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Effects of inspired oxygen fractions in rabbits anesthetized with isoflurane or sevoflurane, maintained on spontaneous ventilation

[*Efeitos de frações inspiradas de oxigênio em coelhos anestesiados com isoflurano ou sevofluorano, mantidos em ventilação espontânea*]

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ABSTRACT

It is important to identify the best inspired fraction of oxygen in a variety of situations, including sevoflurane or isoflurane anesthesia, in spontaneously breathing rabbits. For this, 64 rabbits were assigned to eight groups: GI100 (FiO_2= 1,0 + isoflurane), GS100 (FiO_2= 1,0 + sevoflurane), GI80 (FiO_2= 0,8 + isoflurane), GS80 (FiO_2= 0,8 + sevoflurane), GI60 (FiO_2= 0,6 + isoflurane), GS60 (FiO_2= 0,6 + sevoflurane), GI21 (FiO_2= 0,21 + isoflurane), GS21 (FiO_2= 0,21 + sevoflurane). The induction was performed with (2.5MAC) of the anesthetic. The vaporizer was setted at 1.5 MAC and FiO_2 as attributed for each group. After the induction, the concentration was changed to 1 MAC. Measurements of parameters were performed 30 minutes after induction (T0), and then at 15 minute intervals (from T15 to T60). The arterial partial pressures of oxygen (PaO_2), alveolar oxygen partial pressure (P_AO_2) and alveolar-arterial oxygen gradient [$P(A\text{-}a)O_2$] were higher with the use of high FiO_2. The GI80 showed higher levels of PaO_2 FiO_2 ratio and respiratory index (RI). In conclusion, the FiO_2 of 0.21 is not indicated, because it causes hypoxemia. The isoflurane determines better ventilation when compared to sevoflurane, but isoflurane associated with 80% of oxygen promotes intrapulmonary shunt increase.

Keywords: rabbit, inhalatory anesthesia, ventilation

RESUMO

Tornou-se importante identificar a melhor fração inspirada de oxigênio em variadas situações, incluindo anestesia pelo sevoflurano ou isoflurano, em coelhos respirando espontaneamente. Para isso, 64 coelhos foram distribuídos em oito grupos: GI100 (FiO_2= 1,0 + isoflurano), GS100 (FiO_2 = 1,0 + sevoflurano), GI80 (FiO_2= 0,8 + isoflurano), GS80 (FiO_2= 0,8 + sevoflurano), GI60 (FiO_2= 0,6 + isoflurano), GS60 (FiO_2= 0,6 + sevoflurano), GI21 (FiO_2= 0,21 + isoflurano) e GS21 (FiO_2= 0,21 + sevoflurano). A indução foi com 2,5 CAM do anestésico. Ajustou-se o vaporizador para 1,5 CAM, e a FiO_2 foi atribuída a cada grupo. Em seguida, a CAM foi reajustada para 1,0. Iniciaram-se as mensurações 30 minutos após a indução (M0), seguidas em intervalos de 15 minutos (de M15 a M60). As pressões parciais de oxigênio (PaO_2), a pressão parcial alveolar de oxigênio (P_AO_2) e a diferença alvéolo-arterial de oxigênio [$P(A\text{-}a)O_2$] foram maiores com o emprego de altas FiO_2. O GI80 apresentou maiores valores na relação entre PaO_2 e FiO_2 e índice respiratório (IR). Conclui-se que a FiO_2 0,21 não é indicada, pois provoca hipoxemia. No entanto, utilizada com isoflurano, determina melhor ventilação quando comparado ao sevoflurano, porém seu uso, associado a 80% de oxigênio, promove maior formação de shunt *intrapulmonar.*

Palavras-chave: coelhos, anestesia inalatória, oxigenação

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INTRODUCTION

The primary function of the cardiovascular and respiratory systems is to meet the metabolic needs of tissues in the body through adequate supply of oxygen (O_2) (Romaldini, 1995). Therefore, the maintenance of oxygenation at adequate levels during anesthetic procedures is extremely important. It has been proven that O_2 administered at high concentrations or for an extended period of time can induce pulmonary lesions with formation of atelectatic areas (Hartsfield, 1996). However, in Veterinary Medicine, 100% oxygen is still routinely used during anesthetic procedures.

The choice of adequate FiO_2 seems to be of great relevance, since the closer to 1.0, the greater the risk of occurrence and serious lesions (Capellier *et al*., 1999). Hartsfield (1996) stated that, in humans, 100% oxygen should not be administered for more than 12 hours, but in dogs, it should not be offered for more than 24 hours. In contrast, Nelson and Couto (1998) stated that dogs should not be submitted for more than 12 hours to O_2 above 50%.

The absence of information regarding the effects of FiO_2 lower than those used in the hospital routine on cardiovascular, respiratory and electrolyte balance, in patients during inhalational anesthesia, provides inquiries about the appropriate oxygen concentration to be used in association with isofluorane or sevoflurane, most used halogenated and considered safe for polytrauma patients or with cardiovascular and respiratory problems.

