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Changes in cardiac biomarkers in goats naturally affected by pregnancy toxemia

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ABSTRACT

Pregnancy toxemia (PT) is considered one of the most common metabolic diseases with high impact on the production of small ruminants. The objective of this study was investigate possible myocardial damage in goats affected with PT by the determination of serum myocardial biomarkers CK-MB and cTnI. A total of 44 goats affected with PT, and 10 apparently healthy goats (control group or CG) were used in the study. In goats with PT, the serum concentrations of cTnI (0.43 ng/mL) were significantly higher than that in CG goats (0.06 ng/mL). Although CK-MB showed no significant difference, it was approximately three times higher in animals with PT. The serum concentrations of insulin were significantly lower in PT goats (5.03 ppmol/L) compared to CG goats (10.66 pmol/L). The serum concentrations of cortisol in PT goats (155.41 nmol/L) were significantly higher than that in CG goats (36.58 nmol/L). Results of this study indicate that a clinically significant myocardial damage might occur in goats affected with PT leading to significant elevations in values of cTnI and CK-MB. Therefore, these parameters could be used as a potential prognostic indicator in goats affected with this important disease.

1. Introduction

Pregnancy toxemia (PT) is considered one of the most common metabolic diseases with high mortality rates in small ruminants. This disease could lead to severe economic losses due to compromised production, loss of the fetus, poor milk production, costs of veterinary care and medication, and death of the pregnant does (Abdelaal et al., 2013). PT is characterized by disturbances in the energy, protein, mineral, and hormonal metabolism leading to neurological clinical signs and death of the fetuses and mothers (Rook, 2000; Souto et al., 2013). Negative energy balance can occur at the end of gestation. Depending on the number of fetuses; animals with multiple fetuses may require 180 to 240% more energy than those with singles. Obese goats with multiple fetuses present a high chance of developing the disease through limitation of the ruminal space, caused by the accumulation of intra-abdominal fat, reducing the amount of food ingested (Ermilio and Smith, 2011).

PT is characterized by substantial increase in serum concentrations of Beta hydroxybutyrate (β-OHB) and cortisol which play important roles in the induction of lipid peroxidation and oxidative stress in goats and sheep with high concentrations of ketone bodies (Al-Qudah, 2011; Schlumbohm and Harmeyer, 2004). Oxidative stress is characterized by an increase in the production of free radicals due to increased metabolic activity during gestation and a reduction in antioxidant reserves in the body. This could result in acute or chronic inflammatory reactions leading to endothelial dysfunction and long-term vascular disease development, similar to the complications observed in patients with type I and type II diabetes (Jain et al., 2006). This condition can be monitored through biomarkers and through the use of metabolic indicators of energy metabolism such as glucose, β-OHB, and NEFA (Al-Qudah, 2011; Castillo et al., 2005; Jain et al., 2006).

The use of cardiac biomarkers, such as troponin (cTnI) and creatine kinase-myocardial band (CK-MB), are widely used in human medicine in the diagnosis of patients with myocardial injury. In Veterinary Medicine, these markers have been used in different species in the diagnosis of cardiac lesions, such as in bovines (Gunes et al., 2005, 2008;

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Tunca et al., 2008), sheep (Souza et al., 2019; Tunca et al., 2009), and goats (Abdelaal et al., 2013; Karapinar et al., 2016; Tharwat et al., 2012;).

Given the scarcity of studies relating the use of these cardiac injury biomarkers in goats affected by PT, the objective of this study was investigate possible myocardial damage in goats affected with PT by the determination of serum myocardial biomarkers CK-MB and cTnI.

