Article — Artikel

Cardiovascular effects of lumbar epidural anaesthesia in isoflurane-anaesthetised pigs during surgical removal of the liver

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ABSTRACT

In humans the combined administration of epidural anaesthesia and inhalation anaesthesia may result in cardiovascular instability associated with decreases in heart rate and blood pressure. Anaesthesia was induced with a combination of midazolam/ketamine in 18 female pigs with a mean body weight of 24.9 ± 5.9 kg scheduled for surgical removal of the liver. After tracheal intubation, anaesthesia was maintained on a circle rebreathing circuit with isoflurane. Epidural anaesthesia was administered with ropivacaine (AL-group, $n = 8$) at 0.2 mℓ/kg of a 7.5 mg/mℓ solution to the anaesthetised animals. The A-group ($n = 10$) received isoflurane anaesthesia only. The vaporiser was set at 2.5 % for the A-group and 1.5 % for the AL-group. Heart rate, invasive systolic, diastolic , and mean arterial blood pressure were monitored. Comparisons were made between treatments and within treatments comparing variables during surgical preparation and abdominal surgery. Differences between treatments were not statistically significant ($P > 0.05$) during surgical preparation or during abdominal surgery. For within treatment groups, the differences between surgical preparation and abdominal surgery were statistically significant ($P < 0.05$) for heart rate in the A-group, but not statistically significant ($P > 0.05$) for the other variables. It is concluded that abdominal surgery may be associated with statistically significant changes in heart rate in isoflurane-anaesthetised pigs and that the combined administration of epidural ropivacaine may prevent statistically significant changes in HR during abdominal surgery.

Key words: anaesthesia, cardiovascular, epidural anaesthesia, isoflurane, pigs, ropivacaine.

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INTRODUCTION

In a research project aimed at the development of a bioartificial liver support system using the pig as model, it became essential to ensure optimal perioperative cardiovascular stability[12]. Surgery may activate the neuro-endocrine (stress) response that is associated with sympathetic stimulation and increases in heart rate and blood pressure[17]. In addition, inhalation anaesthesia may alter the response to surgery but it is not completely blocked[2] and isoflurane anaesthesia may be associated with decreases in blood pressure when compared with halothane anaesthesia[9]. A possible management strategy to improve cardiovascular stability is the combined use of inhalation anaesthesia and epidural anaesthesia[7,14]. The epidural administration of local anaesthetics results in a reduction in the minimum alveolar concentration (MAC) of inhalation anaesthetics[8,11] and an increase in cardiovascular stability[3,16]. However, the perioperative use of epidural anaesthesia on its own or in combination with general anaesthesia is a controversial issue as adverse effects such as bradycardia and hypotension[1,10,16,17] may occur. The purpose of this investigation was to evaluate the cardiovascular effects of epidural ropivacaine and a reduction in the inhaled concentration of isoflurane during abdominal surgery in pigs.

MATERIALS AND METHODS

Eighteen female Landrace pigs were used in this investigation with a mean body weight of 24.9 ± 5.9 kg. The pigs were part of a study to develop a bioartificial liver support system, and were scheduled for surgical removal of the liver (hepatectomy). Surgery involved dissection and ligation of the hepatic blood vessels. Approval for the study was obtained from the Animal Use and Care Committee of the University of Pretoria.

The pigs were fasted overnight with water *ad lib*. They were induced in the pens with the intramuscular injection of midazolam (0.3 mg/kg, Dormicum, Roche) and ketamine (10 mg/kg, Anaket, Centaur) and moved to theatre. A 20 G teflon catheter (Jelco, Johnson & Johnson) was placed in the ear vein. Anaesthesia was deepened with intravenous (IV) propofol (Diprivan, Astra Zeneca at 3 mg/kg administered to effect for tracheal intubation with a 7.5 mm cuffed endotracheal tube. Anaesthesia was maintained with an air-oxygen mixture delivered by a precision vaporizer (Isotec 5, Ohmeda). For the anaesthesia only group (A-group, $n = 10$) the vaporizer was set at 2.5 % isoflurane, and for the group that received a ropivacaine epidural (AL-group, $n = 8$) the vaporizer was set at 1.5 % isoflurane. A circle rebreathing circuit with carbon dioxide (CO_2) absorption was used to deliver the inhalation anaesthesic. Fresh gas flow rate for oxygen was set at 300 mℓ/min and 600 mℓ/min for air. Minute volume was maintained with positive pressure ventilation (Ohmeda 7000 Ventilator) to maintain end-tidal CO_2 partial pressure in the range of 4.7–5.3 kPa.