With the research, we aimed to determine among the inspired oxygen fractions of 1.0; 0.8; 0.6 or 0.21, which one was most appropriate in rabbits anesthetized with isofluorane or sevoflurane and maintained under spontaneous respiration. Complementarily, to evaluate the effects of inspired fractions on respiratory variables and comparatively evaluate the effects of sevoflurane and isofluorane on these variables.

MATERIAL AND METHODS

Sixty-four New Zealand White rabbits (Approved by the Committee on Ethics and Animal Welfare of the FCAV / UNESP, under protocol No. 023814/11), adult males (n= 32) or females (n= 32) were used, with weight between 3.5 and 4.5kg, coming from specialized producer. The animals were randomly assigned to eight groups with eight rabbits each, differentiated by FiO_2 and the inhaled anesthetic. GI100, GI80, GI60 and GI21 animals were given 100%, 80%, 60% and 21% oxygen concentrations (O_2), respectively and the anesthesia was maintained with isoflurane. For GS100, GS80, GS60 and GS21 animals, the same methodology was applied, replacing isofluorane by sevoflurane.

For humane and technical reasons, the rabbits have not been subjected to food and water fasting, as this procedure is unnecessary since vomiting is rare in this species (Flecknell and Thomas, 2007). Induction of the anesthesia was performed by means of a sealed naso-oral mask with isoflurane (Isoforine - Cristália, Campinas, SP, Brazil) or sevofluorane (Sevocris - Cristália, Campinas, SP, Brazil) at 2.5 CAM diluted in total flow of 1l/min of oxygen to 100%, provided by anesthetic circuit without gas rebreathing (Mapleson D - Baraka balloon 1/2L - Protec-Cotia / SP), by means of calibrated vaporizer (OHMEDA - ISOTEC mod 5 - Datex Ohmeda-Miami, USA) for the anesthetic agent. The expired anesthetic concentration reading was obtained in a multiparameter monitor (DIXTAL - mod. DX - 2010 LCD - Manaus, AM, Brazil), whose gas analyzer sensor was adapted to the mask during induction. After the laryngotracheal reflex, the animals were intubated with 3.0mm diameter Magill catheter, which was connected to the inhalation anesthesia device. At this time, the gas analyzer sensor was coupled to the proximal end of the orotracheal tube and connected to the anesthetic circuit, the vaporizer being readjusted to 1.5 CAM of isofluorane or sevoflurane.

Afterwards, the animals were placed in the right lateral decubitus position and the right auricular artery was catheterized (Catheter BD Angiocath 22 - Becton, Dickinson Indústria Cirúrgica Ltda - Juiz de Fora / MG - Brazil) with the aim of collecting arterial blood samples for hemogasometry. An incision was made in the skin of the cervical region over the left jugular vein, for its exposure. With the support of a hypodermic needle (40x1,20-Descarpack-São Paulo / SP- Brazil needle), a catheter (PVC urethral catheter No. 04 - Embramed

Ind.Com.Ltda - São Paulo / SP-Brasil) was placed in the cranial vena cava, in order to obtain a venous blood sample for hemogasometry.

After completion of these procedures, the anesthetic concentration was readjusted to 1.0 CAM in all groups. The parameters were measured thirty minutes after intubation (T0). The remaining data were collected at 15 minute intervals for a period of 60 minutes (T15, T30, T45 and T60, respectively). The hemogasometric variables were obtained using specific equipment (Hemochrometer - Roche OmiC-Rochi Diagnostics GmbH-Mannheim, Germany), with a volume of 0.3ml for each sample, using 1ml heparinized syringe.

The arterial oxygen partial pressure (PaO_2) in mmHg, arterial carbon dioxide partial pressure ($PaCO_2$), in mmHg, and oxyhemoglobin saturation in arterial blood (SaO_2), in %, were measured. In the venous blood samples were evaluated: the partial pressure of oxygen in the venous blood (PvO_2), in mmHg, partial pressure of carbon dioxide in the venous blood ($PvCO_2$) in mmHg and oxyhemoglobin saturation in the venous blood (SvO_2), in %. The respiratory dynamics was obtained by means of the calculated variables: Alveolar oxygen partial pressure (P_AO_2) ($P_AO_2 = [F_IO_2 \times (Pb - 47)] - (PaCO_2 / RQ)$, where: Pb= ambient barometric pressure and RQ: Respiratory coefficient 0.8); Alveolar-arterial oxygen difference [$P(A\text{-}a)O_2$], this variable was obtained by subtracting PaO_2 from P_AO_2; Respiratory index IR), IR= $P(A\text{-}a)O_2 / PaO_2$; Relation between PaO2 and P_AO_2, (PaO_2 and $PAO_2 = PaO_2 / P_AO_2$); The relationship between PaO_2 and FiO_2 (PaO_2 and $FiO2= PaO_2 / FiO_2$) (Haskins, 2007); Differences PaO_2 and P_AO_2 , (PaO_2 e $P_AO_2= PaO_2/P_AO_2$) (O'flaherty *et al*., 1994); Arterial oxygen content (CaO_2), ($CaO_2= [1{,}34 \times Hb \times (SaO_2/100)] + (PaO_2 \times 0{,}0031)$), where: Hb is the hemoglobin concentration in arterial blood; 1.34 is the oxygen binding coefficient with hemoglobin in mL/g and 0.0031 is the coefficient of solubility of plasma oxygen in mmHg/mL.

