Kruskal–Wallis tests as appropriate. A P-value <0.05 was taken as significant.

There were no demographic or obstetric differences between groups. Oxygen administration to the mother increased M_2PO_2 in all groups but this produced a significant increase in $UVPO_2$ only in the 1.0 FiO_2 group. This group also showed a significant increase in umbilical venous-arterial oxygen difference ((UV-UA)PO_2) (Table 15).

Fetal oxygenation during Caesarean section under spinal anaesthesia was improved with higher FiO_2 but the difference was significant only with FiO_2 of 1.0.

Table 15. (abstract 40). Blood gases (mmHg, mean and SD); Apgar scores (median and range). *$P<0.05$

FiO_2	0.21	0.40	0.60	1.0
No of Patients	26	32	28	26
M_1PO_2	126 (24.7)	117 (20.1)	123 (22.3)	129 (27.3)
M_2PO_2	123 (13.5)	182 (21.3)*	229 (37.9)*	329 (73.1)*
UVpH	7.36 (0.030)	7.36 (0.058)	7.36 (0.054)	7.38 (0.038)
UAPH	7.310(0.054)	7.304 (0.036)	7.310 (0.067)	7.323 (0.042)
$UVPO_2$	27 (4.5)	29 (5.6)	29(6.0)	34 (7.6)*
(UV-UA)PO_2	12 (4.1)	14 (5.0)	14 (4.2)	16 (7.6)*
APGAR 1 min	8 (7–9)	8 (7–9)	8 (8–9)	8 (8–9)
APGAR 5 min	9 (9–10)	9 (8–10)	9 (9–10)	9 (9–10)

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The results of this study concur with a previous study of Caesarean sections under epidural anaesthesia [2].

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41. Laryngeal mask airway position and gastric insufflation

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The laryngeal mask airway (LMA) is now widely used in daily clinical anaesthesia practice. Despite widespread use due to its safety and efficacy [1], the definitive role of the LMA has yet to be established, particularly in situations where high airway pressures may occur [2].

After approval by the Ethics Commitee and informed patient consent, 108 patients (18–71 y, 150–190 cm, 48–115 kg) undergoing minor surgical procedures were studied. Size 4 LMA was used for females, and size 5 LMA for males. Airway pressure was measured with the Barolog A (Draeger). Gastric insufflation was detected using a epigastric microphone. Tidal volumes were increased breath-by-breath until one of three criteria was fulfilled: (1) insufflation of air into the stomach, (2) airway pressure >40 mbar, (3) air leakage preventing further increases in tidal volume. Fibreoptic assessment of LMA position (LF 2, Olympus) was performed according to a method previously described [3]: LMA position was classified depending on the mask position (central, ventral, dorsal, right, or left) in relation to the laryngeal entrance. The degree of epiglottic obstruction and luminal narrowing was scored visually as 0, 1 to 25, 26 to 50, 51 to 75 or 76 to 100%. Multivariate regression analysis was used to detect correlations between gender, body mass index, narrowing of mask lumen by the epiglottis, LMA position, and gastric air insufflation. Significance level was set at $P<0.05$.

There was no correlation between fibreoptic observations and the clinician's assessment that the LMA was correctly positioned. In 43 of 108 patients (40%), the LMA was found to be malpositioned (ventrally, dorsally, to the left or right). In 21 patients (19%), air entering the stomach could be detected at various airway pressures. 19 of the 21 (90%) had a malpositioned LMA. In 19 of 43 patients with malpositioning (44%) air insufflation into the stomach occurred. According to logistic regression analysis, a malpositioned LMA was associated with a 26 times higher probability of air insufflation than a correctly positioned LMA. Gender, body mass index or obstruction of the mask by the epiglottis had no influence on air insufflation into the stomach via the LMA.

Gastric air insufflation at airway pressures >20 mbar was in 90% of cases associated with lateral, ventral and dorsal LMA malpositioning. All patients were satisfactorily ventilated, even those with gastric air insufflation. Gastric air insufflation, however, occurred independently of gender, body mass index or obstruction of the mask by the epiglottis. Other authors [3] found unobstructed views in 13% of patients compared with 65% in our study; they also noted ventilation to be unimpeded by the epiglottis in the mask lumen. Since gastric air insufflation with the LMA during intermittent positive pressure ventilation above 20 mbar is unequivocally related to mask malpositioning, and since routine fibreoptic confirmation of LMA position is not feasible in daily practice, we conclude that the LMA should be used with caution in obese patients and those with reduced lung compliance.

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42. Clinical evaluation of the Combitube®

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The Combitube® (CT), a twinlumen tube designed to provide ventilation after blind intubation, is either placed into the oesophagus or trachea. It has proved

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to be useful in establishing an airway during CPR and in patients with difficult airway situations. Aim of this study was to determine efficacy and safety of the CT for emergency airway management. To obtain reliable data, the CT was used during the controlled setting of elective general anaesthesia (GA).

After approval of the Local Ethics Committee and informed consent, 50 patients (ASA grade I–II, Mallampati grade I) were included. Haemodynamic parameters, oxygen saturation, pCO_2, ventilatory parameter complications were recorded. GA was induced with thiopentone, fentanyl, atracurium (0.5 mg kg^{-1}) and maintained with enflurane, nitrous oxide/oxygen. For intubation the patients head remained in a neutral position and the CT was inserted blindly until the two markings on the CT were adjacent to the patients upper incisors. Ventilation was first checked with the head in the neutral position followed by a hyperextended position.

All CTs were inserted within 12 to 23 s, always positioned in the oesophagus. In 47 patients a sufficient airway was established at the first attempt. In 3 applications the CT had to be withdrawn 1–2 cm from its initial position to achieve successful ventilation (obstruction of the glottic opening by the upper cuff). Better ventilation conditions were observed in all patients with the head placed in the hyperextended position compared with the neutral position. Major difficulties during ventilation occurred in 11 patients: 60 min after the initial neuromuscular blockade and beginning of positive pressure ventilation, peak pressures increased slightly, accompanied with a sound produced in the laryngeal region. Seconds later sufficient ventilation became impossible. After a repeated dose of atracurium airway pressure returned within 60 s to base-line values. Similar symptoms occurred during recovery from anaesthesia under positive pressure ventilation: sufficient ventilation could be maintained by elevating the jaw with the head in a hyperextended position. After return of spontaneous ventilation, there were no more signs of any airway obstruction. Mucosal bleeding was observed in 12 patients. There were no signs of gastric insufflation or regurgitation.

