Cardiopulmonary Effects of a Partial Intravenous Anesthesia Technique for Laboratory Swine

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Various anesthetic protocols are used in laboratory swine, each with specific advantages and disadvantages. Partial intravenous anesthetic techniques (PIVA) help minimize dose-dependent cardiopulmonary effects of inhalant drugs. The aim of this study was to determine the cardiopulmonary effects of a PIVA in laboratory swine. In a prospective, nonrandomized clinical study, 8 healthy juvenile Landrace–White pigs were premedicated with azaperone (0.20 ± 0.20 mg/kg IM), dexmedetomidine (0.02 ± 0.002 mg/kg IM), and alfaxalone (2.0 ± 0.20 mg/kg IM), and anesthesia was induced with intravenous alfaxalone. Anesthesia was maintained by using constant-rate infusion of dexmedetomidine ($2 \mu\text{g/kg/h}$) and alfaxalone ($25 \mu\text{g/kg/min}$) in combination with isoflurane. After the fraction of expired isoflurane was adjusted to 1.1% to 1.5%, respiratory rate, heart rate, systemic and pulmonary arterial pressure, central venous pressure, cardiac output, bispectral index, systemic vascular resistance, and arterial and mixed venous blood gases were recorded every 10 min for 60 min. Statistical analysis consisted of repeated-measures one-way ANOVA. Significant decreases occurred in heart rate, pulmonary mean arterial pressure, pulmonary diastolic pressure, partial pressure of arterial oxygen, partial pressure of venous oxygen; significant increases occurred in respiratory rate, minute volume index, diastolic arterial blood pressure, systemic vascular resistance, and arterial pH over time. We consider that the observed statistically significant cardiopulmonary changes were clinically important and that the PIVA protocol provided hemodynamic and respiratory stability for short-term anesthesia of laboratory swine.

Abbreviations: BIS, bispectral index; CO, cardiac output; CRI, constant rate infusion; F_E , fraction of expired gas; F_I , fraction of inspired gas; HR, heart rate; PIVA, partial intravenous anesthesia; SVR, systemic vascular resistance.

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Pigs are commonly used in biomedical and translational research studies, for which general anesthesia is often required to facilitate immobilization and surgery. A balanced anesthetic technique supports accurate experimental results as it ensures humane treatment of the animal. An ideal anesthetic regimen provides an effective and predictable level of hypnosis, analgesia, and muscle relaxation with preservation of cardiopulmonary function.

Many anesthetic protocols have been studied in swine for both premedication and maintenance of anesthesia. An intramuscular injection containing multiple anesthetic agents is commonly administered to swine prior to handling, because they are easily stressed and difficult to restrain. Premedication in pigs helps to decrease anxiety, facilitate handling, and establish venous access for subsequent induction and maintenance of anesthesia.

Recently reported injectable protocols have included drugs and drug combinations such as cyclohexane anesthetics (ketamine and tiletamine),^{2,9} dexmedetomidine–ketamine–methadone,⁴ alfaxalone–diazepam,²⁵ dexmedetomidine–ketamine, dexmedetomidine–alfaxalone,²⁶ often an α_2 agonist in combination with either ketamine or an opioid such as butorphanol.^{15,21–23}

Another commonly used tranquilizer in swine is azaperone.¹² Azaperone is a butyrophenone tranquilizer that is commercially available in many countries. In the United States, azaperone is commonly used during wildlife capture and is typically sourced

as a compounded drug from ZooPharm compounding pharmacy.³² Few data are available regarding the effects of azaperone in combination with dexmedetomidine and alfaxalone. Alfaxalone (or alphaxalone) is a neuroactive steroid formulated as 2-hydroxypropyl- β -cyclodextrin (Alfaxan). In the United States, alfaxalone is a schedule IV drug and is labeled for the induction and maintenance of anesthesia in cats and dogs.