2. Material and methods

2.1. Animals

A total of 44 goats naturally affected with PT and 10 apparently healthy control goats (CG) in the third period of gestation were studied. The diagnosis of PT was established through clinical and laboratory testing according to Diffay et al. (2004). For inclusion criteria in the PT group, the clinical signs, ketonuria with different degrees of intensity on the reagent strip (+, ++, +++) and blood concentration of beta hydroxybutyrate (β-OHB) and non-esterified fatty acids (NEFA) above 0.8 mmol/L and 0.4 mmol/L, respectively, were considered according to Andrews (1997), Cal-Pereyra et al. (2015) and Souza et al. (2019). In the CG group, goats that were in the third period of gestation with no clinical signs suggestive of PT, no ketonuria, and blood concentrations of β-OHB and NEFA within the reference values. Control goats were compound of the Saanen breed with an average weight of 50 kg. Goats in the PT group were aged between one and six years. They were reared on properties with a predominantly intensive management system, receiving diets containing concentrated feed. The mean weight of the animals was 50 kg, with a mean body condition score (BCS) 2.5 out of 5 (Villaquiran et al., 2004). The goats were of the Saanen, Anglo Nubiana, Boer, Nambi, Alpine Parda, Toggenburg, and crossbred breeds. Ultrasound examinations were also performed to determine fetal quantity and viability. The project was approved by the Ethics Committee on the Use of Animals (CEUA) of the Federal Rural University of Pernambuco under registration number 86/2018.

2.2. Sampling

Blood samples were collected by jugular venipuncture, using a vacuum tube needle (25 × 0.8 mm), in tubes containing anticoagulant (sodium fluoride and K3EDTA) and in tubes without anticoagulants to obtain plasma and serum, respectively. After centrifugation, the samples were placed in Eppendorf® tubes and kept in an ultra-freezer (−80 °C) for further laboratory processing. Urine specimens were obtained through spontaneous urination, when they were collected and stored in urine collectors for 50 mL, after which the regent strip exams were immediately performed. The study of ketone bodies in the urine was performed using reagent strips for urinalysis (Labtest diagnóstic). Serum concentrations of cTnI (Karapinar et al., 2016), insulin, and cortisol were performed through electrochemiluminescent immunoenzymatic assay using Beckman Couter Acces II equipment (Beckman Couter inc, Fullerton, CA, USA).

2.3. Blood analysis

The following determinations were performed in blood serum: NEFA (Randox laboratories Ltd); β-OHB (Ranbut randox laboratories Ltd); fructosamine (Labtest diagnostica S.A.); aspartate aminotransferase (AST/GOT liquiform labtest diagnostic S.A.), gamma-glutamyl transferase (Gamma-GT liquiform labtest diagnostica S.A.), creatine kinase (CK-NAC liquiform labtest diagnostica S.A.), and plasma glucose concentration (Glucose PAP liquiform labtest diagnostica S.A.) were obtained with the biochemical analyzer Bioplus® - BIO Model 2000 and CK-MB (CK-MB liquiform labtest diagnostica SA) with the Labmax 240 Premium.

2.4. Statistical analysis

The data were processed using the statistical software MINITAB® 18. Initially normality of distribution was tested using the Kolmogorov-Smirnov test. The variables that did not meet the normality assumptions were submitted to the logarithmic (log_{10}) or radical (x + 1) transformation. Next, the variables that presented normal distribution were submitted to analysis of variance (ANOVA one-way). If significance was found in the ANOVA Test (one-way), the difference between the means was performed by the Tukey's least significant difference (l.s.d.). The variables that did not present normal distribution were submitted to the non-parametric Mann-Whitney test. Pearson correlation was performed to evaluate the degree of relationship between pairs of variables according to Little and Hills (1978). High relation was considered present when $r > 0.60$; moderate relation when $0.30 < r < 0.60$ and low relation when $r < 0.30$. For all statistical analyzes, a significance level of 5% was adopted.

3. Results

The main clinical signs were decubitus, behavioral disorders in 37.50% (apathy, depression, and stupor) and neurological signs (bruxism, opisthotonus, reduction in panniculus and threat reflexes, nystagmus, miosis, and paresis of members) in 20.83%. Hyperthermia (51.16%) and hypothermia (4.16%) were also highlighted, as well as a decrease in body condition score (BCS) in 37.50%, moderate to severe dehydration (75%), mucosal congestion (12.5%), reduced appetite in 33.33%, and decreased gastrointestinal tract motility in 45.83%. In the locomotor system, alterations were found, such as increased volume and limb edema in 25%. Some intercurrent diseases were highlighted in 54.16% of the animals affected by PT, such as verminosis, hypocalcemia, bronchopneumonia, polioencephalomalacia, and vaginal prolapse. In the most severe cases, 47.7% of the animals died with clinical evolution of five days, while for those which were discharged, clinical evolution was 10 days.