The CT allowed a reliable airway to be established in all patients, but was always positioned in the oesophagus. The markings on the CT are not suitable for all patients and following the instruction manual (positioning the CT between both markings) led to airway obstruction in 3 cases. In 11 patients a closure of the vocal cords occurred due to obstruction of the glottic opening with impaired ventilation. During controlled ventilation neuromuscular blockade with a deep level of anaesthesia are necessary to prevent this complication.

The CT can be regarded as an alternative airway management device during CPR or during emergency management of a difficult airway, if conventional endotracheal intubation can not be performed immediately. The immediate use of the CT may offer the possibility of prompt ventilation after blind intubation. This is the major advantage of the CT, but for safe use, frequent training is essential.

43. Light-guided endotracheal intubation – benefits and side effects

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The light-guided intubation is based on the principle, that a light brought into the trachea results in clearly visible transcutaneous illumination, whereas no illumination can be observed if placed in the oesophagus. The Trachlight® is a recently introduced instrument incorporating a length-adjustable stylet with a removable internal wire, a source of light, a

Table 16. **(abstract 43)** Intubation outcomes

Criteria	LGI	CI	Criteria	LGI	CI
Successful intubation (*n*)	46	49	Voice changes	26	27
Sore throat (*n*) ($P<0.05$)	14	29	Bleeding	0	1
TMJ: restricted mouth opening (*n*)	2	12	TMJ: pain post-operatively (*n*)	2	6

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stable handle tight fixation of the tube warning device to avoid extended intubations.

The study was designed to evaluate the handling, application, problems, and limitations of the method with the indications for the method, compared with conventional intubation.

One hundred patients (informed consent, ethics committe approval, Mallampati I, ASA I-III) were randomly allocated to one of 2 groups (each $n=50$):

- Testgroup LGI: light-guided intubation (Trachlight®, Laerdal Comp.)
- Testgroup CI: conventional laryngoscopic intubation (Macintosh blade, size 3).

The recorded parameters were: course and duration of intubation, complications and difficulties, changes in cardiovascular responses (20 patients in each group), postoperative incidence of sore throat and temperomandibular joint (TMJ) problems.

Forty-six patients in group LGI were intubated successfully, the mean time needed was 29.9 ± 14.8 s (range: 6–61 s). In group CI 49 patients were intubated without problems, the average time needed was 24.9 ± 13.7 s.

In group LGI the following positive results can be summarized (see Table 16): easy handling and application, no injury to soft tissues or teeth, always correct placement of the tube, reduced incidences of TMJ-disorders and sore throat complaints. As (serious) problems appeared in group LGI: a sufficient transillumination was only achieved after (entire) dimming of the room (<100 Lux), insufficient control over the distal end of the tube due to unfixed metal wire, unintentional switching off of the light, difficulties in drawing back the metal wire, disturbing effects caused by the warning device. Reasons for 4 unsuccessful attempts were: introduction into the oesophagus despite a supposed correct position ($n=2$), insufficiently clear transillumination (2 obese patients). Cardiocirculatory parameters showed no changes during the laryngeal manipulation, clear increases in heart rate and blood pressure were recorded however when pushing forward the tube into the trachea (no difference CI-LGI).

The light-guided intubation technique can be regarded as another technique for airway-management. The indication for the technique is for patients who are not expected to be difficult to intubate but avoids damages to soft tissue and avoids traumatizing TMJ movements. Clinical use may be limited, by the environment brightness when airway difficulty is expected, fibreoptic intubation has still to be considered to be first choice.

44. Depression of movement (MAC) does not indicate depression of nociception during isoflurane anaesthesia in humans

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Isoflurane can suppress the movement response (MAC), but not the haemodynamic reactions, to painful stimulation [1,2]. The aim of the present study was: (a) to compare the effects of isoflurane on the movement response (skin incision simulated with an electrical stimulus [3]) and on the nociceptive reflex to repeated electrical stimulations [4], and (b) to evaluate the direct neuro-muscular effects of isoflurane by recording the M-response (muscle response to direct motor nerve stimulation) and H-reflex (mono synaptic reflex, afferent sensory, efferent motor).

Twelve healthy volunteers (6 female, mean age 24.0 years (22–28)) were anaesthetized with isoflurane at 6 different concentrations (0.80, 1.00, 1.20, 1.40, 1.60, 1.80 vol % end-tidal (random order)). At each concentration, recordings were performed (random order): (1) the movement response to electrical tetanic stimulation (5 sec, 60 mA, 50 Hz, 0.25 ms square-wave) applied to the volar side of the forearm (MAC-tetanus), (2) temporal summation of the nociceptive withdrawal-reflex of the leg to repeated electrical stimulations (five 25 ms trains of five 1 ms square-wave repeated at 2 Hz) of the sural nerve distal to the lateral malleolus, and (3) the M-response and the H-reflex to transcutaneous electrical stimuli of the tibial nerve at the popliteal fossa.

All 12 volunteers moved in response to the tetanic stimulation at 0.80 vol % isoflurane, 10 at 1.000 vol %, 8 at 1.20 vol %, 1 at 1.40 vol %, and none at 1.60 and 1.80 vol %. A temporal summation could be recorded in all volunteers at 0.80 vol % isoflurane. In 9 volunteers a temporal summation could still be recorded at 1.60 and 1.80 vol % isoflurane. Isoflurane

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only slightly depressed the muscle response to direct motor nerve stimulations (max 30%). The H-reflex could be recorded in all volunteers when awake, but only in 8 volunteers during isoflurane. There was no correlation between the effects of isoflurane on the recorded parameters (Cohen's kappa coefficient).

The present study questions the movement response used in the MAC concept as a measure of adequate anesthesia. Depression of the movement response to painful stimulations does not indicate depression of nociceptive transmission. It is very surprising that nociceptive withdrawal reflexes could be recorded at the concentrations of 1.60 and 1.80 vol % when the volunteers would not have moved in response to a surgical skin incision. Muscle afferents and the higher stimulation frequency (TENS analgesia is high frequency stimulation) used during tetanic stimulation may have an influence at the 'spinal gate'.