Isoflurane and other volatile anesthetics have dose-dependent effects on the hemodynamic and respiratory function of domestic species. Reduction or exclusion of volatile anesthetics aids in preserving normal physiologic responses and cardiopulmonary function during general anesthesia. Preservation of normal cardiopulmonary function is an important goal. An equally important goal is maintaining an appropriate depth of anesthesia. A recent article has described the utility of bispectral index (BIS) monitoring in the determination of anesthetic depth in isoflurane-anesthetized pigs.⁸ The current study also describes the use of BIS monitoring, because it can provide important background data for this particular anesthetic protocol.

Combining multiple anesthetic agents exploits additive and synergistic drug effects, therefore reducing the total dose requirement of each agent and the negative side effects of any one drug. Dexmedetomidine and alfaxalone have been studied as constant-rate infusions (CRI) with^{10,16,18,28} and without^{1,11,13,14,20} volatile anesthetics to maintain anesthesia in many species, but the use of this combination in swine has not yet been reported.

The goals of our current study were to measure the sedation quality and cardiopulmonary effects of an anesthetic technique consisting of a novel premedication followed by a PIVA protocol using dexmedetomidine, alfaxalone, and isoflurane in swine.

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We hypothesized that this combination would have minimal adverse effects on hemodynamic and respiratory parameters and would provide adequate analgesia and narcosis as measured by the application of noxious stimuli (claw pinch) and monitoring of BIS.

Materials and Methods

Animals. This study adhered to guidelines from the Canadian Council of Animal Care and was approved by the University of Calgary Animal Care Committee. Juvenile male, Landrace–White pigs (*Sus scrofa domestica*; $n = 8$; weight, 26 ± 2.6 kg [mean ± 1 SD]) were obtained from a SPF commercial herd and transported in groups of 2 to 4 to the experimental facility at least 3 d before use. A laboratory animal veterinarian physically examined all pigs on arrival. The pigs were housed in separate indoor pens and fed 16% hog grower ration with free access to nipple water feeders. Food was withheld for at least 12 h before experimentation; water was not withheld. On completion of the study, the inspired isoflurane concentration was increased to 5%, and the animal was euthanized with a saturated solution of potassium chloride. Gross necropsy was performed with a particular focus on the thoracic and abdominal cavities. Mean barometric pressure was recorded daily throughout the study.

Premedication and induction. Each pig was premedicated in its pen. Premedication consisted of intramuscular injection of an estimated target dose of 0.2 mg/kg azaperone (Stresnil 40 mg/mL, Vétoquinol, Lavaltrie, Quebec, Canada), 2.0 mg/kg alfaxalone (Alfaxan 10 mg/mL, Jurox, Rutherford, New South Wales, Australia), and 0.02 mg/kg dexmedetomidine (Dexdomitor 0.5 mg/mL, Zoetis, Kalamazoo, MI) mixed in the same 6-mL syringe and administered by using a 19-gauge, 1.5-in. hypodermic needle through a primed extension line. The total volume was administered rapidly as a single bolus into the epaxial muscles, located midline between the shoulder blades, and the line was flushed with 1.5 mL sterile saline. Premedication doses were calculated based on an estimated weight derived from the initial order request and visual inspection. The target dose used in this study was based on our experience with this combination in other species,¹⁷ literature review, and pilot studies in pigs performed prior to the current study.

The entire sedation period was observed and filmed. The same investigator recorded time to sternal and lateral recumbencies. The quality of sedation was evaluated on the basis of physical activity, vocalizations, and general behavior. The depth of sedation was tested at 450 s (7.5 min) by an investigator who entered the pen and stroked the head and thorax of the pig. When animals failed to respond to tactile and auditory stimulation, they were transported to the induction room. Body weight was measured by using a manual scale (Toledo Scale, Mettler-Toledo Canada, Mississauga, ON, Canada) and a catheter (22-gauge, 2-port, 0.75 inch, BD Saf-T-Intima IV Catheter, Becton Dickinson) was inserted into a marginal ear vein in each ear. Anesthesia was induced with alfaxalone to effect (1.4 ± 0.4 mg/kg). Pigs were intubated with a 6.5 mm cuffed endotracheal tube. Bispectral index (BIS) transcutaneous electrodes (BIS Pediatric Sensor, Covidien LLC, Mansfield, MA) were placed according to package insert instructions, and pigs were transported to the surgical suite.

