Cardiovascular effects of dopamine hydrochloride and phenylephrine hydrochloride in healthy isoflurane-anesthetized New Zealand White rabbits (*Oryctolagus cuniculus*)

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OBJECTIVE
To determine the cardiopulmonary effects of progressively increasing infusion rates of dopamine hydrochloride and phenylephrine hydrochloride in healthy adult New Zealand White rabbits anesthetized with isoflurane.

ANIMALS
6 New Zealand White rabbits. (*Oryctolagus cuniculus*).

PROCEDURES
Each rabbit was anesthetized on 2 occasions (≥ 2 weeks apart) with isoflurane in oxygen at 1.5 times the published isoflurane minimum alveolar concentration of 2.07%. Carotid artery and pulmonary artery catheters were placed. During each anesthetic episode, each rabbit received 5 progressively increasing doses of either dopamine (5, 10, 15, 20, or 30 μg/kg/min) or phenylephrine (0.125, 0.25, 0.5, 1.0, and 2.0 μg/kg/min). Blood gas and cardiopulmonary measurements were obtained after a 20-minute equilibration period prior to administration of the first drug dose (baseline) and after each subsequent dose administration.

RESULTS
Dopamine increased stroke index at the highest infusion rate of 30 μg/kg/min; however, cardiac output and mean arterial blood pressure remained unchanged from baseline values. Administration of phenylephrine at a rate of 2 μg/kg/min increased mean arterial blood pressure to 62 mm Hg from the baseline value of 45 mm Hg. This was a result of an increase in systemic vascular resistance with a concomitant decrease in heart rate and no change in cardiac output. Blood lactate concentration increased with time when rabbits received either treatment.

CONCLUSIONS AND CLINICAL RELEVANCE
Within the dose range of 5 to 30 μg/kg/min, dopamine was not an effective treatment for isoflurane-induced hypotension in rabbits and phenylephrine was only minimally effective at a dose of 2 μg/kg/min. (*Am J Vet Res* 2015;76:116–121)

Rabbits are a common companion animal and research species[1,2] for which the anesthesia-related mortality rate is 7 to 8 times the rates for cats and dogs.[3] Inhalation anesthetics are popular for use in rabbits because anesthetic depth can be easily adjusted and recovery is rapid. However, the use of inhalation anesthetics in rabbits results in marked cardiovascular depression.[4,5]

Although dose-dependent depressant effects of isoflurane occur across species, the hypotension that develops in rabbits during isoflurane anesthesia is more severe than that in other species with mean ± SD MAPs of 46.8 ± 2.7 mm Hg, 36 ± 2.7 mm Hg, and 29.3 ± 2.0 mm Hg reported at doses of 1.0, 1.5, and 2.0 times the isoflurane MAC, respectively.[4] In anesthetized small animals, an MAP of 60 to 70 mm Hg is considered to be the lowest at which adequate tissue perfusion can be maintained.[6]

ABBREVIATIONS

DAP	Diastolic arterial blood pressure
MAC	Minimum alveolar concentration
MAP	Mean arterial blood pressure
OER	Oxygen extraction ratio
SAP	Systolic arterial blood pressure
SI	Stroke index
SVRI	Systemic vascular resistance index

The hypotensive effects of inhalation anesthetics may be a contributing factor to the high risk of anesthesia-related death in rabbits.

In cats and dogs, positive inotropes or vasopressors have been administered to correct hypotension during anesthesia; however, there is little published information on their effects in isoflurane-anesthetized rabbits. We hypothesized that in isoflurane-anesthetized rabbits, administration of dopamine would increase cardiac output and blood pressure in a dose-dependent manner but that administration of phenylephrine would increase blood pressure with no change in cardiac output. The purpose of the study reported here was to determine the cardiopulmonary effects of progressively increasing infusion rates of dopamine hydrochloride and phenylephrine hydrochloride in healthy adult New Zealand White rabbits (*Oryctolagus cuniculus*) anesthetized with isoflurane.

Materials and Methods

ANIMALS

Six healthy adult female New Zealand White rabbits were used in the study. The mean ± SD weight of

the rabbits was 3.84 ± 0.2 kg. The study had institutional animal care and use committee approval.

