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Hyperbaric oxygen therapy positively interferes with oxidative metabolism in female cats undergoing video-assisted elective ovariohysterectomy

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ABSTRACT

Knowing the low number of studies about the species chosen for the study in hyperbaric medicine and the importance that this technique has to help in several diseases and future studies. This study aimed to determine whether hyperbaric oxygen therapy (HBOT) alters oxidative biomarkers after elective ovariohysterectomy (OHE). For this purpose, 45 healthy female cats were randomized into three groups: the hyperbaric group (HG): 15 animals pretreated with HBOT and submitted to OHE; the hyperbaric control group (HCG): 15 animals pretreated with HBOT without surgery; and the sham group (SHAM): 15 female cats submitted to OHE without pretreatment. The following biomarkers were evaluated: superoxide dismutase (SOD) and catalase (CAT), reactive oxygen species (ROS), thiobarbituric acid reactive substances (TBARS), acetylcholinesterase (AChE), and butyrylcholinesterase (BChE). The collection times were: T1 = before the surgery for the operated groups and after sedation in the HCG; T2 = 30 min after reversal of sedation (HCG) or at the time of extubation in the other groups; T3 = 24 hr after T2. There was a stat. sign. increase in TBARS in the T3 SHAM compared to the T3 HG (P = 0.043). Moreover, it was observed a stat sign that CAT activity decreased in T2 SHAM and T3 SHAM compared to T1 SHAM (p=0.012 and p<0.001 mauric); T2 SHAM had lower CAT activity than T2 HCG (p=0.05). Additionally, the T3 SHAM was significantly lower than the T3 HG (p=0.030) and T3 HCG (p=0.050). It was observed a stat sign. reduction of SOD in the T2 SHAM compared to the T2 HG (p=0.033) and T2 HCG (p=0.027). Similarly, the T3 SHAM decreased compared to the T3 HG (p=0.039) and T3 HCG (p=0.019). The HBOT proved to be of value in promoting a favorable influence on reducing oxidative stress and serum levels of these biomarkers.

1. Introduction

Hyperbaric oxygen therapy (HBOT) is a therapeutic modality in which patients inhale oxygen (O2) at 100% under a pressure level above 1 absolute atmosphere (absolute technical atmosphere, ATA) in a pressurized chamber, enabling higher oxygen perfusion rates in tissues (Edwards, 2010a). Oxygen is necessary to provide energy and enable cellular respiration; hence, a deficient oxygen supply can lead to cell death by hypoxia. Sick animals have reduced O2 transport capacity and their tissues require increasingly higher O2 levels, leading to system collapse and oxidative stress (Yanagisawa et al., 2011). Several mechanisms are proposed to account for the physiological benefits of HBOT, including increased plasma oxygen availability, tissue hyperoxygenation, barometric effects, immunomodulation, and reduced oxidative stress (Birnie et al., 2018).

The organism of animals has an oxidative state, which is completely dependent on a balance between oxidant reagents and antioxidant defenses. Situations such as tissue hypoxia generate molecules with unpaired electrons that interact with other molecules, consequently modifying their biochemical structure. The body can produce antioxidant substances that neutralize this effect, although when the production of oxidant agents is high or there is a physiological inability to neutralize them, a biochemical imbalance occurs, called oxidative stress (Castillo, 2015; Thom, 2009). Oxidative stress can be quantified using different biomarkers by directly measuring free radicals, free radical damage products, or the levels of specific and total antioxidants (Arsalani-Zadeh, 2011).

Reactive oxygen species (ROS) are generated as natural byproducts of metabolism and encompass a variety of chemical species, including superoxide, hydrogen peroxide, hypochlorous acid, and hydroxyl (Thom, 2009); these radicals can be generated exogenously or produced by cells from several different sources (Finkel e Holbrook, 2000). Lipid peroxidation consists of a cascade of reactions resulting from the action of free radicals on lipids. The cell membrane is one of the most affected components, leading to changes in its structure and permeability with consequent release of

organelle content, including malonildialdehyde; this marker can be measured by quantifying thiobarbituric acid reactive species (TBARS). To counteract the oxidative imbalance caused by ROS, the organism produces antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT), products of oxygen oxidation in a peroxidase reaction where the two molecules of hydrogen peroxide (H2O2), are catalyzed into water (H2O) and oxygen (O2) (Basso et al., 2014; Dalmolin et al., 2016; Finkel e Holbrook, 2000).

The enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are used as local or low-grade systemic inflammation indicators. Acetylcholine (Ach) has an important inflammatory suppressive action, albeit it is rapidly hydrolyzed by AChE and BChE. Therefore, increased AChE and BChE activities may lower Ach levels, reducing its anti-inflammatory effects (Das, 2012).

In cats, oxidative stress development is well documented in various diseases such as hypertrophic cardiomyopathy, chronic kidney disease, cognitive dysfunction syndrome, and feline infectious peritonitis, among others (Castillo, 2015; Christiansen et al., 2015; Krofič Žel et al., 2014; Tecles et al., 2015). The interference of HBOT on oxidative stress markers is well documented in human patients, experimental animals, and dogs (Ayvaz et al., 2013; Burgos et al., 2016; Gautier et al., 2020; de Wilde et al., 2021), although data for feline patients is scarce.

Given this lack of research regarding the interference of HBOT on oxidative stress biomarkers in cats and knowing the harmful effects that this disease can promote in the body (Finkel e Holbrook, 2000), we aimed to determine whether treatment with pre-surgical hyperbaric oxygen therapy alters oxidative stress biomarkers during video-assisted ovariohysterectomy with two portals. This study was approved by the Ethics Committee on Animal Use (CEUA) of the Federal University of Santa Maria under protocol no. 5134560820.

2. Materials and Methods

2.1. Animals and treatment groups

Forty-five healthy female cats aged on average 1.89 (+/- 1.06) years and weighing on average 3.05 (+/- 0.52) kg were used for video-assisted OHE. All animals were acclimated for three days, and on the fourth day, they were randomly divided into three groups that received different treatments, namely: Hyperbaric group (HG): 15 animals were pretreated with 100% oxygen at a pressure of 2 ATA for 45 min and subsequently underwent elective video-assisted OHE with two portals. Control hyperbaric group (CHG): 15 animals were pretreated with HBOT at a pressure of 2 ATA for 45 min without interference from the surgical procedure. Elective OHE was performed at the end of the collections. Sham group (SHAM): 15 cats underwent elective video-assisted OHE with two portals without pretreatment.

2.2. Pre-surgical procedures

Patients in the HGs and HCGs were submitted to HBOT with a pressure of 2 ATA for 45 min before the anesthetic-surgical procedure plus 15 min for pressurization and 15 min for depressurization. Preanesthetic medication was performed with dexmedetomidine hydrochloride 20 µg/kg (Dexdomitor, Zoetis, Guarulhos, Brazil) applied intramuscularly (IM) and, in the three groups evaluated, the researchers waited 25 min for total sedation to take effect. Anesthesia induction was performed with propofol 10 mg/ml (Propovan, Cristália Prod. Quím. Farm. Ltda., São Paulo, Brazil) administered intravenously (IV). Anesthesia of periglottic tissues was performed with 1 mg/kg lidocaine spray (Xylestesin, Cristália Prod. Quím. Farm. Ltda., Itapira, Brazil) before orotracheal intubation. Anesthetic maintenance was performed with isoflurane in 100% oxygen concentration to maintain the animals in an adequate anesthetic plan in a system compatible with the animal's size.

After anesthetic stabilization, before surgical antisepsis, atipamezole (10 µg/kg; Antisedan, Zoetis, Guarulhos, Brazil) was administered to reverse the sedative, analgesic, and hemodynamic effects of dexmedetomidine, followed by a continuous infusion of remifentanil hydrochloride (10 µg/kg/h; Remifas, Cristália Prod. Quím. Farm. Ltda, Itapira, Brazil) and fluid therapy with a Lactate Ringer solution (3 ml/kg/h). Immediately after the end of the surgery, the animals in the HGs and SHAMs received dipyrone sodium (25 mg/kg; Analgex V, União Química Farmacêutica Nacional S.A., São Paulo, Brazil) subcutaneously every 12 hr for 3 days. The animals in the HCG received a proportional volume of 0.9% sodium chloride solution.

2.3. Oxidative metabolism

The biomarkers of oxidative stress were evaluated. The collection times were: T1 = immediately before the surgery during anesthetic stabilization; T2 = at the time of extubation; T3 = 24 hr after the surgery. The analyses were performed in the same way in the three groups and at different times. The HCG animals had the T1 sample collected after sedation, T2 after anesthesia reversal (30 min after), and T3 24 hr after anesthesia reversal; SOD and CAT activity were analyzed using whole blood collected in sodium citrate tubes. Serum samples were collected to measure ROS, TBARS, AChE, and BChE.