Isoflurane (Isoflurane USP, Fresenius Kabi Canada, Richmond Hill, Ontario, Canada) was delivered in 40% oxygen (1 L/min) and 60% medical air (2 L/min) by using a rebreathing circuit and titrated to an end-tidal concentration of 1.2%. Automated syringe drivers (Medfusion 3500, Smiths Medical International, St Paul, MN) were used to administer dexmedetomidine at 2

µg/kg/h and alfaxalone at 25 µg/kg/min through the left auricular venous catheter. Intravenous NaCl (0.9%, 5 mL/kg/h) was administered through the right auricular venous catheter. Pigs were placed in dorsal recumbency and spontaneously ventilated for the duration of the experiment.

Monitoring. Pigs were monitored by using a pulse oximeter, 5-lead electrocardiogram, and capnograph (Datex-Ohmeda s/5 Collect, GE Healthcare, Helsinki, Finland). Bupivacaine (Marcaine 0.5% Bupivacaine HCl, Hospira Healthcare, Montreal, Quebec, Canada) was used for local anesthesia to facilitate the surgical exposure of the carotid artery and jugular vein. A 20-gauge, 5-cm catheter was inserted into the carotid artery to enable blood pressure measurements and blood gas analysis. A 5-French, 75-cm thermodilution catheter (Edwards Lifesciences, Irvine, CA) was that was guided into the pulmonary artery through the right external jugular vein.

Instrumentation and measurements. Direct systolic, diastolic (DAP), and mean arterial blood pressures were measured via the common carotid arterial catheter connected to a pressure transducer (PX3X3, TruWave Disposable Pressure Transducers, Edwards Life Sciences, Irvine, CA) by using a 16-gauge needle attached to low-compliance tubing containing heparinized saline. The proximal and distal ports of the pulmonary arterial catheter yielded central venous and pulmonary arterial blood pressures, respectively, as well as core body temperature. The pulmonary arterial catheter also used an Edwards transducer. A flush system was connected to all transducers and pressurized to 300 mm Hg (40 kPa) to administer heparinized saline at a rate of 3 mL/h. A multiparameter monitoring system (Datex-Ohmeda s/5 Collect, GE Healthcare) was used to display and record pressure waveforms. The intermittent bolus thermodilution method was used to measure cardiac output (CO). Systemic vascular resistance (SVR) values were calculated from the measured values. A bispectral index percutaneous electrode and computer system (BIS Vista Monitoring System, Aspect Medical Systems, Norwood, MA) were used to monitor BIS.

A sponge clamp was closed to the first ratchet on the right medial dewclaw to assess somatic response (movement) to painful stimulation. The clamp was released after 4 s or immediately after a response.

Data collection. On completion of instrumentation, animals were stabilized on isoflurane for approximately 10 min at F_I 1.2% to facilitate equilibration (0 min [time 0]). Isoflurane was maintained at F_E 1.2% with F_I O_2 of 40% for the duration of the experiment (time 0 through 60). Starting at time 0, CO was measured at 10-min intervals. Arterial and mixed venous blood gas samples were withdrawn every 10 min starting at time 0. Blood gas samples were immediately stored on ice and analyzed (Nova Biomedical, Critical Care Xpress, Stat Profile, Mississauga, Ontario, Canada) within 10 min of collection. Claw pinches were performed every 10 min starting at time 5. All other physiologic data were collected continuously.