ANESTHESIA AND INSTRUMENTATION

Anesthesia was induced with isoflurane in O_2 (5 L/min) delivered from a calibrated vaporizer (set at 5%) via a Bain circuit to an induction chamber into which each rabbit was placed. Once the righting reflex was lost, the rabbit was removed from the chamber, and a tight-fitting face mask was placed, followed by direct placement of a cuffed orotracheal tube. Anesthesia was then maintained with isoflurane (vaporizer setting, 2% to 3%) in oxygen delivered via a Bain circuit with a fresh gas flow rate of 200 mL/kg/min. Rabbits were allowed to breath spontaneously.

For each rabbit, a 22-gauge, 2.5-cm venous catheter[a] was placed in the left lateral saphenous vein for administration of lactated Ringer's solution[b] at a rate of 3 mL/kg/h. Following surgical preparation of the ventrolateral aspect of the neck and by means of aseptic technique, a 2- to 3-cm-long skin incision was made to allow dissection to the right jugular vein and carotid artery. A 14-gauge, 5-cm catheter[a] was placed in the jugular vein (to function as an introducer), and a 22-gauge, 4.4-cm catheter[c] was inserted into the carotid artery for blood pressure measurement and arterial blood sample collection. A 4F, 75-cm thermodilution balloon catheter[d] was placed with fluoroscopic guidance through the introducer into the pulmonary circulation. This catheter was used for measurement of cardiac output, pulmonary artery occlusion pressure, mean pulmonary artery pressure, and central venous pressure and for collection of mixed-venous blood samples. The jugular and arterial catheters were secured to the rabbit, and the skin was sutured around the insertion sites.

A calibrated temperature probe was inserted into the esophagus to the level of the heart for continuous core body temperature monitoring. Body temperature was maintained between 38° and 39°C with an electric warming blanket[e] and forced air warming unit[f] as needed. A catheter was placed into the lumen of the endotracheal tube to the distal third of the tube for respiratory gas sample collection. A multivariable anesthesia monitor,[g] which was calibrated daily with 3 known isoflurane concentrations, was used to measure inspired and expired P_{CO_2} and O_2 and isoflurane concentrations. A 3-lead ECG system was connected to each rabbit for monitoring cardiac electrical activity and heart rate.

Central venous, pulmonary, and carotid arterial blood pressures (MAP, SAP, and DAP); ECG output; and core body temperature were monitored continuously and recorded with physiologic acquisition hardware[h] and software.[i] The pressure transducers were calibrated with a mercury manometer and the zero referenced to the level of the right atrium.

Arterial and mixed-venous hemoglobin concentrations, pH, P_{O_2}, P_{CO_2}, hemoglobin oxygen saturation (used to calculate oxygen content), and arterial lactate concentrations were measured or calculated by a blood gas analyzer.[j] Arterial blood PCV was analyzed by means of a microcentrifugation technique, and total protein concentration was determined via refractometry.

Cardiac output was determined in triplicate by a thermodilution method and use of a cardiac output computer.[k] Three milliliters of iced 5% dextrose solution[b] was injected into the proximal port of the thermodilution catheter (placed into the right atrium) for each measurement, and the mean cardiac output was calculated.

Stroke index, left ventricular rate pressure product, SVRI, pulmonary vascular resistance index, left ventricular stroke work index, right ventricular stroke work index, arterial and mixed-venous oxygen content, oxygen delivery, oxygen consumption, OER, alveolar-arterial difference in P_{O_2}, and shunt fraction were calculated with standard equations.[7–9] Barometric pressures (used to calculate alveolar P_{O_2}) were obtained from the University of California-Davis climate station. Body surface area (used for indexing variables) was based on published data.[10]

EXPERIMENTAL PROTOCOL

Each rabbit was anesthetized on 2 occasions at least 2 weeks apart. On each occasion, rabbits were randomly assigned to receive either dopamine or phenylephrine so that all rabbits eventually received each treatment. Dopamine hydrochloride[l] (40 mg/mL diluted in saline [0.9% NaCl] solution[b] to 0.6 mg/mL) was administered at progressively increasing infusion rates of 5, 10, 15, 20, and 30 µg/kg/min, and phenylephrine hydrochloride[m] (10 mg/mL diluted in saline solution[b] to 0.04 mg/mL) was administered at 0.125, 0.25, 0.5, 1.0, and 2.0 µg/kg/min. As the infusion rates increased, the rate of administration of lactated Ringer's solution was decreased so that the total volume of fluid administered remained at 3 mL/kg/h.

