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Hemodynamic and respiratory effects in sheep subjected to four ventilation types and anesthetized with isoflurane or propofol

Efeitos hemodinâmicos e respiratórios em ovinos submetidos a quatro modalidades de ventilação e anestesiados com isoflurano ou propofol

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Highlights

Most suitable ventilation modality in sheep under isoflurane or propofol anesthesia.
Propofol is the best anesthetic for mechanical ventilation in healthy sheep.
Pressure-cycled ventilation with PEEP and continuous propofol yields best compliance.
Pressure-cycled ventilation could not maintain normocapnia with isoflurane.

Abstract

The objective of this study was to examine the effects of various ventilation modalities in sheep anesthetized with isoflurane or propofol. Twelve healthy adult crossbred ewes, aged 12 months and weighing 32±5 kg, were used in the study. After instrumentation with conscious animals in the right lateral decubitus position, they were administered morphine (0.3 mg kg^{-1}) and detomidine (20 mcg kg^{-1}) as preanesthetic medication. General anesthesia was induced with propofol (4 mg kg^{-1}), followed by intubation. The sheep were then allocated into two groups: PG (n=6), which received continuous infusion of propofol (0.5 mg kg^{-1} min^{-1}) for maintenance; and IG (n=6), which was maintained with isoflurane inhalation anesthesia (1.3 V %). Each group underwent four different ventilation modalities for 30 min: spontaneous ventilation (SV), volume-cycled mechanical ventilation (VV), pressure-cycled mechanical ventilation (PV), and pressure-cycled mechanical ventilation with positive end-expiratory pressure (PPV). Heart rate and cardiac index were higher in the IG, while systemic vascular resistance was higher in the PG. Hemoglobin levels, intrapulmonary shunt fraction, and tidal volume were higher in the PG.

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Both groups developed metabolic alkalosis. Isoflurane anesthesia resulted in greater hypotension, reduced lung compliance, increased airway resistance, lower PaO_2, and higher $PaCO_2$ values across all ventilation modalities. In contrast, PPV led to improved lung compliance, oxygenation index, and higher PaO_2 values, with lower intrapulmonary shunt fractions. The study concluded that propofol and PPV provide greater hemodynamic stability in anesthetized sheep.
Key words: Isoflurane. Ventilatory modalities. Sheep. Propofol.

Resumo

O objetivo deste estudo foi avaliar diferentes modalidades ventilatórias em ovinos anestesiados com isoflurano ou propofol. Foram utilizadas 12 ovelhas, adultas, mestiças, com 12 meses de idade, pesando 32±5 kg, comprovadamente hígidas. Após instrumentação com os animais conscientes em decúbito lateral direito, foi administrado morfina (0,3 mg kg^{-1}) e detomidina (20 mcg kg^{-1}) como MPA. Foram induzidas à anestesia geral com propofol (4 mg kg^{-1}) e intubadas. Neste momento, foram alocadas em dois grupos: PG (n=6), manutenção com infusão contínua de propofol (0,5 mg kg min^{-1}), e IG (n=6) com anestesia inalatória com isoflurano (1,3 V%). Todas foram mantidas por 30 minutos em cada modalidade ventilatória: ventilação espontânea (VE), ventilação mecânica ciclada a volume (VV), ventilação mecânica ciclada a pressão (VP) e ventilação mecânica ciclada a pressão com PEEP (VPP). A FC e o IC foram maiores em IG e já o IRVS foi maior em PG. Os valores de hemoglobina, fração de shunt intrapulmonar e o volume corrente foram maiores no PG. Os animais apresentaram alcalose metabólica em ambos os grupos. O isoflurano promoveu maior hipotensão, diminuição da complacência pulmonar, aumento da resistência das vias aéreas, menores valores de PaO_2 e maiores valores de $PaCO_2$ em todas as modalidades ventilatórias. A VPP promoveu maior complacência pulmonar e índice de oxigenação, maiores valores de PaO_2 e menores valores de shunt intrapulmonar. Conclui-se que o propofol e a VPP promoveram maior estabilidade hemodinâmica em ovelhas.
Palavras-chave: Isoflurano. Modalidades ventilatórias. Ovinos. Propofol.