3. Statistical analysis

Data were subjected to one-way repeated measures analysis of variance, followed by Duncan's post-hoc test. Data were expressed as mean ± standard deviation of the mean, and $P < 0.05$ values were considered statistically different.

3.1. Results

It was observed a significant effect of prior treatment with HBOT (p=0.028) on serum TBARS levels. There were no significant effects of the time variable (p=0.507) or treatment vs. time interaction (p=0.165) on serum TBARS levels. Duncan's post-hoc test showed significantly higher TBARS levels in the T3 moment, while the SHAM had more lipoperoxidation (14.07±1.44) than the HG (7.95±1.49), with a p-value=0.043 (Figure 1A). One-way ANOVA showed no effect of treatment (p=0.715), time (p=0.600), nor treatment vs. time interaction (p=0.761) on serum ROS generation (Figure 1B).

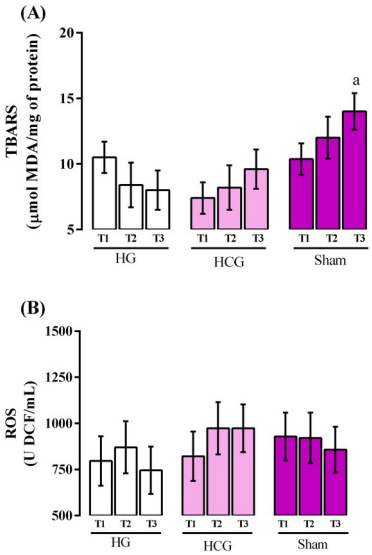

Figure 1 *– Serum analysis of TBARS levels and ROS generation of I) female cats submitted to hyperbaric therapy with subsequent OHE (HG); II) female cats only submitted to hyperbaric therapy (HCG) and III) female cats only submitted to OHE (Sham). Blood samples were collected before surgery (T1), immediately after surgery (T2), and 24 hr after the procedure (T3). Data were expressed as mean ± standard deviation of the mean. Differences were considered significant when p<0.05.*
a Significant difference for the HG at the same time;

CAT activity showed a significant interaction between treatment and time (p<0.001) and an effect of treatment (p=0.021), although no effect of time (p=0.10). Reduced CAT activity in the T2 SHAM (1.75±0.09) and T3 SHAM (1.64±0.07) compared to the T1 SHAM (2.00±0.08), with values of p=0.012 and p<0.001, respectively. In addition, the T2 SHAM (1.75±0.09) had lower CAT activity than the T2 HCG (2.18±0.10), with a p-value=0.05. Moreover, the T3 SHAM showed lower CAT activity than the T3 HG (2.11±0.07) and T3 HCG (1.99±0.07), with p-values=0.030 and p=0.05, respectively (Figure 2A). Repeated measures showed an increase in the treatment variable (p<0.001), albeit without any effect of time (p=0.729) or interaction between treatment vs. time (p=0.496) for serum SOD activity. Duncan's test showed decreased serum SOD activity in the T2 SHAM (1.66±0.09) compared to the T2 HG (2.06±0.09) and T2 HCG (2.10±0.09), with values of p=0.033 and p=0.027, respectively. Similarly, the T3 SHAM (1.66±0.08) showed decreased enzyme activity compared to the T3 HG (2.07±0.09) and T3 HCG (2.13±0.09), with p-values=0.039 and p=0.019, respectively (Figure 2B).