Lumbar epidural anaesthesia was administered with a 20 G spinal needle (Vygon) introduced between lumbar vertebrae 1 and 2 using a 7.5 mg/mℓ ropivacaine solution (0.2 mℓ/kg, Naropin, Astra). Placement of the needle tip in the epidural space was facilitated with the detection of loss of resistance to saline injection. Cardiovascular volume was maintained with a balanced electrolyte solution (Intramed, Ringer Lactate) administered IV at 20 mℓ/kg/hr for the duration of anaesthesia. The medial saphenous artery was percutaneously catheterised using the Seldinger technique with a 20 G polyurethane catheter (Arterial Catheterization Set, Arrow) for arterial blood pressure monitoring. After removal of the liver, the pigs were euthanased with an IV bolus of pentobarbitone (40 mg/kg, Euthabarb, Centaur).

Cardiopulmonary parameters were monitored with a multi-function patient

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monitor (TL-101T, Nihon Kohden, Medical Systems) at 5 min. intervals until the *vena cava caudalis* was ligated immediately before removal of the liver. Heart rate (HR), systolic blood pressure (SYS), diastolic blood pressure (DIA), and mean arterial blood pressure (MAP) were recorded. Variables were recorded with 5 min. intervals between T1 and T5 during surgical preparation (no noxious stimulation) and abdominal surgery (noxious stimulation). The CO_2 censor for the capnometer was placed between the endotracheal tube and the anaesthetic breathing circuit; the electrocardiographic leads were attached to the distal limbs; the pulse oximeter probe attached to the tongue; and arterial blood pressure measured from the medial saphenous artery using an electronic pressure transducer (MX 950 Transtar Pressure Transducers, Medex Medical). Anaesthetic depth during surgery was evaluated from the palpebral reflex and pedal reflex and the masseter muscle tone.

Data analysis

Inspection of the plots made it clear that the standard statistical method of analysing the data for differences over time between treatment groups, *i.e.* a general linear model for repeated measures, would be inappropriate. For both treatment groups, differences were observed between the trend of the means across the first 5 time periods (measured during surgical preparation) and the trend of the means across the last 5 time periods (measured during abdominal surgery). A repeated measure ANOVA tests the equality of treatment group means, while at the same time modelling the correlations between the repetitions. In this experiment, the aim was not to model the correlations across all ten time periods, but between surgical preparation and during surgery. The change in the trend of the 2 sets of means will, however, effectively be cancelled out by using the standard statistical procedure.

To meet the aim of the study, *i.e.* to assess differences associated with surgical preparation and abdominal surgery, as well as comparing changes in the 4 cardiovascular variables during abdominal surgery in pigs anaesthetised with isoflurane, and isoflurane combined with epidural ropivacaine, the following line of investigation was followed:

1. To evaluate differences between procedures within each treatment group, the slopes of the regression lines during surgical preparation and during abdominal surgery were compared for each of the 4 cardiovascular variables (HR, SYS, DIA and MAP). A regression line was therefore fitted to the set of observations for each of the 18 pigs, using a coding scheme that provides 1 regression coefficient for the 5 observations during surgical preparation and another for the 5 observations during abdominal surgery.
2. The evaluation of differences between the 2 treatments was conducted in 4 steps:
   - 2.1. The intercepts were compared to determine whether there were initial differences between the 2 groups.
   - 2.2. The regression coefficients of the surgical preparation period were compared.
   - 2.3. The regression coefficients during the abdominal surgery period were compared.
   - 2.4. The differences between the 2 sets of regression coefficients (surgical preparation period and during surgery) were compared. The latter was done to assess whether the order of the magnitude in the changes before and during surgery between the 2 treatments differ.

Non-parametric tests were conducted because of the small sample sizes. Wilcoxon signed-rank tests for 2 related samples were used to test for differences between procedures within each treatment group and Mann-Whitney *U*-tests for 2 independent samples to test for differences between the 2 treatments. Statistical significance was set at $P < 0.05$. The statistical software package SPSS version 15.0 (SPSS Inc., 233 S. Wacker Drive, Chicago, Illinois) for a personal computer was used for the analysis.