Following anesthetic induction and instrumentation of each rabbit, the end-tidal isoflurane concentration was set to 1.5 times the published isoflurane MAC for rabbits of 2.07%.[4] After a 20-minute period during which the end-expired isoflurane concentration remained stable, baseline cardiovascular measurements were obtained and a 0.4-mL sample of arterial blood and a 0.4-mL sample of mixed-venous blood were collected. Blood was then placed into a microhematocrit tube[n] for determination of PCV and total protein concentration, and two 125-µL heparinized glass capillary tubes[o] that were capped and stored in ice water for blood gas analysis, which occurred within 30 minutes after collection. Cardiac output was measured as described.

End-expired isoflurane concentration was kept constant, and the first assigned infusion was commenced. Thereafter, an adjustment was made to the infusion system to deliver the next higher rate, and measurements and blood sample collections were performed after a 20-minute equilibration period. This

sequence was repeated until all 5 infusion rates had been administered.

On completion of each experiment, end-expired isoflurane concentration was reduced to approximately 2.5% and buprenorphine[p] (0.05 mg/kg) was administered IV. The pulmonary artery, jugular, and carotid catheters were removed from the rabbit, and digital pressure was applied to the insertion sites for 20 minutes to achieve hemostasis. Skin sutures[q] were placed to close the incision, and isoflurane administration was discontinued. Following extubation, meloxicam[r] (0.5 mg/kg) was administered SC and the lateral saphenous catheter was removed once the rabbit was actively moving. Each rabbit was observed twice daily for 7 days; particular attention was given to wound appearance, appetite, urination, defecation, and signs of pain (eg, lack of normal behavior or reaction to wound inspection or palpation). Contingencies for continued administration of buprenorphine or meloxicam (at postoperative doses) were available if needed.

STATISTICAL ANALYSIS

Data are reported as mean ± SD. Following confirmation of normality (by means of a Kolmogorov-Smirnov test), data were analyzed for the effects of dopamine or phenylephrine with a repeated-measures 1-way ANOVA.[s] When significance was detected, pairwise comparisons were made against baseline values with a sequentially rejective Bonferroni technique to correct for multiple comparisons.[11] Significance was set at a value of $P \leq 0.05$.

Results

Among the 6 rabbits, the time required for instrumentation and total duration of anesthesia did not differ between treatments, with overall mean values for all rabbits of 118 ± 40 minutes and 369 ± 43 minutes, respectively. The end-expired isoflurane concentration did not differ when rabbits received dopamine or phenylephrine; the overall mean value was 3.12 ± 0.08%. All rabbits recovered without incident, and none required additional doses of analgesics following recovery.

EFFECTS OF DOPAMINE

At the doses studied, dopamine had minimal effects on all measured variables **(Tables 1 and 2)**. Compared with baseline, SI was increased at the highest infusion rate ($P = 0.015$). Arterial blood lactate concentration progressively increased and was significantly greater than baseline at infusion rates of 20 µg/kg/min ($P = 0.003$) and 30 µg/kg/min ($P < 0.001$).

EFFECTS OF PHENYLEPHRINE

The effects of phenylephrine on measured variables were minimal until the highest infusion rate was administered to the rabbits **(Tables 3 and 4)**. Compared with baseline, infusion of phenylephrine at a rate of 2.0 µg/kg/min resulted in significant increases in SAP ($P = 0.014$), MAP ($P = 0.015$), DAP ($P = 0.015$), SVRI ($P = 0.01$), and left ventricular stroke work index ($P = 0.026$) and a decrease in heart rate ($P = 0.016$). Small but significant increases in $Paco_2$ and mixed-venous Pco_2 and associated decreases in blood pH were

Table 1—Mean ± SD cardiovascular variables before (baseline) and during IV infusion of dopamine at progressively increasing rates (5, 10, 15, 20, or 30 µg/kg/min) in 6 isoflurane-anesthetized New Zealand White rabbits (*Oryctolagus cuniculus*).