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45. The effects of volatile anaesthetics to antioxidant defence systems

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The effects of the volatile anaesthetics that are used to maintain general anaesthesia; on antioxidant defence mechanisms are reported.

Under the permission of the ethics committee of the hospital this study was with 33 female patients ASA-I aged between 20–60 years old. All these patients were prepared for multi nodular goitre surgery. The patients were allocated to one of 3 groups according to the volatile anaesthetics that were used, halothane, enflurane, isoflurane. Pre-operative first hour, post-operative first hour, first and third day blood samples of the patients were taken. Plasma and erythrocytes levels of superoxide dysmutase (SOD), glutathion peroxidase (GSHPx) and cofactors such as selenium (Se), zinc (Zn), copper (Cu) were measured using atomic absorption spectrophotometry.

In the halothane group plasma GSHPx level markedly increased by the third post-operative day ($P<0.01$), Zn level decreased at first hour and third day post-operatively. The erythrocyte SOD level decreases by the first post-operative hour, GSHPx, Zn, Se, Cu levels decrease by first hour, first day and third day post-operatively ($P<0.01$).

In the enflurane group plasma GSHPx level markedly decreased by the third day post-operatively ($P<0.01$), Zn level decreased by the first post-operative day. In the erythrocyte SOD level decreased by the first hour, GHSPx, Zn, Cu, Se levels decreased by the first hour, first day and third day post-operatively ($P<0.01$).

In the isoflurane group plasma antioxidant enzyme levels showed no change, Zn level decreased by the first and third post-operative day ($P<0.01$). In the erythrocyte, SOD level showed a decrease by the first hour and first day. GSHPx, Zn, Cu, Se levels decreased by the first hour, first day and third day post-operatively ($P<0.01$).

In halothane and enflurane group GSHPx was significantly raised by the third day after operation. There were no differences in the isoflurane group. As a result halothane and isoflurane influence the antioxidant defence system by producing free radicals in high quantity from membrane injury but production of free radicals of isoflurane is not as high as following membrane injury. A decrease in trace elements also make us think that anaesthetics destroy the antioxidant defence mechanism.

These results are consistent with studies of Barth [1], Miwako Nakagawara [2] and Kudau [3].

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46. Laboratory analysis of influence of methane, on infrared halothane and isoflurane read-out of volatile anaesthetics

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It has been shown that methane can accumulate in closed circuit conditions [1] and influence falsely the infrared (IR) anaesthetics monitor [1,2].

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Table 17. (abstract 46) Methane influence on halothane analysis

Halothane sensitive	Ultima	Elsa	Cicero	Cicero EM
100 p.p.m. methane	0.13	0	0.1	0
500 p.p.m. methane	0.72	0	0.4	0
1000 p.p.m. methane	1.5	0	0.8	0
100 p.p.m. + 1% halothane	0.99	0.9	1	0.8
500 p.p.m. + 1% halothane	1.7	1	1.6	0.9
1000 p.p.m. + 1% halothane	2.4	0.9	1.7	0.9

Table 18. (abstract 46) Methane influence on isoflurane analysis

Isoflurane sensitive	Ultima	Elsa	Cicero	Cicero EM
100 p.p.m. methane	0.01	0	0	0
500 p.p.m. methane	0.11*	0	0.1	0
1000 p.p.m. methane	0.25*	0	0.2	0
100 p.p.m. + 1% isoflurane	0.83	0.8	0.8	0.7
500 p.p.m. + 1% isoflurane	0.93	0.8	0.9	0.7
1000 p.p.m. + 1% isoflurane	1.1**	0.8	0.9	0.7

*Message 'Halothane detected'; **Message 'Mixed agent detected'.

It was the purpose of this study to analyse *in vitro* the influence of different known methane concentrations: 100, 500 and 1000 p.p.m. in an O_2, N_2O, and CO_2 gas mixture. Four I.R. side stream stand alone or built-in analysers were studied: Ultima (Datex), Elsa Engström (Datex), Cicero (Dräger) and Cicèro EM (Dräger). Respectively halothane and isoflurane sensitivities were analysed. After each set of measurements either 1% halothane or 1% isoflurane were added to the above mentioned methane mixtures.

'Halothane' and 'isoflurane' readings in vol % are shown in tables 17 and 18.

These results show that methane has a dose dependent influence on 'halothane' readings measured at 3.3 μm wavelength, and a lesser influence on 'isoflurane' readings. The measured values are added to the true, correctly measured values. With the Elsa, working at 8.8 μm and the Cicero EM, working at 10 μm wavelength, no methane influence is noticed.

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47. Clinical significance of lipid solubility of non-depolarizing muscle relaxants

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In contrast with the former opinion that lipid membranes (e.g. blood-brain barrier BBB) are not permeable to non-depolarizing muscle relaxants, one now has to assume that permeability of the blood-brain barrier does exist at least in pathological conditions of the central nervous system (CNS). Under these conditions the partition coefficient (relation between distribution in lipid and aqueous phase) may be a useful way to quantify the barrier permeability of drugs.

As previously described [1] the partition coefficient measurements at pH = 7.4 ($VK_{pH=7.4}$) of 3 muscle relaxants (vecuronium, pancuronium and atracurium)

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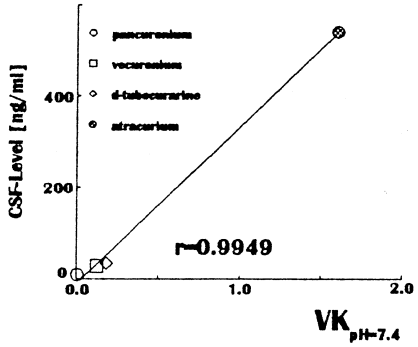

Fig. 10. (abstract 47).

using n-octanol and buffer solution are measured ($n=6$). The measured $VK_{pH=7.4}$-values were completed by data for d-tubocurarine and compared with the data found by van Sluijs & Meijer [2]. In a previously established BBB model in pigs [3], the cerebrospinal fluid (CSF)–concentration levels of vecuronium, pancuronium and atracurium, following a bolus dose and continuous infusion were analysed. The concentrations of muscle relaxants were determined both in intact and after osmotic disruption of the BBB.