RESULTS

The mean ±SD values for heart rate and arterial blood pressure during surgical preparation and abdominal surgery for the A-, and AL-treatment groups are reported in Table 1. A profile plot of changes in mean values over time for the cardiovascular variables is presented in Fig. 1; A, HR; B, SYS; C, DIA; D, MAP. Data were characterised by large variations in SD (Table 1). Anaesthetic plane was satisfactory in both groups and was characterised by the absence of the palpebral- and pedal reflexes and relaxation of the masseter muscles during preparation and surgery. For within treatment group comparison of procedures, assessed by the Wilcoxon signed-rank tests, the only statistically significant difference ($P < 0.05$) was found for HR ($P = 0.03$) in the A-group between surgical preparation and abdominal surgery. For the other variables of the A-group, the significance of the difference for SYS was $P = 0.17$, DIA and MAP, $P = 0.33$. For the AL-group the differences were not statistically significant. For HR $P = 0.58$, SYS $P = 0.48$, DIA $P = 0.52$ and MAP $P = 0.67$.

The results from the Mann-Whitney *U* tests confirmed that no statistically significant differences existed between the 2 treatment groups prior to the experiment (HR $P = 0.46$; SYS & DIA $P = 0.63$; MAP $P = 0.46$), *i.e.* no bias was inadvertently introduced into the experiment. Differences between treatments for the individual variables were also not statistically significant either during preparation (HR $P = 0.52$; SYS $P = 0.17$; DIA $P = 0.70$; MA$P = 0.36$) or during surgery (HR $P = 0.12$; SYS $P = 0.83$; DIA $P = 1.00$; MAP $P = 1.00$). The last set of results, evaluating whether the change before and during surgery between the 2 treatment groups was different, showed no statistically significant results at the 5 % level for any of the 4 cardiovascular variables; however, HR was statistically significant at the 10 % level (HR $P = 0.07$), but not SYS $P = 0.32$; DIA $P = 0.97$ and MAP $P = 0.57$.

Table 1: **Mean** (±SD) **cardiovascular values during surgical preparation and abdominal surgery in isoflurane-anaesthetised pigs.**

Rx	Proc.	HR (b/min)	SYS (kPa)	DIA (kPa)	MAP (kPa)
A	P	98.7 ± 17.7*	12.1 ± 2.4	7.1 ± 1.4	8.9 ± 1.8
	S	104.4 ± 19.0**	11.8 ± 1.9	7.3± 1.1	8.9 ± 1.2
	P+S	101.5 ± 18.5	12.0 ± 2.2	7.2 ± 1.3	8.9 ± 1.6
AL	P	91.1 ± 11.7	13.6 ± 2.1	8.0 ± 1.6	10.2 ± 1.9
	S	87.6 ± 13.4	12.8 ± 1.9	7.8 ± 1.2	9.8 ± 1.7
	P+S	89.4 ± 12.6	13.2 ± 2.0	7.9 ± 1.4	10.0 ± 1.8

Proc, procedure; P, surgical preparation; S, abdominal surgery.
A, isoflurane only; AL, isoflurane and ropivacaine epidural; HR, heart rate; SYS, systolic blood pressure; DIA, diastolic blood pressure.
MAP, mean arterial blood pressure; b/min, beats/minute.
*, **Statistically significant difference ($P < 0.05$).

DISCUSSION

The purpose of this investigation was to compare changes in cardiovascular variables during abdominal surgery in pigs anaesthetised with either isoflurane