Serum cTnI concentrations in the group of goats with PT (0.43 ng/mL) were higher when compared to goats in the control group (0.06 ng/mL) (p = .0238). CK-MB showed no significant difference, however it was approximately three times higher in animals with PT (p = .0680). The CK activity was higher in the PT group compared to the control

Table 1
Mean, standard error of the mean (SEM), median, maximum, minimum, and level of significance of the analysis of variance of serum concentrations of Troponin I, CK-MB, and CK in goats with (n = 44) and without (n = 10) PT.

Variables	Groups	Mean ± SEM	Median	Maximum	Minimum	Pr > F
Troponin I (ng/mL)	Control	0.06 ± 0.02[B]	0.01	0.21	0.00	0.0238
	PT	0.43 ± 0.23[A]	0.06	9.54	0.00	
CK-MB (U/L)	Control	117.18 ± 14.24	118.67	202.45	53.74	0.0680
	PT	307.55 ± 36.20	260.88	933.43	11.12	
CK (U/L)	Control	48.89 ± 15.46[B]	97.14	242.90	72.85	0.0223
	PT	622.04 ± 154.52[A]	255.00	4784.00	24.29	

Different capital letters in the same column differ at the 5% probability level.

Table 2
Mean values, standard error of the mean, and level of significance of the analysis of variance of metabolic variables of the biochemical and hormonal profile of goats with (n = 44) and without (n = 10) PT.

Variables	Unit	Groups		Pr > F
		Control	PT	
β-OHB	(mmol/L)	0.29 ± 0.03[B]	4.78 ± 0.57[A]	< 0.0001
NEFA	(mmol/L)	0.38 ± 0.07[B]	1.40 ± 0.11[A]	< 0.0001
Glucose	(mg/dL)	39.96 ± 1.45[B]	74.42 ± 7.88[A]	0.0325
Fructosamine	(μmol/L)	200.24 ± 5.74	210.43 ± 7.91	0.4822
Cholesterol	(mg/dL)	86.18 ± 4.18	90.42 ± 4.72	0.5925
Triglycerides	(mg/dL)	23.96 ± 3.40	25.95 ± 3.29	0.8833
Insulin	(pmol/L)	10.66 ± 1.98[A]	5.03 ± 1.08[B]	0.0025
Cortisol	(nmol/L)	36.58 ± 8.01[B]	155.41 ± 22.85[A]	0.0032
AST	(U/L)	86.43 ± 5.13[B]	150.12 ± 14.69[A]	0.0204
GGT	(U/L)	32.13 ± 2.22[B]	46.61 ± 2.82[A]	0.0111
Urea	(g/dL)	50.11 ± 2.16	47.94 ± 3.44	0.3774
Creatinine	(mg/dL)	0.85 ± 0.04	1.11 ± 0.10	0.1969

Different capital letters in the same line differ at the 5% probability level.

group (p = .0223) (Table 1). Significant variations were recorded for the following variables: β-OHB (p ≤.0001), NEFA (p ≤.0001), glucose (p = .0325), insulin (p = .0025), cortisol (p = .0032), AST (p = .0204), and GGT (p = .0111). No significant variations were observed for serum concentrations of fructosamine (p = .4822), cholesterol (p = .5925), triglycerides (p = .8833), urea (p = .3774), or creatinine (p = .1969) (Table 2).

Higher plasma concentrations of β-OHB, NEFA, and glucose and serum concentrations of cortisol and enzymatic activities of AST and GGT were observed in the goats of the PT group in relation to the goats of the control group. The highest insulin concentration was recorded in the goats of the control group, with lower values in the PT group.

A positive and high intensity relation was observed between CK-MB with β-OHB (r = 0.60, p < .001) and positive and moderate intensity relation between CK-MB and CK (r = 0.57; p < .001), with fructosamine (r = 0.48, p = .003), cortisol (r = 0.42, p = .013), and glucose (r = 0.41, p = .007), respectively. A negative and moderate intensity relationship was recorded between troponin (cTnI) with albumin (r = −0.31, p = .024) and CK-MB with insulin (r = −0.33, p = .025) (Fig. 1).

4. Discussion

The clinical signs found in goats with PT have been described by other authors (Barakat et al., 2007; Souto et al., 2013). According to Hefnawy et al. (2011) clinical signs arise when the animal fails to meet the glucose demands of the uterine-placental unit and develops a framework of ketonemia, usually in the final third of gestation, with multiple fetuses, with the severity of the clinical condition being related to higher intensities of this framework. This was observed in the present study, with death rates of 47.7% for the most severe cases with clinical evolution of five days, however, in cases with lower severity in which the animals were clinically discharged, the evolution of the case occurred in, on average, 10 days of hospitalization.