At the end of the experiment, each rabbit, before recovering its consciousness, was given antibiotic 30000UI/kg (Multibiótico Reforçado 30000UI/kg - Vitafarma, São Sebastião do Paraíso/MG, Brasil) and tramadol hydrochloride 4mg/kg (Tramadol 50mg/mL - Tramadol hydrochloride 300mg/kg - Vitafarma, São Sebastião do Paraíso, Cristália - Campinas / SP, Brazil), by the intramuscular route.

The data were submitted to statistical analysis by the computer program GraphPad Prism 5 for Windows. Two-way ANOVA was used to detect differences in the means among the groups, followed by the Bonferroni test. For comparison of the time points in each group, one-way ANOVA was used for repeated measurements, followed by the Bonferroni test. Differences were considered significant when $P< 0.05$.

RESULTS AND DISCUSSION

Evaluating the arterial oxygen partial pressure, it was observed that the mean of this parameter increased as larger FiO_2 were used, (Table 1). For the species studied, the values considered normal for PaO_2 are between 100 and 137mmHg with O_2 at 40%; From 140 to 169mmHg with $FiO_2= 0.6$ and between 228 and 304mmHg with $FiO_2= 1.0$ (Egi *et al*., 2007), coinciding with the averages recorded in this research. Additionally, the predicted PaO_2 was approximately two to three times the percentage of inspired oxygen corroborating Lopes *et al*. (2011).

In this study, at different times, there were differences between groups submitted to the same concentration of O_2, in the G100 and G80, and the animals anesthetized with sevoflurane had averages higher than those anesthetized with isoflurane. It is known that, in rats, the response to hypoxia is higher with isofluorane than with sevoflurane, the latter having lower depressant potency (Karanovic *et al.*, 2010). Therefore, it is believed that in the animals submitted to FiO_2 of 1.0 or 0.8, the lower depressant effect of sevoflurane may have contributed to the higher PaO_2, since the hypoxemia, characterized by $PaO_2< 60$mmHg and $SaO_2< 90\%$, (Cortopassi, 2002) was not observed in the groups that received these concentrations of O_2.

However, in GI21 and GS21, hypoxemia was observed, according to the means of PaO_2 and PaO_2 (Table 1), and no differences were recorded between them. Such an event may be justified by the greater response to hypoxia with the use of isoflurane as described by Karanovic *et al*. (2010).

Table 1. Mean values and standard deviations ($\overline{x} \pm s$) of PaO_2 (mmHg), PvO_2 (mmHg), $PaCO_2$ (mmHg), $PvCO_2$ (mmHg), SaO_2 (%), SvO_2 (%),$P(A\text{-}a)O_2$ (mmHg), IR, PaO_2/P_AO_2 (mmHg), PaO_2/FiO_2 (mmHg), CaO_2 (mL/dL) in rabbits anesthetized with isoflurane (GI) or sevofluorane (GS) (1 CAM), maintained on spontaneous ventilation and submitted to fraction Inspired oxygen ratio of 1.0, 0.8, 0.6 and 0.21