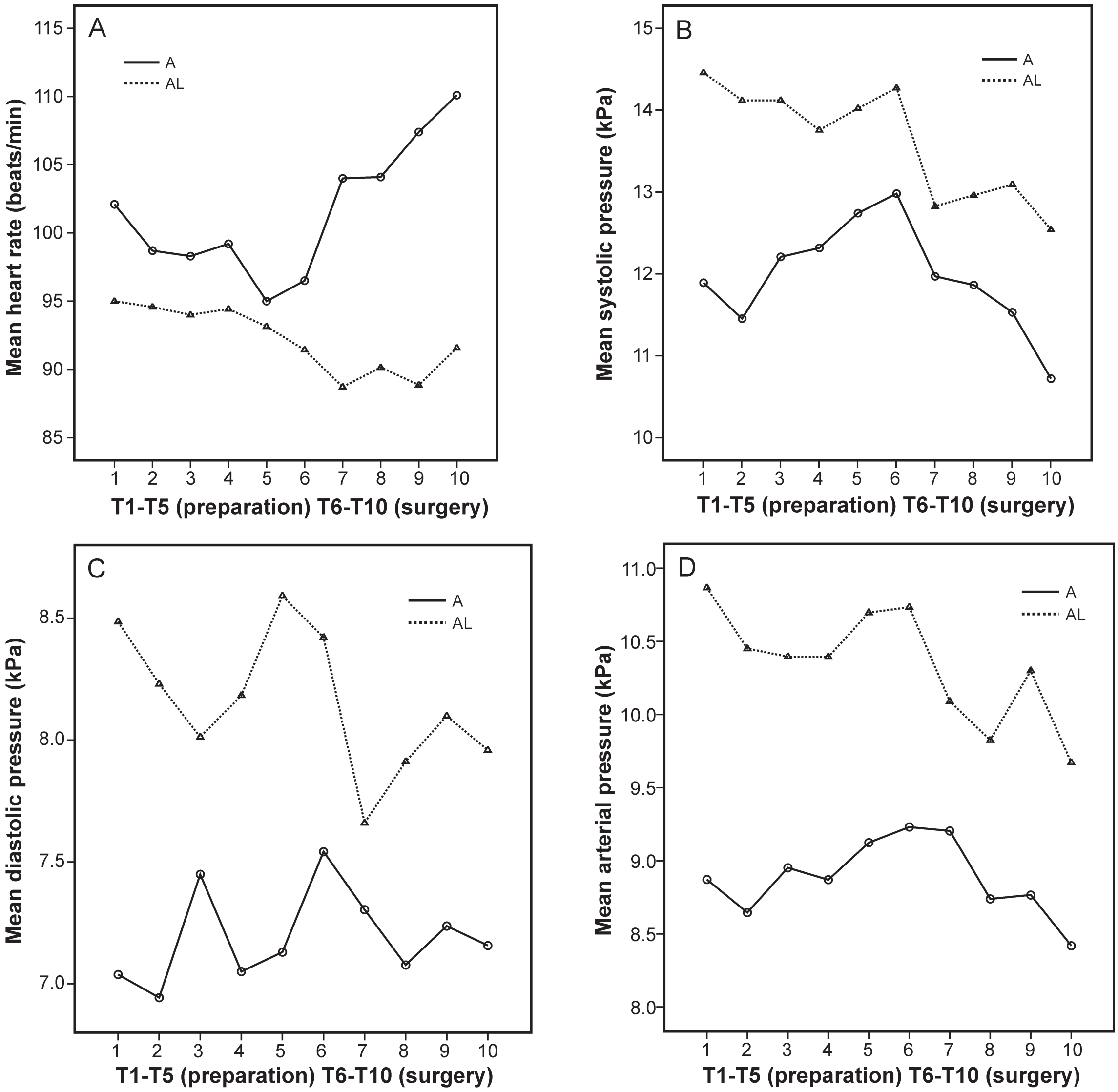

Fig. 1: A, **Mean heart rate;** B, **systolic;** C, **diastolic; and** D, **mean arterial blood pressure during surgical preparation** (T1–T5) **and abdominal surgery** (T6–T10) **at 5-min intervals.**

alone or isoflurane combined with epidural ropivacaine. As far as within treatment comparisons are concerned, only the change in HR, associated with surgical preparation and abdominal surgery in the isoflurane group, was statistically significant. None of the changes associated with surgical preparation or abdominal surgery between treatment groups were statistically significant at the 5 % level, although HR, once again, had a significant result at the 10 % level when comparing changes during preparation and surgery between treatments. If a larger sample could be used it would have allowed the use of parametric tests, which are more sensitive to differences, should they exist, as the actual observations are evaluated instead of the ranks of the observations. Mean heart rates in this investigation (Table 1) were within range of the reported values for anaesthetised pigs (80–130 beats/min)[13] and for isoflurane-fentanyl anaesthetised pigs (108 beats/min)[4]. However, it should be regarded as of clinical significance that the ropivacaine epidural prevented the steep increase in HR in the AL-group that was observed in the A-group during abdominal surgery (Fig. 1A). The increase in heart rate may have been the result of noxious activation of the sympathetic system during surgery, but could also be a compensatory reaction to the decrease in blood pressure (Fig. 1D). Although the differences observed in the mean cardiovascular values between treatment groups at the start of surgical preparation (T1, Fig. 1) were not statistically significant, it continued throughout surgical preparation and abdominal surgery. It could be assumed that these differences were induced by differences in the anaesthetic protocol between the 2 treatment groups, *i.e.* the epidural ropivacaine and a lower inspired isoflurane concentration in the AL-group.