Pancuronium showed a very low $VK_{pH=7.4}$-value, the $VK_{pH=7.4}$-values for d-tubocurarine, vecuronium and atracurium were significantly higher. In the experimental study we found differences between the CSF levels of vecuronium, pancuronium and atracurium with intact BBB. After disruption of the barrier, vecuronium and atracurium concentrations showed a 4–6-fold increase, whereas the pancuronium level was only 2-times higher.

Matteo *et al.* [4] reported similar results for d-tubocurarine, particularly in patients with midbrain tumors or comparable deficits. Fluid levels showed a 5-fold increase in comparison with other patients. It can therefore be supposed that conditions in patients are similar to those in the animal experiment. In case of an underlying disruption of the blood-brain barrier, substances with higher $VK_{pH=7.4}$-values show significantly increased permeability.

We conclude that the partition coefficient can be used to predict the penetration of a substance into CSF and CNS as the $VK_{pH=7.4}$-values and measured fluid levels correlate with an almost linear relation (Fig. 10). As patients with pathological conditions of the CNS in intensive care units may undergo carefully dosed long-term administration of muscle relaxants, only drugs with low $VK_{pH=7.4}$-values should be used in order to avoid serious side effects.

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48. Pharyngeal function and airway protection in partially paralysed humans. The effect of atracurium

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In the post-operative period, residual effects of anaesthetic agents may affect pharyngeal function and airways protection. Until recently, the function of the pharynx and upper oesophagus has been difficult to study in humans. Simultaneous videoradiography and solid state manometry of the pharynx, larynx and upper oesophagus has proved to be a useful method in various patient populations [1–2]. The present study was designed to determine the effects of residual neuromuscular block on pharyngeal function and airway protection and the relation to recovery of adductor pollicis train-of-four (TOF) ratio in awake humans.

Fourteen healthy humans with no history of oral or pharyngeal surgery, gastro-oesophageal reflux disease or neuromuscular disorder were studied. After 4 h fasting, a catheter with 4 solid state pressure transducers located 2 cm apart was introduced through one nostril and positioned in the pharynx and upper oesophagus. The subjects were placed in the right lateral position with a 15° head-up tilt. ECG, intermittent blood pressure and pulse oximetry were monitored. Simultaneous videoradiography and manometry (Synectics®, Sweden) was performed during rest and liquid contrast bolus swallowing. During each recording, the position of the pressure transducers was assured with fluoroscopic control. The following variables were recorded as the mean of five consecutive swallows: Pressure in the upper oesophageal

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sphincter (UES) at rest and contraction, contraction pressure in the inferior pharyngeal constrictor muscle (PHCI) and at the base of the tongue, pharyngeal transit time and coordination of PHCI and UES activity. In addition, tracheal aspiration and penetration events were recorded. The mechanical adductor pollicis TOF response (2 Hz for 2 s every 11.5 s) was recorded using a Myograph 2000® NMT analyser (Organon, Belgium). After control recordings, an i.v. infusion of atracurium (0.5 mg mL^{-1}) was given and adjusted to obtain TOF ratios of 0.60, 0.70 and 0.80. Thereafter the infusion was stopped and a TOF ratio of >0.90 was awaited. Statistical analysis was performed using ANOVA for multiple measures.

At a TOF ratio of 0.60, the resting and contraction pressures in the UES was significantly reduced. Even after recovery to a TOF ratio of >0.90 the UES resting pressure remained reduced. The tongue base and PHCI pressure slopes were reduced at TOF ratio 0.60, but were not significantly reduced at 0.70 or above. Six of 14 studied subjects aspirated one or several times at a TOF ratio of 0.80 or below, and one at a TOF ratio of >0.90.

We conclude that partial paralysis due to atracurium is associated with impaired pharyngeal and upper oesophageal sphincter function, resulting in impaired protection of the airway and risk of aspiration. Videoradiography and simultaneous manometry should be useful in the investigation of other anaesthetic agents and their effects on pharyngeal function and airway protection.

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1 *Dysphagia* 1993; **8**: 270–275.
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49. The effects of age on the onset and recovery of atracurium, rocuronium and vecuronium during enflurane anaesthesia

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Elderly patients might suffer from a number of age-related deteriorations in physiological functions. These may be responsible for prolonged duration of some neuromuscular blocking agents (NMB) [1–3]. The aim of this study was to investigate the onset and recovery of atracurium (A), rocuronium (R) and vecuronium (V), administered to elderly patients under enflurane anaesthesia.

After approval by the Ethics Committee and subjects written informed consent, we studied 108 patients allocated into three Groups (I–III) according to age (18–50, 51–64, $\geq$65 y). Following oxazepam premedication and fentanyl and thiopentone induction, patients were randomly allocated to receive A, R or V (0.5, 0.6, 0.1 mg kg^{-1} respectively) in $\leq$0.8 Vol % enflurane (end-tidal) and N2O anaesthesia. Adductor pollicis muscle responses to supramaximal stimulation of the ulnar nerve at the wrist (single twitch, 0.1 Hz) were recorded with Relaxograph EMG (Datex®). The time to maximum block (onset) and time to 25, 75 and 90% twitch height (T) recovery were measured. Results are presented as means $\pm$ S.E.M. Statistical comparisons were made using Wilcoxon and Log-Rank tests, except for T90%. $P<0.05$ was regarded as significant.