Parameters	Groups	Time Points				
		T0	T15	T30	T45	T60
PaO_2	GI100	254 ± 59^{A}	303 ± 87^{AE}	297 ± 53^{A}	283 ± 82^{A}	331 ± 77^{A}
	GS100	340 ± 41^{Db}	349 ± 30^{Ab}	355 ± 35^{A}	376 ± 29^{Da}	358 ± 14^{A}
	GI80	154 ± 61^{Bb}	187 ± 73^{B}	212 ± 63^{BDa}	217 ± 36^{BEa}	229 ± 44^{Ea}
	GS80	242 ± 59^{AE}	267 ± 65^{E}	233 ± 63^{B}	247 ± 58^{E}	247 ± 59^{E}
	GI60	168 ± 27^{B}	178 ± 28^{B}	181 ± 50^{BD}	172 ± 47^{B}	169 ± 55^{B}
	GS60	185 ± 24^{BE}	167 ± 50^{B}	162 ± 53^{D}	157 ± 54^{B}	164 ± 60^{B}
	GI21	67 ± 15^{C}	68 ± 21^{C}	64 ± 20^{C}	66 ± 14^{C}	64 ± 24^{C}
	GS21	62 ± 12^{C}	57 ± 13^{C}	56 ± 10^{C}	58 ± 9^{C}	56 ± 8^{C}
PvO_2	GI100	74 ± 14^{A}	68 ± 7^{AE}	70 ± 8^{A}	67 ± 8^{AB}	68 ± 9^{A}
	GS100	75 ± 20^{A}	74 ± 16^{A}	68 ± 15^{A}	67 ± 12^{A}	67 ± 16^{A}
	GI80	55 ± 12^{BC}	59 ± 9^{BDE}	52 ± 9^{BC}	55 ± 10^{B}	56 ± 11^{A}
	GS80	69 ± 12^{AB}	68 ± 12^{AE}	68 ± 11^{A}	68 ± 13^{AB}	67 ± 11^{A}
	GI60	59 ± 9^{B}	57 ± 10^{E}	56 ± 7^{AB}	55 ± 6^{ABD}	55 ± 5^{A}
	GS60	59 ± 4^{B}	57 ± 5^{E}	57 ± 4^{AB}	56 ± 4^{ABD}	55 ± 3^{A}
	GI21	45 ± 7^{C}	44 ± 9^{CDE}	43 ± 11^{C}	44 ± 6^{CD}	39 ± 9^{C}
	GS21	45 ± 8^{Ca}	39 ± 11^{Cb}	41 ± 11^{C}	39 ± 9^{Cb}	39 ± 9^{Cb}
$PaCO_2$	GI100	49±6	51±7	48±8	47±7	46 ± 7^{B}
	GS100	43±8	45±11	44±8	47±11	44 ± 12^{B}
	GI80	42±11	53±11	48±9	44±7	44 ± 9^{B}
	GS80	45 ± 14^{a}	54±12	54 ± 21^{A}	57 ± 17^{A}	61 ± 21^{Ab}
	GI60	43±6	42±9	38 ± 9^{B}	41 ± 9^{B}	39 ± 8^{B}
	GS60	44±10	43±9	44±10	44±10	44 ± 11^{B}
	GI21	46±6	47±9	45±7	45±7	47 ± 11^{B}
	GS21	36±7	40±6	42±6	40 ± 9^{B}	42 ± 8^{B}
$PvCO_2$	GI100	56±12	59±11	49±18	54±10	54 ± 13^{B}
	GS100	52±8	53±8	51±10	53±12	53 ± 14^{B}
	GI80	55±5	55±10	54±9	54±6	53 ± 6^{B}
	GS80	60 ± 16^{A}	61±12	64 ± 20^{A}	64 ± 19^{A}	70 ± 27^{A}
	GI60	50 ± 6^{a}	49±6	44 ± 10^{Bb}	48 ± 8^{B}	47 ± 8^{B}
	GS60	52±9	49±8	48 ± 11^{B}	47 ± 11^{B}	53 ± 16^{B}
	GI21	50±8	50±12	52±9	51±10	55±13
	GS21	42 ± 7^{Ba}	51 ± 7^{b}	50 ± 6^{b}	52 ± 8^{b}	51 ± 11^{Bb}
SaO_2	GI100	99.2 ± 0.5^{B}	99.6 ± 0.5^{B}	99.4 ± 0.7^{B}	99.3 ± 0.8^{B}	99.5 ± 0.6^{B}
	GS100	99.9 ± 0.0^{B}	99.9 ± 0.0^{B}	99.9 ± 0.0^{B}	99.9 ± 0.0^{B}	99.9 ± 0.0^{B}
	GI80	96.9 ± 4.0^{B}	98.2 ± 2.2^{B}	99.2 ± 0.9^{B}	99.6 ± 0.1^{B}	99.7 ± 0.1^{B}
	GS80	99.6 ± 0.3^{B}	99.6 ± 0.3^{B}	99.6 ± 0.1^{B}	99.7 ± 0.1^{B}	99.5 ± 0.4^{B}
	GI60	98.9 ± 0.6^{B}	98.9 ± 0.5^{B}	98.3 ± 1.5^{B}	98.3 ± 1.4^{B}	97.8 ± 1.6^{B}
	GS60	99.5 ± 0.2^{B}	99.5 ± 1.2^{B}	99.2 ± 1.0^{B}	98.7 ± 2.1^{B}	98.9 ± 1.4^{B}
	GI21	88.4 ± 6.0^{A}	87.2 ± 10.0^{A}	85.7 ± 9.8^{A}	88.3 ± 6.1^{A}	83.1 ± 12.0^{A}
	GS21	91.8 ± 0.5^{Aa}	92.7 ± 0.3^{Cb}	90.7 ± 0.4^{Ccd}	90.9 ± 0.5^{Ac}	89.9 ± 0.6^{Cde}
SvO_2	GI100	84.8 ± 6.7^{BC}	83.2 ± 3.8^{BCD}	86.4 ± 7.7^{BC}	86.1 ± 7.3^{BC}	88.9 ± 5.9^{B}
	GS100	93.0 ± 3.4^{Ba}	92.9 ± 2.7^{C}	92.0 ± 2.7^{B}	91.3 ± 2.4^{B}	90.2 ± 3.8^{Bb}
	GI80	84.7 ± 11.9^{BC}	82.4 ± 10.3^{BD}	81.9 ± 12.0^{BC}	84.2 ± 9.6^{BC}	84.7 ± 10.2^{B}
	GS80	90.0 ± 2.3^{BDa}	88.6 ± 3.9^{BC}	87.8 ± 5.7^{BC}	88.2 ± 4.8^{BC}	87.0 ± 4.7^{Bb}
	GI60	78.3 ± 5.8^{AC}	78.2 ± 7.5^{AD}	79.3 ± 7.1^{C}	80.8 ± 6.8^{AC}	83.2 ± 4.2^{B}
	GS60	86.3 ± 3.6^{BC}	85.7 ± 3.8^{BCD}	83.2 ± 8.0^{BC}	83.0 ± 6.6^{BC}	83.9 ± 6.0^{B}
	GI21	73.0 ± 7.8^{A}	70.9 ± 16.9^{A}	68.4 ± 18.2^{A}	72.3 ± 8.2^{A}	62.3 ± 18.5^{A}
	GS21	82.1 ± 2.4^{ACD}	81.5 ± 1.8^{BD}	82.5 ± 2.8^{BC}	81.4 ± 2.3^{AB}	81.5 ± 2.6^{B}
$P(A\text{-}a)O_2$	GI100	352 ± 61^{A}	301 ± 88^{A}	312 ± 49^{A}	328 ± 84^{A}	284 ± 79^{A}
	GS100	277 ± 37^{Ba}	265 ± 28^{ABa}	261 ± 31^{AB}	236 ± 31^{BCb}	258 ± 21^{AB}
	GI80	334 ± 59^{Aa}	287 ± 69^{A}	269 ± 62^{ABb}	269 ± 38^{ABb}	256 ± 45^{ABb}
	GS80	245 ± 53^{B}	208 ± 53^{BC}	242 ± 65^{BD}	225 ± 49^{BD}	220 ± 39^{BD}
	GI60	177 ± 28^{C}	170 ± 28^{C}	173 ± 45^{C}	179 ± 39^{C}	185 ± 55^{C}