The concentrations of cTnI in goats with PT were marked, reaching values 7.17 times higher than the CG. This condition was also found by Tharwat et al. (2012), who presumed there was cardiac injury in animals with this metabolic disorder. According to Souza et al. (2019) the expressive elevation of cTnI in ewes affected with PT presumably indicates significant cardiac injury and may have contributed to the death/euthanasia of the 18 ewes, due to the greater expression of the values found, 30 times more in relation to the control and 20 times more to the discharged group with PT.

Sahoo et al. (2009) observed the elevation of this protein may be due to the reduction in antioxidant agents and the elevation of free radicals, which are generated from a framework of hyperketonemia, which can damage the heart muscle. In PT the most evident macroscopic lesion is the fatty infiltration of the liver; however, the focal degenerative alterations in contractile and conducting cells of the myocardium, as well as in the adrenal cortex and proximal tubular epithelium of the kidney can occur through the same mechanism (Tontis and Zwahlen, 1987). This phenomenon may explain the negative correlation of cTnI with albumin (r = −0.31, p = .024), since when elevation of cTnI occurs due to myocardial damage, the decrease in serum albumin concentration can be related to hepatic or renal insufficiency in goats with PT (Yarim and Ciftci, 2009).

With respect to the results found for CK-MB, they are similar to those found by Tharwat et al. (2012), who did not find a significant difference between the groups of healthy animals and those affected by PT, although the latter presented higher values, as in this study, and the authors attributed this increase to the release of CK-MB at the time of delivery, since it is not restricted to the heart, but also the utero-placenta unit, as well as other tissues such as skeletal muscle. However, Souza et al. (2019) found a significant difference of CK-MB between death group in ewes with PT and control group, and was observed a strong correlation between cardiac variables cTnI and CK-MB.

The absence of correlation between the cardiac biomarkers CK-MB and cTnI found in the present study may be related to the characteristics of these biomarkers; cTnI is present about four times more in cardiac muscle when compared to CK-MB, favoring its detection even in small myocardial lesions (Adamcova, 2003). Another important characteristic is the half-life of each of these biomarkers cTnI can be detected from after a few hours to up to 10–14 days in the bloodstream, however, CK-MB reaches its peak between 10 and 24 h after the onset of symptoms and reduces to normal values in 72 to 96 h (Tharwat et al., 2012; Volz et al., 2012).

This condition was analyzed in dogs affected by diabetic ketoacidosis (type II), in which the behavior of this variable was altered, presenting significantly higher values in comparison to the healthy group (Surachetpong et al., 2016). Similar results were found in human patients with the same type of diabetes (Atabek et al., 2004; Eubanks et al., 2012). Moller et al. (2005) showed elevated cardiac markers, such as CK-MB, suggesting that ketoacidemia can contribute to elevation of cardiac enzymes, due to the large amount of NEFA produced by the lipolytic process, generating large numbers of ketone bodies in the blood, especially when the concentrations of insulin levels are correlated with the degree of acidosis. Another possibility is that the high concentrations of NEFA can lead to their incorporation and the formation of micelles in the myocardial plasma membranes, provoking the destabilization and rupture of the membrane (Van der Vusse et al., 1992). These elevation of cardiac enzymes caused by ketoacidemia may explain the relationship of CK-MB with energetic indicator such as β-OHB (r = 0.60, p < .001), with a strong and positive relation.

Another relevant factor to be considered was the increase in the concentrations of energy indicators such as NEFA, β-OHB, and glucose in the PT group compared to the CG. The mean concentration of NEFA was 3.68 times higher in goats with PT, followed by β-OHB which was approximately 16.48 times the mean value found in the CG. High levels of NEFA and its beta-oxidation for energy production and hyperketonemia are the main biochemical alterations recorded in ketosis (Sahoo et al., 2009). According to Cal-Pereyra et al. (2015) significant increase in NEFA concentrations can be observed after 48 h of dietary restriction, suggesting a rapid lipid mobilization caused by dietary restriction at the end of pregnancy in ewes.