Table 19. (abstract 49). Onset and recovery of A, R, V (min) (mean $\pm$ SD), $P<0.05$ between I/III*, I/II▲, II/III●

		Atracurium (A)	*n*	Rocuronium (R)	*n*	Vecuronium (V)	*n*
Onset	I	3.2 $\pm$ 1.4	12	3.3 $\pm$ 1.8	12	3.4 $\pm$ 1.0	12
	II	3.9 $\pm$ 1.6	12	3.5 $\pm$ 2.2	12	3.0 $\pm$ 0.6	12
	III	4.7 $\pm$ 2.5	12	2.6 $\pm$ 1.7	12	4.1 $\pm$ 1.9	12
T25%	I	46.5 $\pm$ 8.9	12	34.8 $\pm$ 9.4*	12	42.7 $\pm$ 14.8*	12
	II	44.8 $\pm$ 6.1	12	54.1 $\pm$ 17.3▲	12	56.9 $\pm$ 21.1	12
	III	52.9 $\pm$ 18.2	12	54.3 $\pm$ 27.3	12	68.6 $\pm$ 20.2	12
T75%	I	62.0 $\pm$ 13.3*	12	55.2 $\pm$ 22.6*	12	70.9 $\pm$ 13.7	10
	II	62.7 $\pm$ 9.8●	12	82.4 $\pm$ 30.1▲	9	94.5 $\pm$ 35.9	11
	III	79.9 $\pm$ 25	11	65.3 $\pm$ 15.9	9	102.2 $\pm$ 19.7	8
T90%	I	70.6 $\pm$ 17.2	10	46.9 $\pm$ 16	4	58.1 $\pm$ 11.2	3
	II	77.1 $\pm$ 20.2	11	91.4 $\pm$ 27.2	4	80.4 $\pm$ 29.4	3
	III	90.2 $\pm$ 4.4	2	79.9 $\pm$ 22.3	6	146.45 $\pm$ 53.4	3

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Patient data were similar in all groups. Table 19 shows onset and recovery for A, R and V. Some patients did not reach T 75% (1 A, 6 R, 6 V) or T 90% (9 A, 14 R, 18 V). In these patients the mean EMG recording times were 118.5 and 131.7 min respectively.

The similar onset time for all groups and relaxants contrasts with previously published results in which onset was found to be directly related to age [1–3] and shorter after R [4]. The fact that some patients did not reach T75% or T90%, respectively may be related to the EMG method [5] and also to age. The long time-course of paralysis after V, calls in question the concept of being an intermediate NMB in elderly patients under enflurane-N20 anaesthesia.

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5 *Br J Anaesth* 1991; **66**: 562–565.

50. Acceleromyography of orbicularis oculi muscle: Optimal position for the stimulating electrodes

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The acceleromyographic (AMG) response of the orbicularis oculi (OO) muscle during facial nerve stimulation can be used for monitoring neuromuscular blockade. In this study we sought to establish the optimal position for stimulating electrodes when measuring the AMG response of the OO muscle.

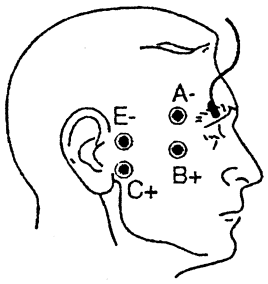

Fig. 11. (abstract 50).

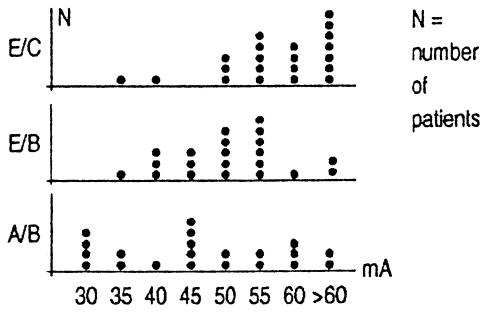

Fig. 12. (abstract 50).

After approval by the local Ethics Committee informed consent was obtained from 21 patients (ASAI–II, age 20–61 years, weight 57–87 kg) scheduled for elective surgery.

The patients were anaesthetized with propofol and opioids. After insertion of a laryngeal mask patients were normoventilated with N_2O 67% or air in O_2. The core and facial skin temperatures were kept above 35°C and 32°C, respectively. A TOF-Guard (1) (Organon Teknika NV, Belgium) was used for monitoring the AMG response with the acceleration transducer fixed on the eyebrow (Fig. 11). Paediatric ECG electrodes were placed over the temporal branch of the facial nerve after cleansing and rubbing the skin with an abrasive. Positions and polarity of the electrodes are given in Fig. 11. The electrodes were stimulated randomly in pairs A/B, E/B and E/C with train-of-four (TOF). A stable first response in TOF (T1) was measured (T1 variation <3% for 3 min) during supramaximal stimulation (stimulation intensity at max T1 + 5 mA) for each of the 3 electrode pairs. Measurement of T1 was repeated in the same random order during complete vercuronium paralysis (0.075 mg kg^{-1}). Complete paralysis was defined as no response to TOF or <1% further reduction following supplemental vecuronium doses of 1–2 mg. In each patient the electrode

Table 20. (abstract 50)

	Score		
	1	2	3
E/C (N)	3	6	12
E/B (N)	12	4	5
A/B (N)	15	6	0

N = number of patients.

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pair with the lowest, intermediate and highest supermaximal stimulation current were scored as 1, 2 and 3, respectively.

The scores are shown in Table 20. The supramaximal stimulation current at electrode pairs A/B, E/B and E/C were 45, 50 and 60 mA, respectively (median) (Fig. 12). Supramaximal stimulation were not obtained at 60 mA in 10, 10 and 33% of the patients (A/B, E/B and E/C, respectively). At complete paralysis T1 varied from 0 to 6% with no significant difference between the pairs.

No significant differences were found between electrode positions A/B and E/B. The position E/C appears less suitable for routine use because of the difficulties in obtaining supramaximal stimulation. In spite of complete paralysis the TOF-Guard sometimes indicate T1 responses of unknown origin up to 6%.

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1 *Anesthesiology* 1993; **79**: A963.

51. Influence of laparoscopic surgery on the ventilation of children

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During the last few years techniques of minimal-invasive surgery have been established in many surgical fields, e.g. gall-bladder surgery, appendectomy or diagnostic procedures in gynaecology. With progressive miniaturization of instruments some operations can be performed on children of appropriate size. There exist reports of surgery in infants down to 4 kg bw, but most of the indications are given in children of 10 kg bw or more and 1 year of age. We describe the physiological aspects and changes during minimal-invasive procedures in children of this typical age and size.