		Infusion rate (µg/kg/min)				
Variable	**Baseline**	**5**	**10**	**15**	**20**	**30**
Heart rate (beats/min)	214 ± 7	219 ± 10	220 ± 12	216 ± 14	214 ± 16	208 ± 15
SAP (mm Hg)	72 ± 9	71 ± 6	70 ± 9	70 ± 7	70 ± 8	75 ± 10
MAP (mm Hg)	46 ± 5	46 ± 5	46 ± 8	46 ± 7	46 ± 8	48 ± 9
DAP (mm Hg)	33 ± 5	33 ± 6	34 ± 8	33 ± 8	34 ± 8	35 ± 9
CVP (mm Hg)	5 ± 3	5 ± 2	6 ± 3	5 ± 2	4 ± 2	4 ± 1
MPAP (mm Hg)	15 ± 2	15 ± 2	15 ± 3	16 ± 3	14 ± 2	14 ± 3
PAOP (mm Hg)	9 ± 2	9 ± 2	9 ± 3	10 ± 2	9 ± 3	8 ± 2
Cardiac output (L/min)	0.47 ± 0.03	0.47 ± 0.04	0.46 ± 0.05	0.47 ± 0.05	0.48 ± 0.06	0.51 ± 0.05
SI (mL/beat/m^2)	9.0 ± 0.7	8.9 ± 0.9	8.7 ± 1.1	8.9 ± 1.0	9.2 ± 1.0	10.1 ± 0.6*
SVRI (dynes•s/cm^5/m^2)	1,743 ± 168	1,682 ± 244	1,685 ± 253	1,692 ± 212	1,681 ± 224	1,672 ± 301
PVRI (dyne•s/cm^5/m^2)	252 ± 76	249 ± 41	246 ± 50	246 ± 89	187 ± 81	236 ± 52
LVRPP (beats•mm Hg/min)	9,932 ± 1,235	9,989 ± 1,372	10,054 ± 1,985	9,803 ± 1,590	9,776 ± 1,753	9,999 ± 1,811
LVSWI (g•m/m^2)	5.99 ± 0.58	5.81 ± 0.82	5.70 ± 1.28	5.90 ± 1.36	6.12 ± 1.55	7.07 ± 1.62
RVSWI (g•m/m^2)	1.99 ± 0.28	1.95 ± 0.36	1.90 ± 0.47	2.03 ± 0.51	1.85 ± 0.44	2.11 ± 0.55

*Within a row, value is significantly ($P \leq 0.05$) different from baseline.

CVP = Central venous pressure. LVRPP = Left ventricular rate pressure product (heart rate X MAP). LVSWI = Left ventricular stroke work index. MPAP = Mean pulmonary artery pressure. PAOP = Pulmonary artery occlusion pressure. PVRI = Pulmonary vascular resistance index. RVSWI = Right ventricular stroke work index.

Rabbits were anesthetized with isoflurane in oxygen at a mean ± SD concentration of 3.12 ± 0.08%. A stabilization period of 20 minutes was allowed before the first drug infusion commenced and after each subsequent increase in infusion rate prior to blood sampling and data collection. Central venous, pulmonary, and carotid arterial pressures (MAP, SAP, and DAP) were monitored continuously and recorded with physiologic acquisition hardware and software; the pressure transducers were calibrated with a mercury manometer and the zero referenced to the level of the right atrium. Heart rate was determined by ECG and cardiac output determined in triplicate by a thermodilution method with the use of a cardiac output computer.

Table 2—Mean ± SD blood gas and derived cardiorespiratory variables before (baseline) and during IV infusion of dopamine at progressively increasing rates (5, 10, 15, 20, or 30 μg/kg/min) in the same 6 isoflurane-anesthetized New Zealand White rabbits in Table 1.