Introduction

With the accelerated demand for surgical research, it is crucial to find effective anesthetic and analgesic protocols that offer enhanced safety and fewer adverse effects. Anesthetic maintenance in sheep typically follows two approaches: inhalation anesthesia and total intravenous anesthesia. However, significant gaps remain in understanding the stability of these modalities and their real impact on the biological systems of the animals.

As ruminant animals, sheep are prone to peri-anesthetic complications such as regurgitation, aspiration, ruminal stasis, and bloating. Diaphragmatic compression due to ruminal tympany can lead to reduced lung compliance and functional residual capacity, increasing the risk of hypoxia, hypercapnia, and decreased efficiency in gas exchange. To address these risks, mechanical ventilation can be an effective option, providing hemodynamic support, enhancing tissue oxygen perfusion, and mitigating metabolic alterations (Lin, 2017).

To further ensure stability and safety during anesthesia and ventilation, adequate monitoring is essential. In this respect, indirect calorimetry is a non-invasive method that provides data on a patient's metabolic state, such as oxygen consumption, carbon dioxide production, energy expenditure, and respiratory quotient. This information can be used to estimate cardiac output, which is invaluable for early detection of complications such as hypooxygenation and tissue hypoperfusion (Gehrcke & Oleskovicz, 2017).

Therefore, the aim of this study is to evaluate the best anesthetic maintenance protocol for sheep, comparing inhalation anesthesia with isoflurane to total intravenous anesthesia with continuous propofol infusion. Additionally, the study will assess the optimal ventilation modality whether spontaneous, pressure-cycled mechanical, volume-cycled mechanical, or pressure-cycled mechanical with positive end-expiratory pressure by examining metabolic, blood gas, hemodynamic, and cardiorespiratory changes.

Material and Methods

This study received approval from the Ethics Committee for the Use of Animals (CEUA) at the originating institution, under approval no. 1.18.15.

The experiment involved 12 crossbred ewes, aged 12 months, with an average weight of 32±5 kg. These animals, sourced from a private farm, were confirmed to be healthy through physical exams and laboratory tests (blood count and biochemical profile). They were housed in collective pens measuring 15 m², with four animals per pen, for a 60-day acclimatization period. During this time, they were fed a diet of commercial feed and corn silage twice a day, with water available *ad libitum.* Before the experiment, the sheep underwent a solid food fast for 24 h and a water fast for 12 h. On the following day, while the sheep were conscious and in the right lateral decubitus position, bilateral venous access was established using an 18G catheter in the cephalic vein, a 22G catheter in the marginal artery of the left ear, and a 22G Intracath central intravenous catheter in the left jugular vein. The animals received 0.3 mg kg^{-1} of intramuscular morphine, followed by 20 mcg kg^{-1} of intravenous detomidine via the cephalic vein catheter 5 min later. After 15 min, they were induced into general anesthesia with propofol at a dose of 4 mg kg^{-1} administered for 1 min. Endotracheal intubation was performed with a tube of diameter suitable to the tracheal diameter, and the sheep were maintained on a partial gas rebreathing system with oxygen flowing at 50 mL kg^{-1} min^{-1} and an FiO_2 of 0.4. The sheep were then randomly divided into two groups (n=6): the isoflurane group (IG), maintained with inhalation anesthesia at 1.3 V% isoflurane, monitored using a multiparametric monitor with a spirometry module (Monitor B650 - GE-Datex-Ohmeda); and the propofol group (PG), maintained with a continuous infusion of propofol at a rate of 0.5 mg kg^{-1} min^{-1}, using a peristaltic pump (Samtronic ST 6000). Both groups received fluid therapy at 10 mL kg^{-1} h^{-1} with a 0.9% NaCl solution in a drip.

All animals underwent tarsometatarsal arthrodesis in a parallel study. They received 0.5 mg kg^{-1} of 0.75% isobaric ropivacaine combined with 0.1 mg kg^{-1} of morphine via the subarachnoid route (L6-S1), using a 19G spinal needle (BD Brasil). The anesthetic solution was diluted with 0.9% NaCl to a final volume of 1 mL 7.5 kg^{-1} of body weight. Successful spinal needle placement was confirmed by observing cerebrospinal fluid (CSF) flow. The effectiveness of the blockade was assessed by monitoring heart rate (HR), respiratory rate (f), and mean arterial pressure (MAP) during surgery. Fentanyl (5 mcg kg^{-1}) was administered if there was a 20% increase in two of the three aforementioned parameters. Following anesthesia, the animals were positioned in the right lateral decubitus and prepared for surgery, maintaining spontaneous ventilation from instrumentation until the completion of spinal anesthesia.