The hyperketonemia reflects the severity of the negative energy balance and clinical manifestation found, causing an intense disturbance of carbohydrate, hormonal, and lipid metabolism (Harmeyer and Schlumbohm, 2006; Hefnawy et al., 2011; Rook, 2000; Souto et al., 2013; Van Saun, 2000). These changes in metabolic balance cause numerous adverse effects on mitochondrial function and the generation of reactive oxygen species, which can cause damage to different tissues

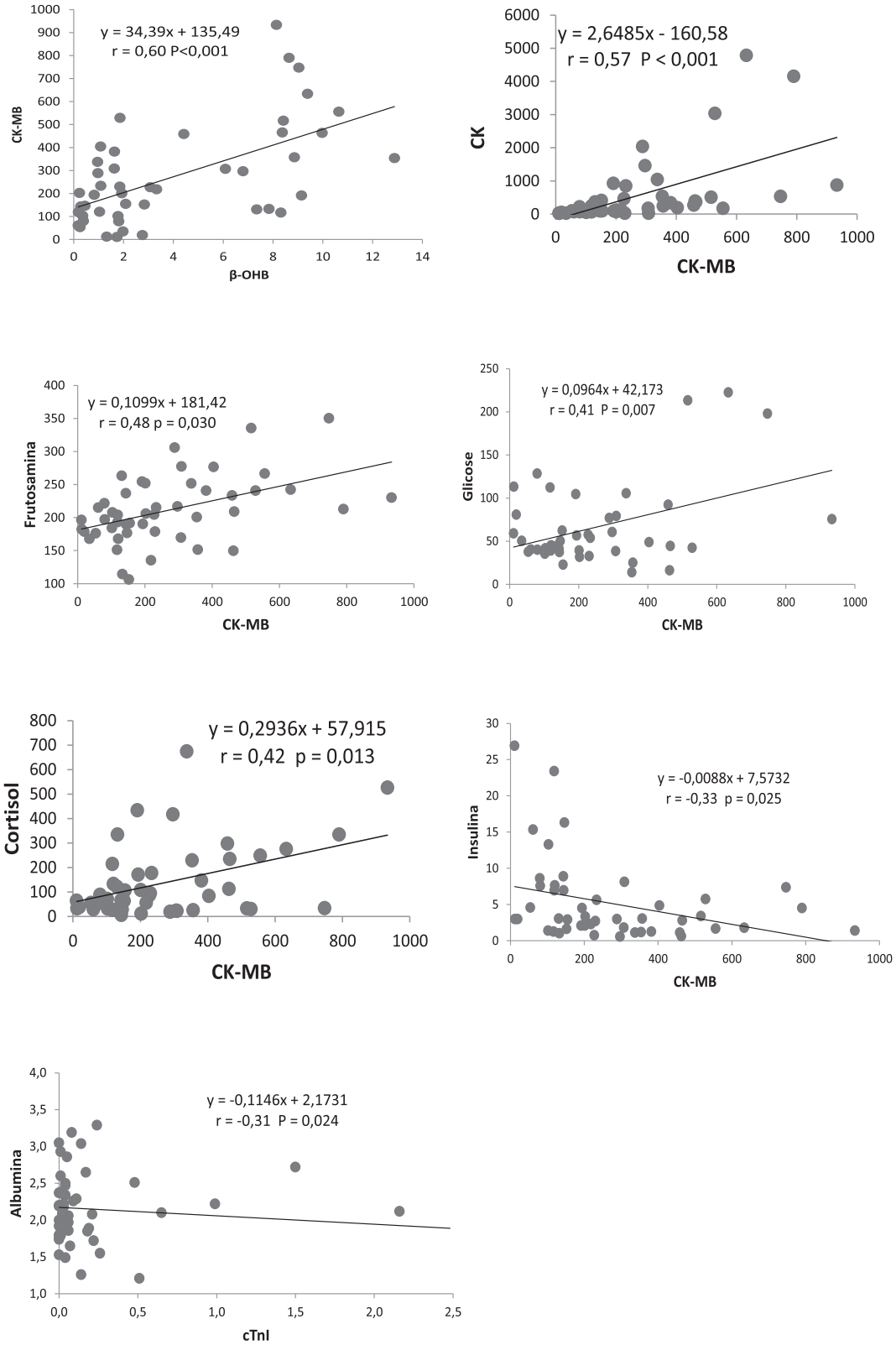

Fig. 1. Graphical representation of the relationship between indicators of muscular heart damage with metabolic parameters in goats with PT, expressed by the linearity equations, Pearson correlation coefficient, and respective level of significance.