		Infusion rate (μg/kg/min)				
Variable	**Baseline**	**5**	**10**	**15**	**20**	**30**
Arterial blood pH	7.43 ± 0.05	7.42 ± 0.05	7.42 ± 0.06	7.42 ± 0.04	7.42 ± 0.04	7.41 ± 0.05
P_{aCO_2} (mm Hg)	38 ± 5	42 ± 3	41 ± 3	40 ± 3	40 ± 1	41 ± 4
P_{aO_2} (mm Hg)	384 ± 27	396 ± 51	386 ± 61	391 ± 48	406 ± 68	426 ± 46
Arterial hemoglobin (g/dL)	9.9 ± 0.8	9.6 ± 0.8	9.4 ± 0.9	9.5 ± 0.9	9.3 ± 0.8	9.4 ± 1.0
Mixed-venous pH	7.40 ± 0.05	7.39 ± 0.04	7.39 ± 0.06	7.40 ± 0.04	7.40 ± 0.04	7.38 ± 0.05
Mixed-venous P_{CO_2} (mm Hg)	46 ± 5	47 ± 3	47 ± 2	45 ± 3	47 ± 2	47 ± 3
Mixed-venous P_{O_2} (mm Hg)	57 ± 5	58 ± 8	58 ± 8	58 ± 9	58 ± 6	61 ± 7
Mixed-venous hemoglobin (g/dL)	10.0 ± 0.7	9.6 ± 0.9	9.5 ± 0.9	9.7 ± 1.0	9.5 ± 0.9	9.5 ± 1.0
Arterial lactate (mmol/L)	1.5 ± 0.5	1.6 ± 0.5	1.8 ± 0.6	2.0 ± 0.6	2.2 ± 0.6*	2.4 ± 0.6*
PCV (%)	30 ± 3	30 ± 3	30 ± 3	29 ± 2	29 ± 3	30 ± 3
Total protein (g/dL)	4.1 ± 0.3	4.0 ± 0.4	4.1 ± 0.3	4.1 ± 0.3	4.0 ± 0.3	4.1 ± 0.3
Arterial oxygen content (mL/dL)	14.6 ± 1.1	14.2 ± 1.1	13.9 ± 1.3	14.1 ± 1.2	13.9 ± 1.2	14.1 ± 1.4
Mixed-venous oxygen content (mL/dL)	12.8 ± 1.3	12.5 ± 1.6	12.3 ± 1.4	12.5 ± 1.7	12.4 ± 1.4	12.5 ±1.6
Oxygen delivery (mL/min)	68 ± 9	68 ± 10	64 ± 13	66 ± 12	67 ± 12	73 ± 12
Oxygen consumption (mL/min)	8 ± 2	8 ± 3	7 ± 2	7 ± 3	7 ± 2	8 ± 1
OER	0.12 ± 0.03	0.13 ± 0.05	0.11 ± 0.04	0.12 ± 0.05	0.11 ± 0.03	0.11 ± 0.02
Alveolar-arterial difference in P_{O_2} (mm Hg)	256 ± 26	240 ± 51	250 ± 63	247 ± 50	232 ± 69	211 ± 46
Q_S/Q_T	0.31 ± 0.05	0.31 ± 0.11	0.34 ± 0.12	0.33 ± 0.09	0.31± 0.09	0.29 ± 0.05

Q_S/Q_T = Shunt fraction (or venous admixture).

Blood pH, P_{CO_2}, P_{O_2}, hemoglobin concentration, and lactate concentration were measured with a blood gas analyzer. Other variables were calculated from standard formulas.

See Table 1 for remainder of key.

Table 3—Mean ± SD cardiovascular variables before (baseline) and during IV infusion of phenylephrine at progressively increasing rates (0.125, 0.25, 0.5, 1.0, and 2.0 μg/kg/min) in the same 6 isoflurane-anesthetized New Zealand White rabbits in Tables 1 and 2.