Fifteen children between the age of 3.5 and 10 (mean 7 years) and body weight of 13.5 to 30 (mean 22.5 kg) with given indication for laparoscopy were enrolled in the study. 0.3 mg kg^{-1} bw midazolam and 0.01 mg kg^{-1} bw atropine were given 30 min before beginning anaesthesia. For induction 0.4–0.5 mg kg^{-1} bw etomidate-lipuro and 3 μg kg^{-1} bw fentanyl were given intravenously. 0.1 mg kg^{-1} bw vecuronium was used to enable intubation and anaesthesia was maintained with 1 vol % isoflurane, 35/65% mixture of oxygen/nitrous oxide with fentanyl, if required. After intubation no further relaxants were given. Ventilation was set at 10 mL kg^{-1} bw tidal volume, frequency adjusted to maintain a steady state of $petCO_2$ at 4.6 kPa until CO_2-inflation began. Twenty min after induction of anaesthesia a capnoperitoneum of 10 mmHg was established by the surgeon. Ventilation parameters were not changed unless $petCO_2$ exceeded 5.9 kPa, which in fact did not occur. $PetCO_2$ was controlled by capillary gas analysis. We recorded ventilation pressure, tidal volume, ventilation frequency, $petCO_2$, heart frequency, SpO_2 by pulsoximetry, blood pressure and body temperature for 40 min. We calculated lung compliance, alveolar lung ventilation and other derived values. To evaluate the influence of laparoscopy, a second group of 15 children of the same age and weight designated for reconstructive urological procedures served as controls.

Lung compliance decreased very homogeneously to 70 ± 8% of the initial value (5 to 10 min after intubation) compared to 86 ± 5% in the control group. The latter may mainly be interpreted as recovery from initial relaxation. There was no apparent correlation between body size, body weight or BSA and lung compliance. $PetCO_2$ rose up to 5.4 ± 0.2 kPa, there was a good correlation between $petCO_2$ and capillary BGA ($r1v2 = 0.71$). All the other sampled parameters did not change during surgery.

There is no special problem of ventilation during laparoscopic surgery in children >10 kg bw. Neither decrease in lung compliance nor increase of CO_2 level in blood reached pathological values or induced any other problems seen so far, but concomitant cardiovascular monitoring must be carried out to complete our knowledge of laparoscopy in children.

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2 *Anaesth Analg* 1993; **76**: 622.

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52. Gasless laparoscopic cholecystectomy

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Induction and maintenance of CO_2 pneumoperitoneum for laparoscopic cholecystectomy (LC) can have serious effects. Post-operative sequelae are not infrequently seen. [1] To avoid use of CO_2 and high intra-abdominal pressure (IAP) we created the surgical view with a mechanical retractor.

Twenty-six ASA I-II patients with Ethics Committee approval and informed consent were randomly allocated to one of two groups. Thirteen patients underwent LC with conventional pressure pneumoperitoneum (CPP) (IAP 11–12 mmHg). In 13 patients a retractor was used to elevate the abdominnal wall by 10–15 cm (retractor group). Anaesthesia (propofol, atracurium, alfentanil, desflurane in oxygen in air) and intravascular volume loading were standardized. End-tidal CO_2 was kept below 5%. Haemodynamic, respiratory and recovery parameters were assessed and urine output registered.

Mean arterial pressure increased in CPP group (P<0.01) during the first 15 min of the insufflation and remained at a higher level throughout the operation (P<0.05) (Fig. 13). In CPP group central venous pressure increased by 146% and remained elevated until 1 h post-operatively (P<0.05). No changes in minute volume of ventilation were required in retractor group. Pulmonary compliance decreased in CPP group (P<0.01) but remained at normal level in retractor group (P<0.001 between the groups). Core temperature decreased by 0.5° in CPP group. Diuresis during the first 30 min of operation was more generous

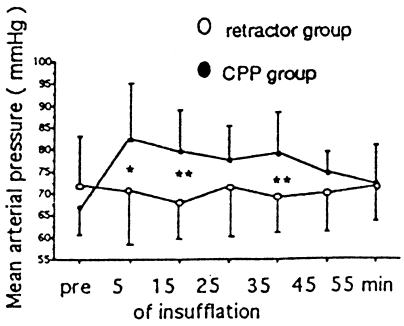

Fig. 13. (abstract 52).

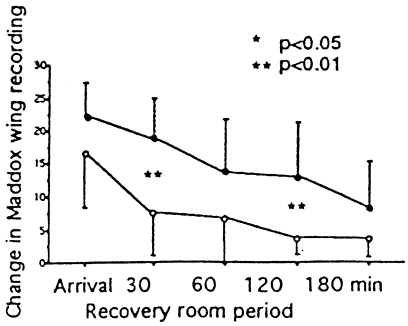

Fig. 14. (abstract 52).

in retractor group than CPP group (1.2 (1.0 SD) mL kg^{-1} vs. 0.4 (0.7) mL kg^{-1}, P<0.05). In 7 patients in CPP group and in one in retractor group urine output discontinued totally during operation (P<0.05).

Extubation could be performed earlier in retractor group than in CPP group (P<0.01). End tidal CO_2 concentrations were higher after CPP for 30 min post-operatively (P<0.01). In CPP group, the deviation in Maddox wing recordings from preoperative values was higher for 3 post-operative h (P<0.01) (Fig. 14). There was a positive correlation between the total amount of CO_2 used (55 (34) 1), the duration of drowsiness (r= 0.61, P<0.01) and the Maddox wing deviation (r=0.62, P<0.001). Post-operative nausea, vomiting (PONV) and right shoulder pain were seen less frequently after the gasless method (P<0.05). Late recovery criteria (ability to drink, void and walk) after the gasless method were fulfilled 7 h earlier than after CPP (P<0.01).

Gasless LC provides stable peroperative haemodynamic conditions and ventilatory profile with adequate urinary output. Postoperative recovery is also faster with less PONV and right shoulder pain than with conventional CO_2 pneumoperitoneum.

Reference

1 *Br J Anaesth* 1995; **75**: 567–572.

53. The Sima project

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Education and maintenance of skills for the diagnosis and treatment of serious and uncommon events have

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long been of concern in anaesthesiology. The use of simulation in training and education has become extensively used in other subjects. In aviation technicaly advanced full scale simulators provide realistic surroundings for training and certification of pilots. The technological evolution has now brought simulation within reach, both technically and economically, for teaching, diagnosis and treatment of complex problems in anaesthesiology. For the last 3 years the Sophus simulator has been used for this purpose. This simulator was developed by a team from Herlev Hospital, Roskilde University and Risø National Laboratory. It is a near replica of the anaesthetic work environment. The simulation system consists of a PC, a simulation software and a commercially available resuscitation mannequin creating a realistic experience in the simulator [1,2].