After spinal anesthesia and stabilization of the anesthetic plane, the animals underwent spontaneous ventilation (SV) for 30 min. They were then randomly assigned to one of the following ventilation modalities: a) Volume-cycled mechanical ventilation (VV) with a tidal volume of 13 mL kg^{-1}; b) Pressure-cycled mechanical ventilation (PV) with a peak inspiratory pressure (Ppeak) of 15 cmH_2O; c) Pressure-cycled mechanical ventilation with positive end-expiratory pressure (PPV) with a Ppeak of 15 cmH_2O and a PEEP of 5 cmH_2O. For all modalities, f was adjusted to maintain normocapnia (between 35 and 45 mmHg), with an inspiration-expiration ratio (I:E) of 1:2. If bradycardia (HR < 50 bpm) or hypotension (SBP < 90 mmHg and MAP < 50 mmHg) occurred, atropine (0.044 mg kg^{-1}) and dobutamine (5 mcg kg^{-1} min^{-1}) were administered intravenously, respectively. Calorimetric parameters were measured by ensuring the proper positioning of the calorimetry sensor, maintaining a 45° angle.

The parameters measured with the multiparametric monitor included HR (bpm), f (mpm), MAP (mmHg), central venous pressure (CVP, cmHO), end-tidal carbon dioxide concentration ($EtCO_2$, mmHg), tidal volume (mL kg^{-1}), oxygen consumption (VO_2, mL min^{-1}), carbon dioxide production (VCO_2, mL min^{-1}), respiratory quotient (RQ), energy expenditure (EE, Kcal day^{-1}), lung compliance (mL cmH_2O^{-1}), and airway resistance (cmH_2O L s^{-1}). Additional determined parameters included cardiac index (CI, L min^{-1} m^{-2}), calculated as the ratio of cardiac output to body surface area (BSA = 10.1 x $kg^{0.67}$ 100^{-1}); systemic vascular resistance index (SVRI, dynes s m^{-2}), as SVRI = (MAP - CVP) × 79.92 ÷ CI; arterial oxygen content (CaO_2, mL dL^{-1}), as CaO_2 = (Hb x SO_2 x 1.39) + (0.003 x PO_2); venous oxygen content (CvO_2, mL dL^{-1}); oxygen delivery (DO_2), as DO_2 = CaO_2 × (CI × 10); oxygenation index (OI), as PaO_2 FiO_2^{-1}; and intrapulmonary shunt fraction (Qs/Qt, %), as Qs/Qt = ([$CcaO_2$ - CaO_2]/[$CcvO_2$ - CvO_2]) * 100, where $CcaO_2$ = (Hba x 1.31 x $ScaO_2$) x (0.0031 x PAO_2), $CcvO_2$ = (Hbv x 1.31 x $ScvO_2$) x (0.0031 x PAO_2), and PAO_2 = FiO_2 x (Patm - PH_2O) – ($PaCO_2$ RQ^{-1}).

Blood gas analysis was performed by collecting blood from the marginal artery of the ear and the jugular vein. Before collecting samples, 1 mL was discarded to ensure accurate readings, followed by the collection of 0.6 mL of arterial blood in a syringe with

lytic heparin and 0.6 mL of venous blood in a syringe with sodium heparin. These samples were analyzed immediately after collection using an Omni C analyzer (Roche Diagnostics, São Paulo, Brazil). The following parameters were measured: partial pressure of oxygen (PaO_2, in mm Hg), partial pressure of carbon dioxide ($PaCO_2$, in mm Hg), pH, bicarbonate (HCO^{3-}, in mEq L^{-1}), base deficit or excess (BD or BE, in mEq L^{-1}), oxyhemoglobin saturation (SaO_2, in %), and total hemoglobin (tHb, in g dL^{-1}). Simultaneously, additional arterial and venous samples were collected and sent to the institution's Clinical Pathology laboratory to measure hemoglobin (Hb, in g dL^{-1}) using an automatic counter (SDH-3 Vet, Labtest Diagnóstica, Lagoa Santa, Brazil).