Calculations. The following equation was used to determine systemic vascular resistance (SVR, dynes/s/cm⁻⁵):

$$SVR = 80 \times (\text{mean arterial pressure} - \text{central venous pressure}) / CO.$$

Cardiac index (CI) was calculated as follows:

$$CI = CO (\text{in mL} / \text{min}) / \text{body weight (in kg)}.$$

Statistical analyses. All data are reported as mean ± 1 SD unless otherwise stated. Shapiro–Wilk analysis was used to

test data for normality. Parametric analyses were used when data approximated normal distribution. Nonparametric data comparisons were analyzed by using a Mann–Whitney test. Variables were compared over time by using ANOVA for repeated-measures and posthoc Dunnett multiple-comparison tests. Differences were considered significant at a *P* of 0.05 or less. Statistical analyses were performed by using Prism 5.04 (GraphPad Software, La Jolla, CA).

Results

All 8 pigs were included in the data analyses. Body weight ranged from 22 to 31 kg (mean $\pm$ 1 SD, 26 ± 2.6 kg). Delivered premedication doses included 5.3 ± 0.3 mg (0.20 ± 0.02 mg/kg) azaperone, 0.53 ± 0.03 mg (0.020 ± 0.002 mg/kg) dexmedetomidine, and 53.3 ± 3.4 mg (2.0 ± 0.2 mg/kg) alfaxalone. Six pigs required a single intramuscular injection to administer the entire dose. In the remaining 2 animals, the needle exited the muscle before the extension set could be flushed with saline. In both of these pigs, the needle was replaced immediately within the same muscle group, and the remaining drug volume delivered.

Sedation in all pigs was characterized by a wide-based stance followed by mild ataxia and subsequent sternal and lateral recumbency. Mild trembling and quiet snoring occurred intermittently in all animals. Three animals were underdosed due to incorrect initial weight estimates; these pigs received doses of 0.17 to 0.19 mg/kg azaperone, 0.017 to 0.019 mg/kg dexmedetomidine, and 1.7 to 1.9 mg/kg alfaxalone. The remaining 5 pigs received doses of 0.21 to 0.23 mg/kg azaperone, 0.021 to 0.023 mg/kg dexmedetomidine, and 2.1 to 2.3 mg/kg alfaxalone.

For the purpose of reporting times until sternal and lateral recumbency, pigs were divided into target-dosed (target dose and higher; *n* = 5) and underdosed (*n* = 3) groups (Table 1). Two underdosed animals responded to tactile stimulation and repositioning with sudden ambulation or moderate limb and head movement, although they were sufficiently tractable to transport after 13 min (780 s) and 10.5 min (630 s). They resumed a sleep-like state when left undisturbed. In addition, 3 of the 8 pigs demonstrated purposeful movement of the head when being placed on the transport cart, though this behavior did not prevent transportation to the induction room. Two of these pigs received less than the target dose, whereas the remaining animal was in the target dosed group.

All 3 underdosed animals reacted to insertion of auricular venous catheters with mild head shaking, whereas the 5 target-dosed pigs had no response. Of the 16 catheters placed (1 catheter per ear per pig), 4 of the attempts resulted in mild head-shaking behavior. Seven pigs required a total induction dose of 2 mg/kg alfaxalone or less. The remaining animal receiving 3.5 mg/kg; this pig was underdosed, having received premedication doses of 0.19 mg/kg azaperone, 0.019 mg/kg dexmedetomidine, and 1.89 mg/kg alfaxalone. The mean dose of alfaxalone required for endotracheal intubation was 1.6 ± 0.8 mg/kg.