The SIMA project is a development from this with collaboration between private and institutional resources. The group behind this project is composed of Department of Anaesthesiology, Herlev Hospital, Department of Mathematics at Roskilde University and two private companies: Math-Tech, Gentofte, who have previously been working with advanced modelling in a different context and S&W MT, Albertslund, a manufacturer of anaesthetic monitors.

The software in this simulator will be based on explicit mathematical models whenever possible. In particular the simulator development involves modelling the cardio-vascular (CV) system and its regulation, the respiratory system, and the kinetics and dynamics of drugs used in anaesthesia.

The work follows a two-step approach. The first step is the development of rather detailed models (reference models) which are subsequently used to understand the behaviour of the system. This results in the selection of simpler models that can run in real time and mimic the physiological response sufficiently well. The mathematical approach studies the wave fronts in the blood and their deformation through flexible and branching tubes as well as the details of the flow patterns in the pulsating heart.

The CV regulation with the full baroreceptor-system, exhibits substantial delays and oscillations in its response to changes in blood pressure. The study details the effects of the various baroreceptor responses (through heart rate, contractility, peripheral resistance, and venous pool) on the dynamics of regulated CV-models as well as the effects of various delays – fixed or distributed – in the feedback system.

The respiratory model uses the reaction kinetics of the O_2/CO_2 system to obtain a pH model. Dissociation curves describing the uptake of substances in blood and tissue can now be combined with a compartment model of the blood-flow and the distribution in the body.

In addition a number of interesting questions are currently dealt with by script based models or on a simple ad hoc basis: ECG, electrolyte balances, temperature, and metabolism. For some of these questions theoretical models will be developed in the near future.

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54. Quality assessment in continuous medical education

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Medical performance is subject to quality control. Continuous advanced training (CAT) and continuous medical education (CME) are essential, and quality must be checked and assured in respect of structure (contents, organizational form, framework, demands on teachers), process (CAT, interaction between teachers and participants) and results (satisfaction and acceptance, increased knowledge, influence on medical treatment, improvement of the success rate of medical treatment).

In emergency medicine the necessity for CAT (e.g. certified proof required for working as an emergency physician) and a desire for CME (the individual task of the physician) must be differentiated. The diversity of forms for CAT/CME reflects the qualification as an emergency physician, 'Fachkundenachweis Rettungsdienst' offers measures for quality assessment.

The recommendations for obtaining the 'Fachkundenachweis Rettungsdienst,' valid until now date from

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the year 1983, were set in very different ways by the individual countries medical boards. This led to our problems in the comparability of the essential CAT. The quality of the structure has now been improved by establishing new and uniform requirements for clinical activity, specification of particular knowledge, number of supervised calls for the emergency car as well as participation in interdisciplinary CAT courses, dealing with general and special aspects of emergency medicine. The aim of these measures is not the (senseless) regimentation of CAT training measures, but the qualified transfer of specific medical knowledge and treatment guidelines.

On qualifying, the physician must make a personal effort to obtain a qualification of this kind. Conventional forms of learning must therefore be set aside in favour of modern teaching methods (e.g. problem-orientated learning). This will lead to a better acceptance of CAT/CME measures. It is essential for quality of the process that the teachers' education meets the following requirements: relevant knowledge of preclinical emergency medicine, didactic abilities, employment of relevant teaching techniques, flexibility in presentation, extensive experience in emergency medicine as well as an enthusiasm for high-quality education.

Questionnaires can be used to evaluate the satisfaction and acceptance of the participants, as well as their rating of individual speakers. The results are decisive in planning future CAT/CME measures. The transfer of knowledge can be estimated at the end of advanced training by questionnaire.

55. The anaesthesia simulator as an educational tool

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Anaesthesia simulation has been suggested to improve a doctors' management of critical incidents without exposing patients to risks. The full scale anaesthesia simulator (SOPHUS) has been developed at Herlev Hospital. The simulator is set up in an operation theatre with a simulator team acting as surgeons and nurses. The anaesthetists' performance during critical incidents is videotaped.

The purpose of this study was to evaluate whether simulator training could improve the performance of residents during critical incidents.

Twenty-two residents agreed to take part in this study. Twelve residents received a full training program while 10 residents acted as a control group and received only the theoretical part of the program and a simulator demonstration session. All participants received instruction in diagnostic strategies and treatment of selected critical incidents. Furthermore, they were taught the importance of good coordination, leadership and communications during critical incidents. Twelve residents then participated in six simulator training sessions followed by debriefing sessions using videotapes of their simulator performance. The following day all residents participated in a test scenario (abdominal aortic aneurism). The scenario was videotaped and the tape evaluated by three specialists in anaesthesia, who were unaware of the grouping. The residents' performance was characterized on a 4 point rating scale, where 1 (poor) and 4 (best). The specialists were asked to answer 20 questions about the residents' performance in the critical situation. The total scoring of these 20 questions is shown in the table. The performance score in the two groups was compared using a χ^2 test.

The performance of the simulator trained residents was significantly better than the performance of the residents in the control group. The trained residents had a tendency towards better leadership, communications and coordination.

This study suggests that simulator training improves

Table 21. (abstract 55)

	Number of residents	Rating 1	2	3	4
Trained group	12	26	45	106	63
Control group	10	15	90	69	26

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the ability of anaesthesia residents to manage a critical situation during anaesthesia.

56. Mild hypothermia reduces systemic oxygen consumption – cooling dynamics are independent of the anaesthetic

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Induced mild hypothermia is used to reduce the risk of cerebral ischaemia during neurosurgical procedures. Because of the different effects of Isoflurane and Propofol anaesthesia on vasoactivity, we hypothesized a difference in the effects of cooling on the reduction of systemic oxygen consumption.