		Infusion rate (μg/kg/min)				
Variable	**Baseline**	**0.125**	**0.25**	**0.5**	**1.0**	**2.0**
Heart rate (beats/min)	218 ± 13	217 ± 21	215 ± 16	209 ± 9	202 ± 10*	194 ± 14*
SAP (mm Hg)	71 ± 9	70 ± 8	72 ± 9	73 ± 8	75 ± 9	83 ± 7*
MAP (mm Hg)	45 ± 10	47 ± 7	48 ± 8	49 ± 7	52 ± 7	62 ± 7*
DAP (mm Hg)	32 ± 11	34 ± 7	36 ± 8	37 ± 7	40 ± 6	51 ± 8*
CVP (mm Hg)	7 ± 3	6 ± 2	8 ± 2	7 ± 2	8 ± 2	8 ± 2
MPAP (mm Hg)	17 ± 3	15 ± 1	15 ± 2	15 ± 1	17 ± 3	17 ± 2
PAOP (mm Hg)	9 ± 4	9 ± 4	9 ± 4	9 ± 2	9 ± 2	9 ± 2
Cardiac output (L/min)	0.49 ± 0.03	0.48 ± 0.06	0.49 ± 0.05	0.48 ± 0.06	0.47 ± 0.05	0.45 ± 0.06
SI (mL/beat/m^2)	9.25 ± 0.56	9.19 ± 1.35	9.44 ± 0.69	9.44 ± 0.69	9.56 ± 1.04	9.61 ± 1.25
SVRI (dynes•s/cm^5/m^2)	1,530 ± 505	1,661 ± 355	1,570 ± 313	1,698 ± 238	1,804 ± 230	2,341 ± 297*
PVRI (dynes•s/cm^5/m^2)	371 ± 180	436 ± 242	252 ± 210	312 ± 135	389 ± 139	404 ± 145
LVRPP (beats•mm Hg/min)	9,758 ± 2,162	10,170 ± 2,298	10,357 ± 2,452	10,341 ± 1,920	10,485 ± 1,928	12,029 ± 1,904
LVSWI (g•m/m^2)	5.97 ± 1.35	6.13 ± 1.13	6.50 ± 1.13	6.72 ± 1.35	7.14 ± 1.33	8.57 ± 1.42*
RVSWI (g•m/m^2)	2.23 ± 0.31	1.98 ± 0.28	2.00 ± 0.33	2.08 ± 0.23	2.34 ± 0.46	2.38 ± 0.43

See Table 1 for key

observed at infusion rates of 1.0 and 2.0 μg/kg/min. Arterial blood lactate concentration progressively increased and was significantly higher than baseline at the infusion rates of 0.5 μg/kg/min ($P = 0.003$) and 1.0 μg/kg/min ($P = 0.005$).

Discussion

In the present study, dopamine and phenylephrine were administered to healthy rabbits at infusion rates similar to and greater than those used clinically to manage hypotension in other small animal species. Both drugs had minimal efficacy for management of hypotension in isoflurane-anesthetized rabbits.

The physiologic actions of dopamine are mediated through stimulation of dopaminergic and β_1- and α_1-adrenergic receptors and release of endogenous norepinephrine.[12-14] Administration of exogenous dopamine to humans results in dose-dependent increases in MAP because of increased cardiac contractility with or without changes in SVRI and heart rate.[12] In isoflurane-anesthetized cats, dopamine infusion at rates up to 20 μg/kg/min results in significant increases (from baseline) in cardiac index and MAP because of increas-

Table 4—Mean ± SD blood gas and derived cardiorespiratory variables before (baseline) and during IV infusion of phenylephrine at progressively increasing rates (0.125, 0.25, 0.5, 1.0, and 2.0 μg/kg/min) in the same 6 isoflurane-anesthetized New Zealand White rabbits in Tables 1, 2, and 3.