Four pigs (3 underdosed, 1 target-dosed) had positive responses to claw pinching; 2 animals consistently responded throughout the experimental period, whereas the remaining 2 pigs each responded once (T15 and T65). Of the 2 pigs that responded throughout the experimental period, one responded from T25 until T55 (4 of 6 time points). This subject was the largest pig (31 kg), had received the lowest dose of premedication (0.17 mg/kg azaperone, 0.017 mg/kg dexmedetomidine, 1.7 mg/kg alfaxalone), and had the highest mean BIS number over time (65 ± 9). The second animal responded to claw pinches at 5 of 6 time points and demonstrated minor avoidance behaviors

Table 1. Times for swine (*n* = 8) to reach sternal and lateral recumbency after receiving a novel intramuscular premedication drug combination (azaperone, dexmedetomidine, and alfaxalone)

Pig no.	Time (s) to	
	Sternal recumbency	Lateral recumbency
Underdosed		
1	254	486
2	501	604
3	210	570
	322 ± 157	553 ± 61
Target-dosed		
4	130	450
5	195	323
6	132	450
7	319	403
8	172	450
	190 ± 77	415 ± 55

Swine are separated into target-dosed and underdosed groups. Underdosed swine received less than 0.2 mg/kg azaperone, 0.02 mg/kg dexmedetomidine, and 2.0 mg/kg alfaxalone.

(BIS, 54 ± 5). This pig received sufficient premedication but had the lowest mean F_E isoflurane over time ($1.13\% \pm 0.04\%$).

Mean HR decreased significantly (*P* < 0.0001) over time and at T30 through T60 compared with T0 (*P* ≤ 0.05; Table 2). Diastolic arterial pressure (DAP) increased significantly (*P* = 0.0002) over time and at T30, T40, T50, T55, and T60 compared with T0. Pulmonary diastolic (*P* = 0.001) and mean (*P* < 0.0001) arterial blood pressures both varied significantly over time. The pulmonary diastolic pressure was lower (*P* ≤ 0.05) at T35 through T45 and T60 compared with T0 (Table 2). Mean barometric pressure throughout the study period was 663 ± 3 mm Hg. The remainder of physiologic parameters recorded throughout the experiment are reported in Tables 2 and 3, as are statistical differences within groups (*n* = 8). No gross lesions were observed on postmortem examination.

Discussion

The first aim of the experiment was to evaluate the efficacy of a novel premedication combination in pigs prior to general anesthesia. A previous swine study reported a mean induction time of 206 ± 36 s by using a combination of alfaxalone (5 mg/kg IM) and dexmedetomidine (10 µg/kg IM).²⁶ In addition, a combination of alfaxalone (5 mg/kg) and diazepam (0.5 mg/kg) yielded a similar mean induction time (203 ± 45 s) as for alfaxalone–dexmedetomidine.²⁵ The shorter duration to lateral recumbency in both of these previous studies (compared with 415 ± 55 s in the target-dosed pigs of the current study) might have resulted from the higher dose of alfaxalone in the previous studies. Once lateral recumbency was achieved in the current study, all pigs were sufficiently sedated to tolerate physical manipulation, including transportation and insertion of peripheral intravenous catheters.

The second phase of our study evaluated the cardiorespiratory effects of premedication in combination with PIVA and isoflurane general anesthesia. Hypoventilation, defined by an elevated partial pressure of arterial CO₂ relative to that in awake healthy pigs,⁷ occurred from T0 through T60. The overall result was a mild respiratory acidosis with little change in arterial or venous pH over time. Dexmedetomidine, when administered for sedation alone, is reported to cause decreased respiratory rate in dogs and cats,²⁸ but administration at 3 µg/kg/h in dogs

Table 2. Physiologic parameters of swine ($n = 8$) that received a novel intramuscular premedication drug combination (azaperone, dexmedetomidine, and alfaxalone) followed by a partial intravenous anesthetic protocol (CRI, alfaxalone and dexmedetomidine; F_1 isoflurane, 1.2% to 1.5%; F_1 O_2 , 40%) for 60 min