Parameters	Groups	Time Points				
		T0	T15	T30	T45	T60
IR	GS60	165±25^{C}	184±49^{C}	189±47^{CD}	194±56^{CD}	187±52^{CD}
	GI21	14±18^{D}	11±24^{D}	17±25^{E}	16±20^{E}	14±33^{E}
	GS21	31±14^{D}	31±14^{D}	30±10^{E}	29±09^{E}	29±10^{E}
	GI100	1.46±0.60^{B}	1.13±0.66	1.09±0.38	1.32±0.74^{C}	0.95±0.51
	GS100	0.84±0.26^{BCa}	0.77±0.14^{BC}	0.75±0.18	0.63±0.14^{BCb}	0.72±0.08
	GI80	2.88±2.15^{Aa}	2.02±1.50^{AC}	1.52±1.04^{B}	1.30±0.45	1.19±0.46^{b}
	GS80	1.12±0.56^{BC}	0.88±0.54^{BC}	1.15±0.53	0.99±0.41	0.97±0.39
	GI60	1.08±0.40^{BC}	0.99±0.38^{BC}	1.09±0.67	1.18±0.69	1.35±1.01
PaO_2/P_AO_2	GS60	0.92±0.26^{BC}	1.43±1.36^{C}	1.55±1.44^{B}	1.66 ±1.50^{AC}	1.54±1.40^{A}
	GI21	0.27±0.34^{C}	0.28±0.46^{BC}	0.40±0.48^{A}	0.31±0.34^{B}	0.41±0.57^{B}
	GS21	0.55±0.34^{BC}	0.65±0.56^{B}	0.58±0.31	0.53 ±0.23^{BC}	0.55±0.28
	GI100	0.42±0.09^{BC}	0.50±0.14^{BC}	0.49 ±0.08^{BC}	0.46 ±0.13^{BC}	0.53±0.12^{B}
	GS100	0.54±0.06^{CDa}	0.56±0.04^{BCa}	0.57 ±0.05^{BC}	0.61±0.04^{b}	0.58±0.02^{B}
	GI80	0.31±0.12^{B}	0.39±0.15^{B}	0.44±0.12^{B}	0.44±0.07^{B}	0.47±0.09^{B}
	GS80	0.49±0.12^{BCD}	0.55±0.12^{BC}	0.49 ±0.12^{BC}	0.52 ±0.11^{BC}	0.52±0.10^{B}
	GI60	0.49±0.08^{BCD}	0.51±0.08^{BC}	0.51 ±0.13^{BC}	0.49 ±0.12^{BC}	0.47±0.15^{B}
PaO_2/FiO_2	GS60	0.52±0.06^{CD}	0.47±0.14^{BC}	0.45 ±0.14^{BC}	0.44±0.15^{B}	0.46±0.15^{B}
	GI21	0.83±0.22^{AD}	0.88±0.35^{A}	0.80 ±0.31^{AC}	0.81 ±0.24^{AC}	0.87±0.50^{A}
	GS21	0.67±0.14^{D}	0.64±0.14^{C}	0.65±0.11^{C}	0.66±0.09^{C}	0.65±0.10^{B}
	GI100	261.2±59.6	308.9±87.4	301.5±52.7	287.6±82.3	331.9±77.5
	GS100	339.8±40.6^{Ba}	349.2±29.9^{Ba}	355.6±35.1	376.1±29.3^{Ab}	357.9±14.5
	GI80	192.5±77.0^{Aa}	234.5±91.3^{A}	265.9±78.3^{b}	271.6±45.1^{Bb}	287.0±54.6^{b}
	GS80	302.5±73.5^{B}	334.5±81.0^{B}	291.7±78.7	309.2±73.2	308.8±73.9
	GI60	288.6±46.9^{B}	301.7±47.4	306.0±80.9	290.8±75.4	282.4±90.1
$P(a\text{-}ET)CO_2$	GS60	308.5±40.1^{B}	279.8±83.2	270.2±89.0	261.9 ±89.8^{B}	273.9±99.6
	GI21	320.5±72.2^{B}	323.9±99.0	306.5±98.7	315.0±68.8	307.7±117.4
	GS21	296.3±56.8^{B}	270.7±63.4	267.6±49.0	278.8 ±45.7^{B}	269.8±40.7
	GI100	20.0±10.8^{A}	16.6±10.1	13.7±14.1	11.4±11.2	10.0±10.0
	GS100	12.9±9.3	12.9±12.5	7.7±9.7	8.3±12.8	7.3±14.0
	GI80	11.5±17.0	23.1±18.4^{A}	15.3±10.7	8.7±6.9	8.2±5.4
	GS80	5.2±17.9^{B}	10.0±14.8	7.7±13.8	7.8±7.6	8.9±8.0
	GI60	14.4±10.0	14.6±10.9	9.2±12.8	11.3±10.5	10.1±9.9
CaO_2	GS60	17.5±11.2	15.5±11.1	14.9±13.8	13.1±10.0	15.4±13.0
	GI21	13.9±6.9	15.3±10.0	12.9±10.4	13.6±8.9	15.3±12.4
	GS21	4.4±4.8^{B}	5.6±4.1^{B}	4.7±5.7	2.4±9.3	2.7±6.6
	GI100	14.7±3.1^{AC}	14.7±2.4^{BCD}	15.2±1.6	14.4±1.5^{AC}	14.7±1.8
	GS100	16.9±2.6^{C}	17.0±2.5^{CD}	17.9±2.1^{AC}	17.6±1.7^{BC}	17.4±2.6^{ACD}
	GI80	15.1±1.3^{AC}	15.5±1.2^{D}	16.2±1.7^{C}	16.0±2.2^{C}	16.2±1.7^{D}
	GS80	15.6±1.5	15.1±2.2	14.7±1.0^{BC}	15.9±2.1^{C}	15.9±2.0^{D}
	GI60	14.2±2.1^{AC}	14.2±1.9^{BCD}	13.5±3.1^{BC}	11.8±5.2^{A}	13.8±2.5^{BD}
	GS60	18.0±2.1^{BC}	17.9±2.2^{ACD}	17.7±2.2^{AC}	17.5±2.3^{BC}	17.7±2.1^{CD}
	GI21	13.1±1.5^{A}	13.2±1.7^{BD}	13.0±0.9^{B}	13.6±1.6^{AC}	12.6±1.7^{B}
	GS21	13.0±1.2^{A}	12.5±1.8^{B}	13.4±1.5^{B}	12.6±1.6^{A}	12.1±1.9^{B}