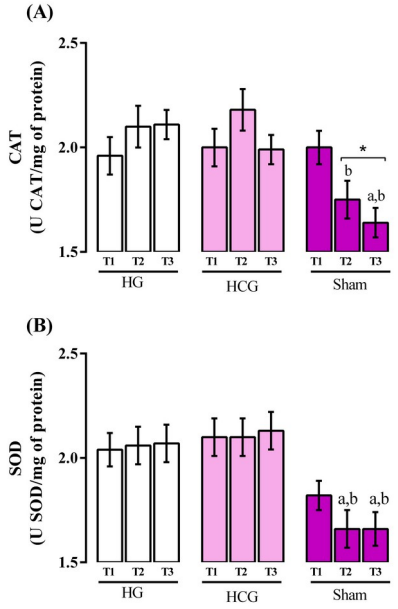

Figure 2 *– Serum analysis of catalase (CAT) and super dismutase (SOD) activity of I) female cats submitted to hyperbaric therapy with subsequent OHE (HG); II) female cats only submitted to hyperbaric therapy (HCG), and III) female cats only submitted to OHE (Sham). Blood samples were collected before surgery (T1), immediately after surgery (T2), and 24 hr after the surgical procedure (T3). Data were expressed as mean ± standard deviation of the mean. Differences were considered significant when p<0.05. * Significant difference for T1 within the same experimental group; a significant difference for the HG at the same time; b Significant difference for HCG at the same time.*

It was not observed any effect of treatment (p=0.959), time (p=0.768), or treatment vs. time interaction (p=0.259) on AChE activity (Figure 3A). Similarly, no effect of treatment (p=0.544), time (p=0.566), or treatment vs. time interaction (p=0.670) on BChE activity (Figure 3B) was observed.

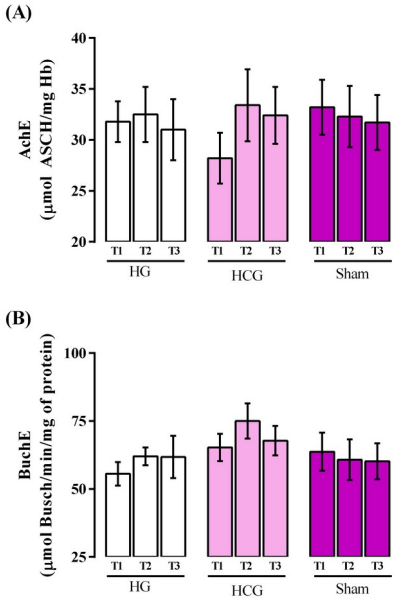

Figure 3 *– Serum analysis of AChE and BChE activity of I) female cats submitted to hyperbaric therapy with subsequent castration (HG); II) female cats only submitted to hyperbaric therapy (HCG), and III) female cats only submitted to castration (Sham). Blood samples were collected before surgery (T1), immediately after surgery (T2), and 24 hr after the procedure (T3). Data were expressed as mean ± standard deviation of the mean. Differences were considered significant when p<0.05.*

4. Discussion

Hyperbaric oxygen therapy is a therapeutic modality in which the patient is subjected to a chamber with pure (100%) oxygen at a pressure typically 1.5 to 3 times higher than standard air pressure at sea level (i.e., absolute technical atmosphere) (Benett e Mitchell, 2018; Edwards, 2010a). Studies have demonstrated safety and few side effects in small animals after HBOT. Recently, prospective clinical trials have been published, showing that cats tolerate HBOT sessions very well (Birnie et al., 2018; Montalbano et al., 2021). With this in mind, each session's pressure regimen and time were based on these trials using a pressure of 2 ATA and a 45-min duration. No adverse effects or complications occurred during the 45 sessions.

This is a low-complexity treatment with numerous well-documented biochemical effects in humans and animals, including increased endogenous synthesis of antioxidants, modulation of inflammation, angiogenesis, and antimicrobial activity (Bennet e Mitchell, 2018; Edwards, 2010b; de Wolde et al., 2021). In most studies in small animals, HBOT is performed after the lesion has been produced (Bimbarra et al., 2021; Gautier et al., 2020) although the preventive treatment with hyperbaric oxygen therapy is still little reported and has aroused the interest of many researchers (Fontoura-Andrade et al., 2020) including this trial, in which HBOT was performed preventively.

To minimize variation in induced inflammatory effects, all surgeries were performed by the same surgeon and camera operator. The room was kept at a stable temperature and humidity control during the procedures, and no anti-inflammatory drugs were administered before the last collection time because it is already known that surgical procedures, like any other trauma, produce oxidative stress associated with oxidant production and deplete antioxidant mechanisms due to incisional injuries, visceral manipulation, and inflammatory cell activation (Baysal et al., 2009; Thomas e Balasubramanian, 2004). It is also known that less tissue trauma results in less inflammation and that laparoscopic surgeries cause less oxidative stress compared to open procedures (Arsalani-Zadeh et al., 2011; Basso et al., 2014).