Statistical analysis was conducted using GraphPad Prism software, version 6. Data were tested for normality using the Shapiro-Wilk test. To assess differences in mean values over time within the same group, a one-way repeated-measures analysis of variance (ANOVA-RM) was applied, comparing each time point with all others, followed by Tukey's test. To evaluate statistical differences between groups at the same time point, Student's t-test ($p \leq 0.05$) was used.

Results and Discussion

The groups were homogeneous, with no significant differences in weight, instrumentation time, or anesthesia time (Table 1). This discussion will focus on the effects of different ventilation modalities (SV, VV, PV, and PPV) on metabolic (oxygen consumption, carbon dioxide production, energy expenditure, and respiratory quotient), hemodynamic, blood gas, and respiratory variables. Mean arterial pressure (Table 2) was lower in SV ($p=0.0005$) and VV ($p=0.0331$) in the IG compared to the PG. Despite these lower values in the IG, the MAP never fell to a level considered hypotensive (SBP ≤ 90 mmHg and MAP ≤ 50 mmHg). Isoflurane depresses the cardiovascular system in a dose-dependent manner, reducing MAP values primarily by lowering afterload, resulting from significant peripheral vasodilation and a reduction in peripheral vascular resistance (Steffey & Howland, 1977).

Table 1
Mean values ± standard deviation of weight, instrumentation time, and anesthesia time in sheep undergoing anesthesia with isoflurane (IG) or propofol (PG)

			p
Weight (kg)	**PG**	**33.7±2.5**	**0.3503**
	IG	**30.9±6.6**	
Instrumentation time (min)	**PG**	**32±29**	**0.9121**
	IG	**33±15**	
Anesthesia time (min)	**PG**	**209±23**	**0.7003**
	IG	200±46	

Central venous pressure (Table 2) was higher in the PG from SV through the final ventilation modality (p=0.01337). In addition to depressing right ventricular contraction, isoflurane can reduce venous return by causing peripheral vasodilation (Grosenbaugh & Muir, 1998).

Cardiac index (Table 2) decreased at all times from SV in the PG and VV in the IG, with a notable difference between groups in PV (p=0.0015) and PPV (p=0.0119), with higher values in the IG. The decrease in CI after the initiation of ventilation modalities may be attributed to the reduction in intrathoracic negative pressure, minimizing its contribution to cardiac output (Tonkovic et al., 2014). Adding PEEP can further interfere with CI, as seen in this study, where the lowest CI values for the PG were in PPV. The observed difference in CI between groups can be explained by increased VO2 values in PV and PPV in the IG. The decrease in CI in the PG coincided with moments when VO2 remained higher in the IG. This study is among the first to measure CI using indirect calorimetry in sheep. There are no existing CI values for direct comparison, but the literature indicates that CI values measured by thermodilution tend to be lower. This overestimation of CI in indirect calorimetry compared to thermodilution, as noted in other studies, may be related to VO_2 and the arteriovenous oxygen content difference, which has an inverse relationship with cardiac output. Gehrcke et al. (2015) also observed an overestimation of CI as measured by indirect calorimetry, when compared to thermodilution, in dogs subjected to different hemodynamic states.

The systemic vascular resistance index was higher in SV (p=0.0186), PV (p=0.0014), and PPV (p=0.0482) in the PG, indicating significant differences between SV and PPV in the PG, and between SV and VV in the IG (Table 2). These differences align with the previously discussed CI values. Arterial oxygen content (p=0.0006) and CvO_2 (p=0.0033) were higher in the PG at all evaluated times. This increase in the PG may be related to higher Hb levels, as Hb, PaO_2, and SaO_2 are the primary factors for calculating oxygen content. The higher Hb

and PaO_2 in the PG (Table 2) may be due to the continuous infusion of propofol in a lipid emulsion, which can cause lipemia in blood samples, leading to an overestimation of Hb concentration due to increased turbidity in the photometric membrane (Kerr, 2003).

Variations in Hb values (Table 2) were observed using two different techniques: blood gas analyzer (p=0.0003) and semi-automatic counter (p=0.00027), showing a significant difference at all moments. Linear regression-based Pearson's correlation analysis between these two Hb measurement methods yielded a strong correlation of 0.83 (Callegari-Jacques, 2003). Given the reliance on indirect calorimetry for measuring cardiac output, Hb values are critical, and even minor variations can lead to the error being multiplied.