Among groups: averages followed by upper case letters in the column differ from each other (P< 0.05).
Among time points: averages followed by different lowercase letters in the line differ among them (P< 0.05).

The value of PvO_2 considered normal is 40 to 50mmHg, for animals breathing in ambient air (Haskins, 2004). With the exception of GI21 and GS21, in the other groups PvO_2 was greater than 50mmHg. Such a difference can be attributed to the inspired concentration of oxygen. Thus, in this study, PvO_2 behaved in a similar way to PaO_2, presenting higher mean values, the higher the FiO_2 used (Table 1). This same relation between PvO_2 and FiO_2 was observed by O'Neill *et al*. (1995), when studying oxygen therapy (100%, 50% and 30%) in rabbits submitted to anesthesia with halothane and by Borges *et al*. (2011), with the same species, anesthetized with propofol, maintained under controlled ventilation with different FiO_2 and induced to hypovolemia. In GS21, there was a decrease in PvO_2 in T15, T45 and T60 in relation to T0, with mean values below 40mmHg (Table 1). PvO_2 represents the overall balance between the oxygen consumed

(VO_2) and its release, and is therefore dependent on (VO_2) and hemoglobin concentration. However, hemoglobin averages were within the normal range for species, ranging from 9.4 to 17.4g/dL (Suckow and Douglas, 1996).