		Infusion rate (μg/kg/min)				
Variable	**Baseline**	**0.125**	**0.25**	**0.5**	**1.0**	**2.0**
Arterial blood pH	7.46 ± 0.04	7.45 ± 0.03	7.44 ± 0.04	7.43 ± 0.04	7.42 ± 0.04*	7.40 ± 0.05*
$Paco_2$ (mm Hg)	39 ± 3	41 ± 3	42 ± 3	43 ± 3	43 ± 4*	45 ± 4*
Pao_2 (mm Hg)	261 ± 124	239 ± 130	307 ± 100	368 ± 95	351 ± 66	341 ± 127
Arterial hemoglobin (g/dL)	10.2 ± 0.8	9.9 ± 1.0	9.6 ± 1.0	9.9 ± 0.9	9.8 ± 1.0	10.0 ± 1.2
Mixed-venous pH	7.44 ± 0.04	7.43 ± 0.03	7.42 ± 0.04	7.41 ± 0.03	7.39 ± 0.04*	7.37 ± 0.04*
Mixed-venous Pco_2 (mm Hg)	44 ± 3	46 ± 3	47 ± 3	48 ± 5	50 ± 3*	52 ± 4*
Mixed-venous Po_2 (mm Hg)	50 ± 5	49 ± 6	51 ± 5	55 ± 7	54 ± 6	54 ± 6
Mixed-venous hemoglobin (g/dL)	10.4 ± 0.8	10.0 ± 1.0	10.0 ± 0.8*	9.9 ± 0.9*	10.0 ± 0.9*	10.4 ± 1.0
Arterial lactate (mmol/L)	1.7 ± 0.3	1.7 ± 0.5	1.9 ± 0.4	2.2 ± 0.5*	2.3 ± 0.6*	2.5 ± 0.7
PCV (%)	31 ± 2	31 ± 2	30 ± 3	31 ± 2	31 ± 3	32 ± 3
Total protein (g/dL)	4.3 ± 0.1	4.2 ± 0.2	4.0 ± 0.3	4.2 ± 0.3	4.1 ± 0.4	4.3 ± 0.2
Arterial oxygen content (mL/dL)	14.7 ± 1.0	14.1 ± 1.2	14.0 ± 1.3	14.5 ± 1.4	14.3 ± 1.3	14.7 ± 1.6
Mixed-venous oxygen content (mL/dL)	12.7 ± 0.8	12.0 ± 1.3	12.5 ± 1.0	12.4 ± 1.3	12.4 ± 1.1	12.6 ± 1.1
Oxygen delivery (mL/min)	71 ± 8	68 ± 12	69 ± 11	70 ± 13	67 ± 12	67 ± 13
Oxygen consumption (mL/min)	10 ± 3	10 ± 4	7 ± 4	10 ± 3	9 ± 2	9 ± 3
OER	0.13 ± 0.04	0.15 ± 0.05	0.11 ± 0.06	0.15 ± 0.03	0.13 ± 0.03	0.14 ± 0.04
Alveolar-arterial difference in Po_2 (mm Hg)	378 ± 123	397 ± 129	329 ± 98	266 ± 97	283 ± 67	290 ± 128
Q_S/Q_T	0.36 ± 0.03	0.38 ± 0.08	0.43 ± 0.13	0.27 ± 0.07	0.31 ± 0.06	0.31 ± 0.12

See Tables 1and 2 for key.

es in heart rate and SVRI.[15] In isoflurane-anesthetized dogs, infusion of dopamine at a rate of 10 μg/kg/min results in significant increases in cardiac output and MAP owing to increased contractility.[16] In the present study, although SI was increased from baseline at the highest infusion rate of 30 μg of dopamine/kg/min, that increase was not associated with any significant increase in cardiac output or MAP.

It is possible that the drug doses administered in the present study were insufficient to induce an effect in the isoflurane-anesthetized rabbits. The pharmacokinetics of dopamine in rabbits has not been evaluated, to our knowledge, and is deserving of further investigation in both awake and isoflurane-anesthetized rabbits.

Phenylephrine is a selective α_1-adrenergic receptor agonist that is used commonly to increase blood pressure.[12] In a study[15] of isoflurane-anesthetized cats, treatment with phenylephrine caused a significant increase in MAP owing to an increase in SVRI without alteration in cardiac index. In that study,[15] phenylephrine administered at a rate of 2 μg/kg/min resulted in an increase in MAP of 109%, whereas in the present study in isoflurane-anesthetized rabbits, the increase in MAP was only 38%. It should be noted that the baseline MAP was lower in the rabbits of the present study (45 mm Hg), compared with the baseline MAP in the cats of the other study[15] (66 mm Hg) at the same MAC-equivalent dose (1.5X MAC). For the rabbits used in the present study, the isoflurane MAC used was 2.07%, which was higher than that used for the cats in the other study (1.28%); this may have contributed to the difference in MAP. The determination of MAC is based entirely on movement. The greater inhalation anesthetic requirements to prevent movement in rabbits may explain the greater degree of cardiovascular depression associated with inhalation anesthetics in this species.

In isolated vascular preparations, perfusion pressure has been shown to alter the magnitude of effect of exogenous vasoconstrictors on vascular resistance.[17] In those preparations, low perfusion pressures were associated with poor response to vasoconstrictors. Whether this phenomenon occurs in vivo in isoflurane-anesthetized rabbits is unclear.