Respiratory rates (*f*, Table 3) decreased with the introduction of mechanical ventilation (MV), where *f* was adjusted to maintain normocapnia. General anesthetics tend to depress the respiratory system, allowing for lower respiratory rates under MV. The pressure-cycled ventilation modalities showed significant differences (p=0.0165), likely because acceptable $EtCO_2$ values (Table 3) were not consistently maintained in the IG for PV and PPV, causing a significant difference between the groups (p=0.017). In the PG, $EtCO_2$ levels showed significant differences in VV, PV, and PPV compared to SV, which is expected, given that SV often accumulates more CO_2 due to anesthetic-induced respiratory depression. With MV, it is possible to maintain lower CO_2 levels. When comparing the pressure (in mm Hg) in volume-cycled ventilation (Table 3), it was observed that these pressures were higher than those established in PV (15 cmH_2O), which might explain the failure to maintain normocapnia in the IG, with PV having higher levels compared to SV. Additionally, propofol is known to decrease diaphragmatic contractility more than isoflurane, possibly explaining why the PG was able to maintain normocapnia with pressure-cycled ventilation modalities and showed higher compliance and lower airway resistance during these times (Fujii et al., 1999).

Table 2
Mean values ± standard deviation of heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), cardiac index (CI), systemic vascular resistance index (SRI), arterial oxygen content (CaO_2), venous oxygen content (CvO_2), hemoglobin content by automatic counter (Hb Lab) and blood gas analyzer (Hb H), hydrogen potential (pH), arterial oxygen pressure (PaO_2), arterial carbon dioxide pressure ($PaCO_2$), arterial saturation of oxygen (SaO_2), bicarbonate (HCO^{3-}), and base excess (BE) in sheep under anesthesia with isoflurane (IG) or propofol (PG)

		SV	VV	PV	PPV	p-ANOVA
HR (bpm)	PG	103±13	86±15	90±23	77±16	0.0994
	IG	105±14	91±22	101±24	96±24	0.6922
MAP (mm/Hg)	PG	78a±6	75a±9	72±7	72±13	0.7226
	IG	63b±4	63b±7	66±14	68±6	0.7552
CVP (cm/H_2O)	PG	10.8a±5	9.1a±3.3	9.3a±4	9a±3	0.8426
	IG	4.7b±0.8	5.1b±1.2	4.5b±0.5	4.3b±0.5	0.3365
CI ($L/min/m^2$)	PG	13.8A±4.7	7.6B±2.2	7.5Ba±2.2	6.5Ba±2.3	0.0019
	IG	18.1A±3.4	9.2B±2.2	16.5Ab±4.6	12.3b±3.8	0.0020
SVRI ($dynes/s/m^2$)	PG	409Aa±108	745±262	715a±189	893Ba±448	0.0486
	IG	267Ab±62	543B±197	321b±114	453b±170	0.0151
CaO_2 (mL/dL)	PG	11.6a±0.9	11.7a±1	11.5a±1.2	11.4a±1.4	0.9703
	IG	8.7b±0.8	8.5b±1	8.4b±0.9	8.6b±0.7	0.9189
CvO_2 (mL/dL)	PG	9.6a±0.9	9a±0.7	8.9a±1	8.5Aa±1.2	0.3330
	IG	7.2b±0.7	6.3b±0.7	6.9b±0.7	6.8b±0.7	0.1960
Hb Lab (g/dL)	PG	8.8a±0.6	8.9a±0.8	8.8a±1	8.6a±1.1	0.9823
	IG	6.5b±0.5	6.1b±0.7	6b±0.6	6.3b±0.6	0.6601
Hb H (g/dL)	PG	9.8a±0.9	10a±0.9	10.2a±1.2	10.4a±1.3	0.8118
	IG	7.5b±0.4	7.3b±0.8	7.3b±0.7	7.4b±0.6	0.9525
pH (mpm)	PG	7.4A±0.03	7.51B±0.02	7.47Ba±0.02	7.49B± 0.04	<0.0001
	IG	7.38A±0.035	7.49B±0.05	7.4Cb±0.05	7.43A±0.06	0.0041
HCO^{3-} (mEq/L)	PG	33.87±1.6	32.92±2.06	34.05±2.71	33.45±2.5	0.8251
	IG	32±1.8	33±2	34±1.8	34.5±2.2	0.2890
BE (mmol/L)	PG	7.8±1.85	9±2.2	9.3±2.26	9.2±2.5	0.6188
	IG	6.5±1.87	8.8±2.4	9.3±2.3	9.2±2.8	0.1652
PaO_2 (mm/Hg)	PG	162a±32.6	178.1±23.2	178.1a±23.2	188.4a± 10.9	0.3072
	IG	125b±21.8	158±23.15	148.2b±23.02	155.9b±27.38	0.0996
$PaCO_2$ (mm/Hg)	PG	56.17A±2.69	41.75BC±0.59	47.82BCa±4.9	44.63Ba±4.5	<0.0001
	IG	56.73B±4.39	44.27A±4.8	57.23Bb±5.83	53.57Bb±6	0.0013
SO_2 (%)	PG	94a±0.13	93a±0.18	93a±0.15	93a±0.2	0.8317
	IG	96b±0.16	97b±0.07	97b±0.1	97b±0.1	0.1818