Parameter	Time (min)						
	0	10	20	30	40	50	60
Heart rate (bpm)*	118 ± 20	116 ± 18	114 ± 16	112 ± 16 ^b	111 ± 16 ^b	110 ± 15 ^b	108 ± 14 ^b
Systolic arterial blood pressure (mm Hg)	98 ± 11	100 ± 12	98 ± 13	102 ± 14	101 ± 15	103 ± 14	103 ± 14
Diastolic arterial blood pressure (mm Hg) ^a	57 ± 12	62 ± 14	62 ± 16	67 ± 16 ^b	66 ± 16 ^b	69 ± 15 ^b	68 ± 15 ^b
Mean arterial blood pressure (mm Hg)	75 ± 12	80 ± 13	80 ± 14	87 ± 15	83 ± 15	87 ± 15	86 ± 15
Cardiac output (L/min)	4.3 ± 0.9	4.2 ± 0.8	4.2 ± 0.9	4.1 ± 0.9	4.1 ± 0.8	4.0 ± 0.7	4.1 ± 0.8
Cardiac index (L/kg/min)	0.16 ± 0.03	0.16 ± 0.02	0.16 ± 0.03	0.17 ± 0.02	0.16 ± 0.02	0.15 ± 0.02	0.16 ± 0.02
Central venous pressure (mm Hg)	0.25 ± 1.83	0.13 ± 2.30	0.13 ± 2.17	0.25 ± 2.25	0.38 ± 2.00	-0.13 ± 2.23	0.13 ± 2.17
Pulmonary systolic blood pressure (mm Hg)	21.3 ± 4.2	22.5 ± 5.0	22.4 ± 4.8	22.4 ± 5.1	21.8 ± 5.1	22.3 ± 5.4	22.1 ± 5.6
Pulmonary diastolic blood pressure (mm Hg) ^a	10.4 ± 3.0	9.3 ± 2.6	8.0 ± 2.5	8.4 ± 2.9	7.5 ± 2.4 ^b	8.2 ± 2.3	7.5 ± 2.3 ^b
Pulmonary mean blood pressure (mm Hg) ^a	16.0 ± 3.8	16.1 ± 4.0	15.6 ± 3.7	16.2 ± 4.0	15.9 ± 3.8	15.8 ± 4.0	15.6 ± 4.2
Bispectral index (no.)	60 ± 13	55 ± 9	55 ± 12	52 ± 9	53 ± 6	54 ± 9	55 ± 10
Core body temperature (°C)	37.9 ± 0.8	37.9 ± 0.8	37.9 ± 0.8	37.9 ± 0.8	37.9 ± 0.8	37.8 ± 0.8	37.0 ± 0.8
Systemic vascular resistance (dynes/s/cm ⁻⁵) ^a	1457 ± 382	1590 ± 391	1581 ± 473	1724 ± 413 ^b	1666 ± 423	1769 ± 359 ^b	1707 ± 400 ^b

*Significant ($P < 0.05$) difference over time.

^bSignificant ($P < 0.05$) difference compared with time 0.

Table 3. Respiratory and acid-base values of swine ($n = 8$) that received a novel intramuscular premedication drug combination (azaperone, dexmedetomidine, alfaxalone) followed by a partial intravenous anesthetic protocol (alfaxalone and dexmedetomidine, CRI; F_1 isoflurane, 1.2% to 1.5%; F_1 O_2 , 40%) for 60 min