It should be considered that the doses of phenylephrine infused in the present study were insufficient to induce the desired effect on MAP. To our knowledge, the pharmacokinetics of phenylephrine in isoflurane-anesthetized rabbits has not been investigated.

When rabbits received phenylephrine at the 2 highest infusion rates, there were small but significant increases in $Paco_2$ from a baseline value of 39 mm Hg to 43 mm Hg (at an infusion rate of 1.0 μg/kg/min) and 45 mm Hg (at an infusion rate of 2.0 μg/kg/min). These increases were not associated with any significant change in end-expired isoflurane concentration; however, it is possible that undetected regional alterations in blood flow may have altered delivery of the anesthetic agent to the brain. Increases in $Paco_2$ enhance sympathetic output secondary to chemoreceptor stimulation.[18] It is possible that this contributed to the increase in blood pressure associated with phenylephrine in the present study. The improvement in MAP was of greater magnitude than would be expected for a small increase in $Paco_2$ if rabbits have a response like that of people in whom an increase in end-expired Pco_2 of 1 mm Hg results in a gain in MAP of 0.94 ± 0.55 mm Hg.[19]

The ultimate goal of hemodynamic monitoring during anesthesia is to maintain adequate tissue perfusion. In the present study, oxygen delivery, oxygen

consumption, and OER remained unchanged under all conditions. Baseline blood lactate concentrations in the rabbits of the present study were similar to those reported for anesthetized rabbits.[5,20] In the present study, lactate concentration progressively increased over time in rabbits regardless of whether they were treated with dopamine or phenylephrine.This progressive increase occurred in the absence of any change in mixed-venous P_{O_2}, oxygen delivery, or OER, which does not support the notion of a global increase in anaerobic metabolism. However, we cannot rule out changes in regional perfusion that may have increased lactate production.

The rabbits in the present study were anesthetized for more than 6 hours and were hypotensive for that entire period, on the basis of the classic definition of MAP < 60 to 70 mm Hg. Despite this, the rabbits recovered from anesthesia without any clinically obvious adverse effects. Admittedly, this is a crude assessment of any potential or actual tissue or organ damage, and the rabbits in this study were healthy, unlike many clinical cases. Although minimal effects on measured global cardiovascular variables were evident in the present study, regional changes in blood flow may have occurred undetected.

The infusion rates, and hence doses, of both dopamine and phenylephrine administered in the present study were selected on the basis of those used clinically in other species. However, the study results highlighted the ineffectiveness of both dopamine and phenylephrine in the management of isoflurane-induced hypotension in rabbits. Whether there is a pharmacodynamic or pharmacokinetic explanation for this finding is unclear at this point but warrants further investigation.

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Footnotes

a. Insyte catheter, Becton-Dickson, Sandy, Utah.
b. Baxter Healthcare, Deerfield, Ill.
c. Intracan B Braun, Melsungen, Germany.
d. Thermodilution balloon catheter, Arrow International, Reading, Pa.
e. Hotdog, Augustine Temperature Management, Eden Prairie, Minn.
f. Bair Hugger, Arizant Healthcare Inc, Eden Prairie, Minn.
g. GE Healthcare, Helsinki, Finland.
h. PowerLab, ADInstruments, Dunedin, New Zealand.
i. LabChart, ADInstruments, Dunedin, New Zealand.
j. ABL 705, Radiometer, Copenhagen, Denmark.
k. COM-1, American Edwards Laboratories, Irvine, Calif.
l. Dopamine HCl, Hospira Inc, Lake Forest, Ill.
m. Phenylephrine HCl, Baxter Healthcare Corp, Deerfield, Ill.
n. Fisherbrand, ThermoFisher Scientific, Waltham, Mass.
o. Clinitube, Radiometer Medical, Copenhagen, Denmark.
p. Buprenex injectable, Reckitt Benckiser Healthcare, Richmond, Va.
q. Ethilon, Ethicon, Somerville, NJ.
r. Loxicom, Norbrook Laboratories Ltd, Newry, Northern Ireland.
s. Prism, version 6, GraphPad Software Inc, La Jolla, Calif.

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