Different uppercase letters in the same row indicate differences between times (ANOVA-RM followed by Tukey's test at p≤0.05). Different lowercase letters in the same column indicate differences between groups. Student's t test (p≤0.05). SV – Spontaneous ventilation; PV – Pressure-cycled ventilation; VV – Volume-cycled ventilation; PPV – Pressure-cycled ventilation with PEEP.

Table 3
Mean values ± standard deviation of respiratory rate (*f*), end-tidal carbon dioxide concentration ($EtCO_2$), compliance, airway resistance, tidal volume, pressure reached by the ventilator in volume-cycled mechanical ventilation, respiratory quotient (RQ), intrapulmonary shunt formation (Qs/Qt), oxygen delivery (DO_2), energy expenditure (EE), oxygen consumption (VO_2), carbon dioxide production (VCO_2), and oxygenation index (OI) in sheep undergoing anesthesia with isoflurane (GI) or propofol (GP)

		SV	VV	PV	PPV	p-ANOVA
f	PG	26A±6	10B±2	14Ba±5	11Ba±5	<0.0001
(mpm)	IG	33A±8	15B±5	24b±6	21b±8	0.0038
$EtCO_2$	PG	52A±4	36BC±2	43BCa±2	38Ba±4	<0.0001
(mm/Hg)	IG	53±6	41±6	54b±8	51b±11	0.0457
Compliance	PG		31.5a±4.7	31.8a±4.4	33.3a±6.7	0.8225
(mL/cmH_2O)	IG		24b±2.4	23.7b±3.2	23.2b±3	0.8830
Resistance	PG		9a±1	8.7a±0.8	9a±1.2	0.8271
(cm/L/s)	IG		12.8b±3.1	12.8b±3.8	14.5b±4.6	0.7032
Tidal volume	PG	188AD±26	433BD±28	307BCa±30	436BDa±78	<0.0001
(ml/kg)	IG	189B±27	391A±76	215Bb±52	268Bb±84	0.0001
Pressure in VV	PG		20.5±1.2			
(mm/Hg)	IG		24.3±5.4			
RQ	PG	0.66A±0.05	0.75B±0.03	0.73B±0.03	0.72B±0.03	0.0027
	IG	0.63A±0.01	0.74B±0.05	0.7B±0.03	0.7B±0.03	<0.0001
Qs/Qt	PG	27.44±10	23.33±9	27.42a±7.7	20.78±6.5	
(%)	IG	33.2±10.2	16.23±9.4	15Ab±6.97	19.57±17.45	
DO_2	PG	1549A±409	868B±241	826Ba±183	704B±196	0.0001
($mL/min/m^2$)	IG	1548A±357	748BC±116	1337Db±299	1038B±338	0.0008
EE	PG	1768Aa±84	1465B±155	1472B±158	1365B±139	0.0004
(Kcal/day)	IG	1529b±242	1432±309	1471±318	1427±383	0.9399
VO_2	PG	260A±23	190B±18	185B±23	176B±41	0.0001
(mL/min)	IG	258±51	190±25	235±70	223±48	0.1673
VCO_2	PG	155±26	140±11	137±18	128±32	0.2714
(mL/min)	IG	153±22	147±19	160±34	157±36	0.8788
OI	PG	404a±81	445±58	445a±58	471a±27	0.3072
(mm/Hg)	IG	312b±54	394±58	371b±58	390b±68	0.0996

Different uppercase letters in the same row indicate differences between times (ANOVA-RM followed by Tukey's test at p≤0.05). Different lowercase letters in the same column indicate differences between groups. Student's t test (p≤0.05). SV – Spontaneous ventilation; PV – Pressure-cycled ventilation; VV – Volume-cycled ventilation; PPV – Pressure-cycled ventilation with PEEP.