Reactive oxygen species are generated as natural byproducts of metabolism and have a dual role in the body; moreover, ROS can be beneficial through their participation in defenses against infectious agents, cell signaling, and induction of mitogenic response, among others (Poli et al., 2004; Thom, 2009). Nevertheless, their excess can be harmful, leading to protein and nucleic acid oxidation. These free radicals may often be increased in many organs in cases of hypoxia (Thom, 2009), however, it was not possible to detect this increase in this study, and no difference in ROS values was evidenced between cats that were and were not submitted to HBOT.

When evaluating the TBARS values 24 hr after surgery (T3), we noted a significant decrease in the values in the animals that underwent the HBOT session (HG) compared to the animals that did not (SHAM). Knowing that TBARS evaluates the levels of malondialdehyde and that this is a secondary product of oxidative stress formed during lipid peroxidation (Matsunami et al., 2010; Paprocki et al., 2019), we evidenced that HBOT could reduce this effect. Another piece of data that corroborates this hypothesis was that there was no statistical difference between the two groups submitted to HBOT (HG or HCG), which further strengthens the efficacy of HBOT in reducing lipid peroxidation.

We believe that this is because the surgical technique used induces an insufficient inflammatory reaction for this detection in the immediate postoperative period. We know that installing the oxidative stress process occurs at the expense of an imbalance between oxidant and antioxidant compounds. Superoxide dismutase and catalase are enzymes intimately involved in the antioxidant system and are considered part of the first line of defense of the organism in protecting tissues against oxidative damage caused by ROS (Finkel e Holbrook, 2000; Todorova et al., 2005).

The profile of antioxidant enzymes in this study was similar to TBARS, with no statistical difference between the groups that underwent HBOT (HG and HCG), regardless of the surgical procedure. We believe that the reduced SOD and CAT activities occurred due to the surgical stimuli in the SHAM. Nonetheless, there was an increase in the activity of these enzymes with the HBOT pretreatment, and these observations support our suspicions that HBOT is beneficial in maintaining endogenous antioxidant levels. This is evidenced in the decrease of enzymes in the group without HBOT pretreatment (SHAM) compared to the two groups pretreated with HBOT (HG and HCG).

When we evaluated the first 24 hr post-surgery of the cats in the SHAM, we noticed a significant decrease over time, evidencing the consumption of antioxidant enzymes in the body. Similar findings were observed in a study with rats in which bile duct ligation was performed (with and without HBOT), and treatment with HBOT sharply increased the mean SOD and CAT activity and decreased TBARS levels (Ayvaz et al., 2013). These data further support the theory that HBOT can minimize the deleterious effects of surgery on oxidative stress.

There was no difference between the groups for AChE and BChE, nor was an increase or decrease detected with a statistical difference in our study. In surgical procedures of OHE in bitches, one study identified the elevation of these biomarkers in the first three postoperative hours (Christiansen et al., 2015). We believe that there was not enough inflammatory process to detect this increase because we are dealing with minimally invasive procedures.

Another study conducted with bitches after OHE also reported unaffected AChE and BChE activity, both in a conventional surgical approach and in laparoscopic surgery; however, unlike our study, anti-inflammatory drugs were used postoperatively, which may have modulated pro-inflammatory cytokine production (Dalmolin et al., 2016). Regarding the use of HBOT, one study evaluated other inflammatory biomarkers (e.g., C-reactive protein, circulatory

cytokines, and changes in iron homeostasis) in bitches that underwent OHE and subsequently received or not two sessions of HBOT, and there were no significant differences in these biomarkers (Krofič Žel et al., 2014).

The present study achieved its objective of elucidating the effects of preoperative hyperbaric oxygen therapy on the expression of some biomarkers of oxidative damage and evaluating this therapeutic effect on oxidative enzymes in female cats submitted to elective ovariohysterectomies up to 24h postoperatively. Considering the positive effects of HBOT in cats, associated with the tendency of using video-laparoscopic techniques in these animals, we believe that the union of these treatment modalities constitutes an advance in feline medicine. The results obtained in this study may also serve as a basis for future investigations covering effectiveness and a better understanding of HBOT in cats and other domestic species.

5. Conclusions

The present study may be one of the few experiments addressing the significantly positive results of preoperative HBOT for video-assisted elective ovariohysterectomy in healthy cats. The HBOT proved to be of substantial value in treating inflammatory responses, promoting a favorable influence on reducing oxidative stress and serum levels of these biomarkers.

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