After approval by the local ethics committee, 30 patients scheduled for elective craniotomy were included in the study. The patients were randomly allocated to the Isoflurane ($n=15$) or Propofol group ($n=15$). Cooling was achieved using circulating-water-blankets (Blanketrol™, Hoyer Engström, Bremen, Germany) placed under and above the patient after induction of anaesthesia in the operating room. Vesical and tympanic temperature were monitored and documented every 10 min from the beginning of cooling until recovery from anaesthesia. Oxygen consumption was measured with a computer controlled closed circuit anaesthesia system (PhysioFlex™, Physio-Dräger, Hoofddorp, The Netherlands). At dural closure, rewarming was initiated with the water blankets temperature set to 42°C. Patients were rewarmed to 35°C before extubation of the trachea. Wilcoxin's test was used for intergroup comparison.

The groups did not differ with respect to weight (77.27 kg ± 16.7 kg [range 50 kg–115 kg]), body surface area (1.91 m^2 ± 0.24 m^2 [range 1.51 m^2–2.47 m^2]), or body mass index (25.43 ± 3.82 [range 19.05–33.95]). There was no difference in body temperature and oxygen consumption at initiation of cooling. Patients were cooled to 34°C ± 0.12°C (range 33.6°C–34.4°C) at a rate of 0.94°C h^{-1} (range 0.53°C h^{-1}–1.57°C h^{-1}). Cooling-time was 124 min ± 52 min (range 30–250 min) and patients were kept at this mild hypothermia for 180 min ± 100 min (range 30 min–480 min). The reduction of oxygen consumption was 0.3 mL min kg^{-1} ± 0.19 mL min^{-1} kg^{-1} (range 0.08 mL^{-1} min^{-1} kg^{-1}–0.83 mL^{-1} min^{-1} kg^{-1}).

Before extubation patients were rewarmed to 34.9°C ± 0.24°C (range 33.9°C–35.1°C) at a rate of 0.68°C h^{-1} (range 0.09–1.2°C h^{-1}). There was no difference in the reduction in oxygen consumption per kg ($P=0.71$) and per kg/C° ($P=1.0$).

The results of this study, suggest that in spite of their different effects on vasoactivity there is no difference in reduction of oxygen consumption during mild hypothermia using either Isoflurane or Propofol anaesthesia. We conclude that vasodilation caused by Isoflurane has no influence on the reduction in oxygen consumption.

57. Isoflurane hepatotoxicity

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We have encountered a patient with unexplained persistent pyrexia and liver dysfunction following isoflurane anaesthesia (bilirubin 13 μmol L^{-1} alkaline phosphatase 217 iu L^{-1} aspartate transaminase 40 iu L^{-1} alanine aminotransferase 94 iu L^{-1} gamma glutamyl transferase 163 iu L^{-1}. Viral screening was negative, but his serum tested positive using an immunoblotting assy [3] for antibodies to a 60 kDa CF_3CO-modified hepatic protein adduct.

Halothane related hepatotoxicity is well documented, and ranges from transient hepatitis to fulminant hepatic failure. Halothane hepatotoxicity is believed to arise via immune responses to trifluoroacetylated (CF_3CO-) protein adducts which are produced by cytochrome P450-mediated bioactivation of halothane to CF_3COCl [1]. Enflurane hepatitis is much rarer, but similar mechanisms have been described [2]. Whether isoflurane is hepatotoxic remains controversial, but it undergoes P450-mediated

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Table 22. (abstract 57)

	BR μmol L^{-1}	ALP iu L^{-1}	AST iu L^{-1}	γGT iu L^{-1}
Preop	10.7 (0.9)	78.1 (6.9)	21 (1.7)	25.8 (4.4)
Postop	8,6 (0.9)	73.1 (6.6)	24.7 (2.5)	32.4 (6.9)

Values expressed as mean (SEM).

metabolism to CF_3COCl albeit to a 100-fold lower extent than halothane, thus providing a potential mechanism for isoflurane hepatitis.

Ten ASA I or II patients scheduled for neurosurgical, gynaecological or orthopaedic procedures with no history of liver or gastrointestinal disease, alcoholism or drug abuse gave informed consent and were studied.

Isoflurane was the only volatile anaesthetic agent administered. None received blood transfusion perioperatively. Blood samples were taken pre-operatively and 4–6 days post-operatively for liver function tests and for immunoblotting analysis of antibodies to CF_3CO-hepatic proteins [3].

Mean exposure to isoflurane was 125 min (SEM 17.7). No subject tested positive for antibodies to CF_3CO-adducts.

An immune response to these adducts is the likeliest aetiology of liver dysfunction in our patient, since other known causes of liver dysfunction were excluded. Antibodies to CF_3CO-hepatic protein antibodies are diagnostic of anaesthetic-induced hepatotoxicity [1], and we have shown that they do not occur incidentally in the serum of normal subjects following isoflurane exposure.

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58. Value of autologous blood for intra-operative massive bleeding

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We studied 108 patients ASA Grade I–IV classification randomly selected for elective or emergency major orthopaedic and abdominal surgery with massive bleeding. They were allocated into two groups. In group A′ (55 patients) the patients were transfused with stored blood from the blood bank and in group B′ (53 patients) with autologous blood from the autotransfusion device (red cell saver). Pre-operatively and post-operatively, haemoglobin (Hb), haematocrit (Ht), prothrobin time, bilirubin level, the number of platelets, mean arterial pressure (MAP), heart rate (HR), the values of blood gases, potassium (K^+) and sodium (Na^+) were evaluated.

Intra-operatively the blood loss, the amount of transfused blood, MAP, HR, Hb, Ht, the number of platelets, the values of blood gases, K^+ and Na^+ in the bags of the stored blood and saved red cells were measured.

Our statistics showed a significant increase in Hb, Ht, PaO_2, $PaCO_2$ and SaO_2 values in group B (saved red cells $P<0.05$). In this group the value of pH was approximately of normal level, but the statistical comparison of the two groups gave significantly higher results for group B (saved red cells $P<0.001$) in this study.

In conclusion the rapid and effective restoration of an adequate circulating blood volume is crucial in the early management of major haemorrhage, as mortality increases with the duration and severity of shock. This study supports our experience that autologous blood transfusion is safe for the patients and offers rapid restoration of circulating blood volume, with reduction of the workload and conserves blood bank stores.

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