In the PG, compliance values were higher compared to the IG (p=0.0057). Conversely, airway resistance was higher in the IG than in the PG (p=0.0212) (Table 3). Additionally, tidal volume (Table 3) remained higher in the PG, with a significant difference observed between groups in PV (p=0.0037) and PPV (p=0.0049). Among the ventilation modalities, PV exhibited the lowest compliance values in both groups. Fujii et al. (1999) reported a dose-dependent decrease in diaphragmatic contractility with propofol, which explains the greater compliance and tidal volume in the PG across all ventilation modalities, with a more pronounced increase in PPV. This might also clarify why normocapnia was not achieved in pressure-cycled modalities in the IG, as these modalities resulted in increased airway resistance and reduced lung compliance, limiting the ability to maintain adequate tidal volumes and achieve normocapnia.

The intrapulmonary shunt fraction (Qs/Qt) (Table 3) was higher in the PG during PV (p=0.0149). Although there were no significant differences at other times, the PG generally exhibited higher shunt fraction values throughout the MV. Halogenated anesthetics like isoflurane can inhibit hypoxic vasoconstriction, an important physiological mechanism that minimizes shunt formation by redirecting blood flow from non-ventilated lung areas to ventilated alveoli. In contrast, intravenous anesthetics do not interfere with this mechanism (Abe et al., 1998). While isoflurane can maintain high levels of Qs/Qt, this was not observed in the present study. Among the various factors contributing to the shunt calculation, we believe that the Hb values accounted for the high percentage observed in the PG. Additionally, along with Hb values, PaO_2 also remained higher in the PG, which are two significant factors for calculating the shunt.

The respiratory quotient (RQ, Table 3) serves as a tool to monitor patient energy, indicating which substrate is being used. It can range from 0.67 to 1.3 (O'Toole et al., 2004), with values close to 0.71 indicating lipid use, 0.82 for proteins, 0.85 for the oxidation of a mixed diet, and up to 1 for glucose oxidation. An increase in RQ was noted with the introduction of ventilation modalities, but without changes in the primary substrate lipids indicating minimal metabolic effort by the patients (Diener, 1997).

Oxygen delivery (Table 3) decreased by an average of 48% in the PG and 33% in the IG after the institution of MV, with a significant difference in PV (p=0.0051), where the drop was 38% in the PG. The reduction in oxygen delivery was due to a decline in CI following the institution of MV 48% in the PG and 30% in the IG. In the case of PV, the difference in CI between the groups was more pronounced, with a 54% drop in CI in the PG. Regarding EE (Table 3), there was a significant difference in SV between the groups (p=0.0451), with higher values in the PG, which decreased after the introduction of MV. This decrease might be attributed to the progressively longer anesthesia durations, leading to reduced metabolism with extended anesthesia (Nikolaidis et al., 2002; O'Toole et al., 2004). Although not statistically significant, a slight reduction in VV, PV, and PPV was observed in the IG. This reduction might not have been more intense due to increased oxygen consumption in PV and PPV, combined with greater airway

resistance. According to Diener (1997), respiratory discomfort can increase patient energy expenditure. As the monitor provided only average values every 2 h, with SV not yet reached, the difference between groups at this time might not be fully significant.

Oxygen consumption (Table 3) decreased in both groups after MV was initiated. This decrease persisted in the PG, with lower values in PV and PPV, but returned to baseline in the IG after the introduction of pressure-cycled ventilation. Spontaneous breathing requires energy, unlike controlled ventilation, which is mechanical. This fact explains the decrease in VO_2 after the institution of MV in the PG and VV in the IG. Gehrcke et al. (2015) noted a 25% reduction in VO_2 in dogs anesthetized with isoflurane after MV was initiated. The normalization in the IG with pressure-cycled modalities was likely related to respiratory function, as these moments had increased airway resistance and decreased lung compliance, along with a need for a higher f to maintain normocapnia.