(Al-Qudah, 2011; Gurdogan et al., 2014).

The higher glycemia condition in goats with PT is derived from the hormonal mechanisms described above, especially cortisol, and the action caused by the increase in serum concentrations of NEFA, which together can directly interfere with the glycemic state of these animals (Bassett et al., 1966; Ford et al., 1990; Henze et al., 1998; Souto et al., 2013). In agreement with Lima et al. (2012), Souto et al. (2013), and Macedo et al. (2015), the condition of hyperglycemia found in some

situations can also be considered as an indicator of poor prognosis in goats and sheep with PT, with high mortality rates in this glycemic state. The high mean values of fructosamine in goats with PT depict the chronicity of this state of hyperglycemia. This result is associated with the glycemic state occurring in the previous two weeks and not just the current condition (Enemark et al., 2004; Filipovic et al., 2011; Rook, 2000).

A significantly reduced serum concentration of insulin in animals affected with PT has been reported by Santos et al. (2011), Souto et al. (2013) and Macedo et al. (2015), who attributed this to the abnormalities in the energy profile, responsible for generating changes in insulin utilization by the cells, causing tissue resistance, negatively reflecting glucose consumption and oxidation. Duehlmeier et al. (2011) concluded that insulin has an important regulatory influence on lipolysis and ketogenesis, a possible insulin resistance in the ewes with higher risk for pregnancy toxemia may explain the increased plasma NEFA and β-OHB concentrations during late pregnancy.

For Jain et al. (2006) and Ormazabal et al. (2018), in humans, this mechanism of resistance, which alters the glucose balance, generating a condition of hyperglycemia, constitutes one of the main risk factors in the development of vascular complications, contributing to the increase in oxidative stress and endothelial cell dysfunction, which may induce the development of cardiac complications.

The stress condition in goats of the PT group can be verified by the cortisol concentration, this state of stress was also found by other authors in goats with PT (Ismail et al., 2008; Souto et al., 2013). For Bassett et al. (1966) and Schlumbohm and Harmeyer (2008) this effect, induced by the elevation in cortisol concentrations in the animals with PT, may interfere in the glycemic profile of these animals due to its gluconeogenic characteristics, associated with its inhibitory action to insulin interfering in the use of glucose by peripheral receptors.

According to Ford et al. (1990), working with ewes affected by PT, approximately 80% of the animals presented cortisol concentrations above 275.88 nmol/L, and further stated that this value may be an indicator of poor prognosis in advanced stages of the disease. In our study with goats with PT, these results were not similar, only 18% were above this value; however, taking into account the mean of the sick group, 34% of the goats presented concentrations above this mean. These results are similar to those reported by Ismail et al. (2008), who found concentrations below this value in most animals and defined the severity of the disease as moderate, however, the authors report that in the advanced stages a significant change occurs in the values of this hormone, due to the increase in the adrenal output or reduction in the excretion of cortisol by the liver.

Impairment in hepatic function can be observed by the high values of AST and GGT activity in the group of goats with PT, indicating strong lipid mobilization in hepatic metabolism, which can lead to hepatic lipidosis (Cal et al., 2009; Herdt, 2000). These results are similar to those found by Campos et al. (2010), Santos et al. (2011), and Souto et al. (2013), in sheep and goats with a clinical framework of PT. The elevation in AST activity may also be related to damage to muscle function, indicated by the mean values found in CK activity, which were significant in this group (622.04 U/L) compared to the control group (48.89 U/L) ($p = .0223$). According to Andrews et al. (1996) and Henze et al. (1998) this increase may occur due to the appearance of cardiac and skeletal muscle lesions in cases of PT, probably induced by lipid degeneration. This fact can be proved by the relation of CK-MB with CK ($r = 0.57$; $p < .001$).

5. Conclusion

The greater expression found in cardiac biomarkers in goats with PT, more evident in cTnI, was sufficient to evidence the cardiac injury caused by the disease. The use of these can be a good indicator of the prognosis of the disease. Although more studies are needed to ratify this proposal.

Declaration of Competing Interest

The authors declare no conflict of interest.

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