The MAP range reported for anaesthetised pigs is 9.98–13.3 kPa[13], and for isoflurane anaesthetised pigs 9.6–11.1 kPa with the end-tidal isoflurane concentration approximately 0.85 %[6]. The values MAP reported by Riebold[13] were somewhat higher compared with the values observed in this investigation, but were similar to the values of Malavasi[8]. The trend in MAP during surgical preparation, *i.e.* absence of surgical stimulation was towards an initial decrease in the AL-group as opposed to an increase in the A-group (Fig. 1D). This could possibly be ascribed to the vasodilatation associated with the epidural block[16]. The increase in MAP in the A-group was reversed during surgery as a decrease in MAP occurred in both groups during surgery. Preventing or reducing the transfer of noxious stimuli to the central nervous system did not prevent changes in cardiovascular variables during abdominal surgery. The decrease in blood pressure during surgical manipulation of the liver and *vena cava* could be the result of partial obstruction of the portal vein during surgery resulting in a decrease in venous return and cardiac output. The lowest mean value recorded for MAP in the AL-group was higher than the highest mean value for MAP recorded in the A-group (Fig. 1D). A similar tendency for SYS and DIA (Fig. 1 B, C) was also observed. Cardiovascular stability as evaluated from increases in heart rate was therefore better maintained in the AL-group after ropivacaine epidural when subjected to abdominal surgery. The decrease in blood pressure could be regarded as an adverse effect but this should be seen in the context that the blood pressure was higher in the AL-group compared with the A-group and that the pressures were within range of pressures reported for isoflurane-anaesthetised pigs[6,8].

Possible complications reported in humans after the combined administration of inhalation anaesthesia and lumbar epidural anaesthesia were bradycardia and hypotension[1,10,16]. Epidural anaesthesia may result in changes in heart rate and blood pressure as result of a sympathetic blockade[10,16]. In isoflurane-anaesthetised dogs the combined administration of epidural bupivacaine or epidural bupivacaine and morphine had no influence on cardiovascular variables[5]. Epidural morphine in isoflurane-anaesthetised pigs resulted in minimal effects on MAP values with end-tidal isoflurane concentration reduced to 0.6 % as opposed to 0.9 % in the control with only isoflurane anaesthesia[8]. It therefore appeared that the response to epidural anaesthesia in this investigation was similar to published findings in the dog[5] and pig[8]. In this investigation the vaporiser setting for isoflurane was decreased from 2.5 % in the A-group to 1.5 % in the AL-group representing a 40 % decrease in the isoflurane concentration delivered to the breathing circuit and could explain the higher blood pressure values observed in the AL-group. An additional measure to limit changes in blood pressure during this investigation was the administration of a balanced electrolyte solution to reduce the effects of vasodilatation induced by sympathetic blockade[16]. It therefore appeared that in pigs the hypotensive effect of epidural anaesthesia is possibly smaller compared with observations in humans, and in pigs the anaesthetic sparing effect of epidural anaesthesia may result in an improved blood pressure during inhalation anaesthesia. In humans a common sequel to epidural anaesthesia is a decrease in arterial blood pressure[1], but in this investigation the systolic-, diastolic-, and mean arterial blood pressures were higher in the epidural/isoflurane group compared with the isoflurane group. In conclusion, in pigs, the administration of lumbar epidural anaesthesia with ropivacaine may have some cardiovascular stabilising effects as evidenced by the absence of a statistically significant increase in heart rate during abdominal surgery and maintaining a statistically non-significant higher arterial blood pressure when compared to isoflurane anaesthesia on its own.

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