Carbon dioxide production (mL min^{-1}) (Table 3) did not differ significantly between groups or moments, but saw a slight decrease in both groups after VV introduction. This continued in the PG and increased in the IG. Thus, these fluctuations in VCO_2 values can be attributed to respiratory function. The oxygenation index (Table 3) was higher in the PG in SV (p=0.0438), PV (p=0.0489), and PPV (p=0.0222), linked to higher PaO_2 values (Table 2) in the PG. Despite these differences and lower oxygenation in the IG, oxygenation remained above 300 at all times from SV onwards, a threshold to avoid compromised oxygenation, as indicated by human studies (Carvalho et al., 2007).

Regarding blood gas variables (Table 2), following the reference values for sheep (Sobiech et al., 2005), metabolic alkalosis was observed in both groups after the institution of MV, characterized by increased pH, bicarbonate accumulation, and elevated BE. This occurred despite normal $PaCO_2$ values in the PG. Mechanical ventilation likely caused metabolic alkalosis by eliminating accumulated CO_2, leading to plasma alkalinization. After pressure-cycled ventilation modalities were introduced, pH normalized in the IG but stayed high in the PG. In the IG, despite the reduced pH, bicarbonate and BE values stayed elevated, with $PaCO_2$ and $EtCO_2$ remaining elevated when pressure-cycled.

Partial oxygen pressure (Table 2) was higher in the PG in SV (p=0.0438), PV (p=0.0489), and PPV (p=0.0222). Moreover, lung compliance was greater and airway resistance was lower at all times in the PG, suggesting more efficient gas exchange. Minimum acceptable PaO_2 values were not maintained in the IG, which should be four times the FiO_2, according to human data (Rinaldo, 1992). Isoflurane can inhibit hypoxic vasoconstriction and reduce oxygenation despite smaller shunt fractions in the IG. Propofol is associated with better tissue oxygenation compared to volatile anesthetics (Abe et al., 1998).

Partial carbon dioxide pressure (Table 2) showed significant differences in the PG, with high values in SV and lower values in VV. In the IG, VV differed from other modalities with lower values, demonstrating a difference between groups in PV (p=0.0128) and PPV (p=0.0154). The high values in SV were expected, as anesthetic drugs tend

to cause respiratory depression, leading to carbon dioxide accumulation. After MV was instituted, levels remained within acceptable ranges (between 35 and 45 mmHg) in VV for both groups. However, in PV and PPV, the IG exceeded these limits at the same times that $EtCO_2$ remained high. As mentioned earlier, the pressure (mm Hg) generated in the ventilator when programmed for volume cycling was higher than in pressure-cycled ventilation (15 cm H_2O), which might be a factor contributing to normocapnia not being maintained in the IG. It suggests that higher pressure is needed to ventilate sheep anesthetized with isoflurane. Additionally, the inhibition of hypoxic vasoconstriction by isoflurane may have impaired gas exchange, keeping values above acceptable levels.

Oxyhemoglobin saturation (Table 2) showed significant differences from SV to PPV, with higher values in the PG (p=0.0242). However, all readings stayed within the minimum reference range for the species (92.81%) in both groups, indicating acceptable results when linked with the oxygenation index. Propofol can redistribute erythrocytes to non-splenic sites when administered as a prolonged continuous infusion, which might have reduced SaO_2 levels (Eroglu, 2014). No significant differences were observed in the levels of potassium (K), sodium (Na), ionized calcium (iCa), and chlorine (Cl) between times and groups. Similarly, the times for extubation (4.2 ± 3 min in the PG and 3 ± 2 min in the IG), sternal decubitus (19.3 ± 6.4 min in the PG and 18.8 ± 8 min in the IG), ambulation (40 ± 12.6 min in the PG and 32 ± 16 min in the IG), and total recovery (74.2 ± 23.3 min in the PG and 52 ± 24 min in the IG) did not show significant differences between groups.

Conclusions

Continuous infusion of propofol at a dose of 0.5 mg kg^{-1} min^{-1} for anesthetic maintenance provided better tissue oxygenation and ventilatory quality. Pressure-cycled ventilation (15 cm H_2O) with PEEP (5 cm H_2O) resulted in higher lung compliance, oxygenation index, and partial oxygen pressure, with lower intrapulmonary shunt, when paired with anesthetic maintenance using continuous propofol infusion. However, pressure-cycled ventilation (15 cm H_2O) was insufficient to maintain normocapnia in sheep anesthetized with isoflurane.

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