$PaCO_2$ can be used to measure early respiratory changes. The normal range of $PaCO_2$ in rabbits is from 20 to 46mmHg (Suckow and Douglas, 1996), and these values were observed in groups that received oxygen at 21%, 60%, and GS100. In GI100, GI80 and GS80, $PaCO_2$ was greater than 46mmHg at most time points, characterizing hypercapnia (Table 1). This is commonly related to pulmonary abnormalities (Jefferies, 1994), and means above 60mmHg may be associated with the presence of hypoxemia and respiratory acidosis. In dogs anesthetized with propofol and maintained in spontaneous ventilation, Lopes *et al*. (2007) observed higher $PaCO_2$ values with the use of FiO_2 of 1.0 and 0.8. These authors attributed this clinical change to the occurrence of atelectasis due to the use of high concentrations of O_2. However, in the study that was the object of this discussion, the clinical differences between the $PaCO_2$ values were not relevant, as observed by the aforementioned authors.

Increasing levels of $PaCO_2$ may be correlated with the administration of anesthetics, which alter the response of central and peripheral chemoreceptors to carbon dioxide and oxygen, occurring in a dose-dependent manner (McDonell and Kerr, 2007). The hypercapnia found must not be related to the anesthetic administered or both determine elevation of $PaCO_2$ in the same manner, since the finding was similar with the use of sevoflurane or isofluorane.

According to Lopes *et al*. (2007), in dogs submitted to two and a half hours of general anesthesia, by continuous infusion of propofol, pulmonary collapse can be found in animals breathing 80 to 100% oxygen. Therefore, the presence of atelectasis was not observed in this study, since, at most times in the G100, $PaCO_2$ remained within the range of normality (Capellier *et al*., 1999). With this, it can be deduced that, in this study, the duration of the anesthesia of one hour and thirty minutes was not sufficient for the formation of atelectasis areas. Observing the values in the GS80, it was possible to verify that this group presented the highest averages, coinciding with the high values observed in the variable and P_VCO_2. However, the means observed in GS80 remained below 60mmHg.

According to Luna (2002), the partial pressure of carbon dioxide in the venous blood is 5 to 10mmHg higher than $PaCO_2$, therefore, the values found remained within the physiological limits, except in T0, GS80. In which the difference between the carbon dioxide partial pressure in the venous and arterial blood (ΔPCO_2) exceeded 15mmHg (Table 1). In addition, it was observed that $PvCO_2$ remained unchanged compared to the different FiO_2, a fact already observed by Cole and Bishop (1963), who did not observe alterations of this variable with the use of FiO_2 of 1.0; 0.5 and 0.21 in sedated humans and maintained under pressure-controlled ventilation. Although there was stability of P_VCO_2, it is proposed that in GS80, in T0, cardiac output was not sufficient to meet the global metabolic needs (Lamia *et al*., 2006).

SaO_2 is an index measuring the lungs' ability to deliver O_2 to blood (Haskins, 2004). In rabbits, values above 94% are considered normal. In this study, GI21 and GS21 showed $SaO_2 < 94\%$, probably due to the lower concentration of O_2 supplied to these animals, indicating that the lungs were not able to properly distribute oxygen to the blood. These results corroborate those found by Lopes *et al*. (2007), who obtained values below 90% in dogs anesthetized with propofol and maintained on spontaneous ventilation with FiO_2= 0.21, in addition to observing the presence of cyanosis. In this study, although the mucous membranes were not cyanotic, $PaO_2 < 60$mmHg and $SaO_2 < 90\%$ were observed, characterizing hypoxemia (Cortopassi, 2002) in GI21 and GS21 (Table 1).

The values considered normal for SvO_2 are between 68% and 77%, indicating a normal balance between supply and demand for oxygen, provided by normal distribution of peripheral blood flow. According to Marx and Reinhart (2006), $SvO_2 > 75\%$ indicates normal extraction with O_2 supply greater than consumption, averages between 50 and 75% show the occurrence of compensatory extraction, due to increased consumption or decreased supply. The means found in the groups that received FiO_2 of

1.0, 0.8 and 0.6 remained above 75%, providing a normal distribution of O_2 to the tissues. In this study, GI21 presented values below 75%, confirming that there was not a good supply of oxygen. The low mean recorded indicates hypoxemia, which is in agreement with the data obtained in the SaO_2 variable that remained below 90%.

Elevations in P(A-a) O_2 occur mainly due to the presence of increased ventilation / perfusion (V/Q) imbalance, decreased pulmonary capillary perfusion and increased FiO_2 (Carvalho and Schiettino, 1997). In this study, the higher the FiO_2 used, the higher were the means found between the groups (Table 1). Thus, the groups that received FiO_2 of 0.21, presented the lowest values. In addition, differences were found between GI100 and GS100 and between GI80 and GS80. This difference was characterized by higher averages found in animals receiving isoflurane. As discussed above, high P(A-a)O_2 values may be related to a V/Q imbalance or a decrease in pulmonary capillary perfusion.