	Time (min)						
	0	10	20	30	40	50	60
Respiratory rate (breaths per min) ^a	28 ± 12	30 ± 12	30 ± 11	31 ± 11 ^b	31 ± 11 ^b	32 ± 13 ^b	31 ± 11 ^b
PaO ₂ (mm Hg) ^a	120 ± 20	120 ± 19	118 ± 19	117 ± 19	115 ± 19	115 ± 19	114 ± 18 ^b
PvO ₂ (mm Hg) ^a	59 ± 5	58 ± 4	57 ± 4 ^b	56 ± 3 ^b	57 ± 3 ^b	56 ± 4 ^b	56 ± 3 ^b
PaCO ₂ (mm Hg)	52 ± 6	52 ± 5	52 ± 6	52 ± 5	53 ± 6	51 ± 7	52 ± 6
PvCO ₂ (mm Hg)	61 ± 7	59 ± 7	59 ± 7	59 ± 7	61 ± 7	62 ± 13	59 ± 7
SaO ₂ (%)	97 ± 2	97 ± 2	97 ± 2	97 ± 2	97 ± 2	97 ± 2	97 ± 2
Tidal volume index (L/min/kg)	6.6 ± 1.4	6.4 ± 1.3	6.4 ± 1.2	6.5 ± 1.3	6.4 ± 1.3	6.4 ± 1.3	6.2 ± 1.1 ^b
Minute volume index (L/min/kg) ^a	0.19 ± 0.06	0.20 ± 0.06	0.20 ± 0.05	0.20 ± 0.06	0.20 ± 0.06	0.21 ± 0.06 ^b	0.21 ± 0.06 ^b
HCO ₃ ⁻ (mmol/L)	30.0 ± 3.0	30.4 ± 2.6	30.7 ± 3.1	30.5 ± 2.9	31.5 ± 2.5	30.4 ± 2.9	31.0 ± 2.3
Arterial pH ^a	7.37 ± 0.04	7.38 ± 0.03	7.38 ± 0.04	7.38 ± 0.04 ^b	7.38 ± 0.04 ^b	7.38 ± 0.04 ^b	7.39 ± 0.04 ^b
Venous pH	7.35 ± 0.04	7.35 ± 0.04	7.35 ± 0.04	7.35 ± 0.04	7.35 ± 0.04	7.35 ± 0.04	7.35 ± 0.04

^aSignificant ($P < 0.05$) difference over time.

^bSignificant ($P < 0.05$) difference compared with time 0.

anesthetized with isoflurane had little effect on ventilation.¹⁶ However, alfaxalone can cause dose-dependent respiratory depression in dogs and cats when administered for induction or as a constant-rate infusion.^{1,13} The combination of alfaxalone-dexmedetomidine and isoflurane likely produced the effects observed in the current study, the main result being hypercarbia.

Clinically relevant observations regarding hemodynamic parameters consist of changes in HR and SVR over time. The significant decrease in HR observed over time had minimal clinical effects, with a total relative difference of 10 bpm. The accompanying increase in SVR was expected. Increased SVR and decreased HR are characteristic hemodynamic changes associated with the administration of α_2 -adrenergic agonists and, in this case, likely contributed to the effects of dexmedetomidine.^{3,5,19,30}

The effects of alfaxalone on HR and SVR are less clear. Alfaxalone administered at a rate of 10 mg/kg/h after a 2-mg/kg bolus did not significantly change mean arterial pressure in sheep, but a significant increase in HR was observed.¹¹ This

increase in HR might be compensatory for decreased SVR, but SVR was not measured in that study.¹¹ If alfaxalone does indeed cause a decrease in SVR in swine, it may have been masked by the concurrent administration of an α_2 -adrenergic agonist. The possibility also exists that alfaxalone had little effect on mean arterial pressure and SVR at the reported dose.

The observed decrease in the cardiac index did not reach statistical significance, in contrast with previous reports of dexmedetomidine infusion in other species. In cats, dexmedetomidine is reported to produce a dose-dependent decrease in HR and cardiac index with a concurrent increase in SVR.¹⁶ Decreases in HR, CO, and cardiac index have also been observed in dogs receiving CRI of dexmedetomidine and alfaxalone,²⁰ though the cardiovascular effects of the infusions in swine have not been documented. The decrease in HR we observed here is likely attributable to the dexmedetomidine infusion, because CRI of alfaxalone in other domestic species is reported to have minimal cardiovascular effects.^{1,11,29} Alfaxalone produces dose-dependent cardiorespiratory depression,^{13,29} but it is unlikely

that the alfaxalone doses we used had a significant effect on cardiopulmonary parameters.