The respiratory index is a more specific quantifier of lung dysfunction than P(A-a)O_2 and correlates more closely with the shunt (Terzi and Dragosvac, 2006). Values of 0.1 to 0.37 are considered adequate (Siggaard-Andersen *et al*., 1990). However *et al.* (1993) defined that RI <0.4 would be normal, but its increase would indicate worsening of intrapulmonary shunt. Thus, in this study, in T0 and T15, GI80 presented greater intrapulmonary shunt than the other groups, since it presented the highest respiratory indexes (Table 1). In addition, in GI80, it was observed that in some moments the RI was higher than 2.0, which may indicate refractory hypoxemia and elevated pulmonary shunt (Lundstrom, 2011). As hypoxemia refractory to oxygen administration is demonstrated by PaO_2/FiO_2 <200mmHg (Fioretto *et al*., 2006), which was not observed in this study, it is suggested that this value may be associated with increased shunt.

As the use of high FiO_2 for long periods is related to the formation of pulmonary collapse (Magnusson and Spahn, 2003), it is believed that in this study, the time of anesthesia was short, one hour and thirty minutes, to observe the presence of atelectasis and its consequences.

However, differences were found between GI80 and GS80, in T0 and T15, with higher IRs recorded in GI80 (Table 1). Thus, it is suggested that, for these two groups that received the same FiO_2, the animals submitted to sevoflurane anesthesia, the shunt was smaller. This hypothesis corroborates the claim that isoflurane provides deficient gas and V/Q changes when compared to sevofluorane (Terzi and Dragosvac, 2006). Thus, the hypothesis of shunt increase by the use of isoflurane in the test species strengthens.

The relation between PaO_2 and P_AO_2 is also a pulmonary disturbance quantifier and the normal value of this variable is 0.75 to 0.9 (Terzi and Dragosvac, 2006). When their value is less than 0.75, there is evidence of inadequate ventilation / perfusion or diffuse pulmonary dysfunction, while means below 0.6 indicate ineffective gas exchange, which was found in the groups submitted to FiO_2 of 1.0, 0.8 and 0.6 (Table 1). In GI21 and GS21 the values remained higher. In addition, in GI21, the means were higher than in GS21 (in T15 and T60), which again can be attributed to the better isoflurane response to pulmonary hypoxia, observed in animals submitted to FiO_2 of 21% when compared to sevoflurane (Karanovic *et al*., 2010). This is because in cases of hypoxia blood is diverted from poorly ventilated areas to better ventilated areas of the lung, characterizing hypoxic vasoconstriction, more effectively with the use of isofluorane when compared to sevofluorane (Ishibe *et al*., 1993).

The relationship between PaO2 and FiO2 reflects shunt or arteriovenous mixture, with values considered normal above 400 (Terzi and Dragosvac, 2006). In this study, GI80 obtained the lowest values, close to 200, in T0 and T15, indicating that these values were inadequate (Table 1). Thus, it was noted that PaO_2/FiO_2 behaved in a manner similar to IR. In T0 and T15, GI80 presented greater intrapulmonary shunt than the other groups, because it had the lowest means of PaO_2/FiO_2 and higher mean of IR.

The difference between $PaCO_2$ and $ETCO_2$ indicates the alveolar dead space index and ranges from 2 to 3mmHg (O'flaherty *et al*., 1994). This variable is also considered a good indicator of the quality of the V/Q relation

(Carvalho and Schiettino, 1997). In addition, large differences between the $ETCO_2$ and $PaCO_2$ parameters generally occur as a result of the absence of gas exchange, which may suggest that there is no adequate pulmonary perfusion or that the alveoli are not adequately ventilated or even during prolonged anesthesia in which they may cause changes in the exchange (O'flaherty *et al*., 1994). In this study, P (a-ET)CO_2 was greater than 3mm Hg in all groups, probably due to changes in V/Q. In T0 and T15, in GS21 smaller averages were recorded (Table 1). However, GI21, who also received FiO_2= 0.21, presented high values for P(a-ET)CO_2, although not statistically significant.

CaO_2 represents the amount of oxygen transported in arterial blood through binding to hemoglobin or dissolved in the blood, and its normal value is 17 to 20ml/dL (Espada and Carmona, 1995). In this study, this variable remained within the expected values only in GS100 and GS60 (Table 1). Hemoglobin is the most important factor contributing to oxygen content (Haskins, 2007); however, the low result cannot be justified by changes in hemoglobin, since the values found for Hb were within the normal range, 9.4 to 17.4g/dL (Suckow and Douglas, 1996).

CONCLUSIONS

Based on the results obtained with the proposed methodology, the inspired fractions of oxygen interfere in the respiratory variables. It was possible to verify the greater formation of intrapulmonary shunt in the groups that received FiO_2 0.8. In addition, isofluorane determined better ventilation compared to sevoflurane when administered in a 21% oxygen atmosphere. Therefore, it is suggested that the best FiO_2 for rabbits anesthetized with sevoflurane or isofluorane is close to the fractions 0.6 and 0.21.

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