In our pigs, the absence of significant changes in MAP over time and the clinically acceptable range (75 to 85 mm Hg) was expected, given the low dose of each anesthetic agent. The increase in DAP might partially be explained by the contribution of SVR, which also increased over time. Interestingly, although systemic DAP increased over time, the pulmonary DAP decreased significantly compared with baseline. To our knowledge, a decrease in pulmonary DAP associated with dexmedetomidine administration or with any of the agents in the current study has not been reported. However the decrease in pulmonary DAP might be the result of dexmedetomidine administration. A significant decrease in mean pulmonary arterial pressure occurred in pigs of a similar weight that received a dexmedetomidine infusion of 0.5 µg/kg/h.³¹ Unfortunately, the pulmonary DAP was not reported, but given that the decrease in mean pulmonary arterial pressure was believed to be the result of sympatholysis through the activation of α_2 adrenergic receptors, a concurrent decrease in diastolic pulmonary arterial pressure would be expected.

Few data are available regarding intravenous infusions of dexmedetomidine and alfaxalone in swine,^{24,31} and the physiologic effects of these agents combined with isoflurane have not been described. The cardiovascular changes induced by dexmedetomidine and other α_2 -adrenergic agonists are predictable in terms of causing bradycardia and increased SVR. The cardiovascular effects of alfaxalone infusions have been studied previously in dogs, cats, and sheep^{1,14,29} and appear similar to the effects we observed in our pigs. Based on these consistent results, the investigated PIVA technique may be a suitable option for a maintenance anesthetic protocol in laboratory swine.

Although we did not use a standardized scoring system to grade various markers of anesthetic depth, all pigs maintained an adequate plane of anesthesia for the duration of the experiment. No animals demonstrated swallowing or limb movement that necessitated rescue anesthesia. Studies of BIS in pigs have yielded conflicting results. In one previous study, BIS values in unstimulated pigs did not reliably correlate with isoflurane anesthesia,⁶ whereas a more recent study found BIS to be a reliable indicator of anesthetic depth in piglets anesthetized with isoflurane.⁸ Reliable correlation of BIS values to anesthetic depth during surgery using propofol anesthesia has been reported in swine.²⁷ In the current study, mean BIS values did not increase significantly over time. These results support the use of the reported PIVA for maintaining an adequate depth of general anesthesia for short procedures (60 min). However, further studies may be required to validate BIS monitoring as a measure of anesthetic depth in laboratory swine using the reported anesthetic protocol.

We used a claw pinch to mimic the stimulation induced by a minimally invasive procedure. The largest pig (31 kg), which received the lowest dose of premedication (dosed for a 27-kg animal) relative to the other subjects, responded the most frequently (4 of 6 time points) to claw pinch. This animal also demonstrated the highest mean BIS value and was suspected to have experienced a lighter plane of anesthesia. These findings support the use of BIS monitoring to aid in determining an appropriate plane of anesthesia for minor stimulation. These findings are in agreement with the previous study⁸ that found both BIS and toe pinch response to be reliable indicators of light anesthesia in isoflurane-anesthetized piglets.

The reported anesthetic technique is best suited for minimally invasive diagnostic or therapeutic procedures, and additional

analgesia such as opioids or local anesthetic techniques are indicated for more invasive surgical procedures. In future studies, it would be beneficial to weigh animals immediately prior to premedication and to have baseline parameters in awake animals that could be compared with parameters measured throughout the premedication and anesthetic periods. In addition, an extended experimental timeline of 2 to 3 h may more accurately reflect the duration of common anesthetic protocols, and a larger study population would be ideal, to increase the study power.

Intramuscular administration of azaperone, alfaxalone, and dexmedetomidine induced a level of sedation sufficient to handle, transport, and place intravenous catheters in laboratory swine. The novel premedication and PIVA technique provided rapid immobilization and adequate muscle relaxation, analgesia, and narcosis for minimally invasive procedures, including carotid arterial and jugular venous dissections (after local anesthetic infiltration) in laboratory swine. We recommend additional analgesia in the form of local or systemic anesthesia when more invasive procedures are performed. The reported technique was associated with minimal hemodynamic and pulmonary effects, we consider that the cardiopulmonary changes observed were minor and clinically acceptable.

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