Ciência Animal Brasileira
Brazilian Animal Science

DOI: 10.1590/1809-6891v27e-83718E

e-ISSN 1809-6891
Veterinary Medicine | Research article

Effects of LPS-induced inflammation on leukogram and biochemical parameters in feedlot beef heifers

[Efeitos da inflamação induzida por LPS sobre o leucograma e os parâmetros bioquímicos em novilhas de corte confinadas]

Andressa Stein Maffi[1], Joao Alveiro Alvarado Rincón[2], Antônio Amaral Barbosa[1], Rutiele Silveira*[1], Eliza Rossi Komninou[1], Francisco Augusto Burkert Del Pino[1], Viviane Rohrig Rabassa[1], Cássio Cassal Brauner[1], Marcio Nunes Corrêa[1]

1 Universidade Federal de Pelotas (UFPEL), Pelotas, Brazil
2 Universidad de La Salle (UNISALLE), Yopal, Colombia
*corresponding author: silveirarutiele@gmail.com

Received: Aug 19, 2025. Accepted: May 29, 2026. Published: Jul 09, 2026. Editor: Luiz Augusto B. Brito

Abstract: Beef cattle in feedlot systems may develop diseases associated with endotoxin release, such as lipopolysaccharide (LPS). However, few studies have evaluated experimental acute endotoxemia in beef heifers. Therefore, this study aimed to evaluate the effects of LPS-induced inflammation on biochemical and leukogram parameters in feedlot beef heifers. Sixteen beef heifers were randomly assigned to two groups: the LPS group (n = 8), which received two intravenous doses of 0.5 µg/kg BW *Escherichia coli* LPS (O111:B4) administered with a 24-hour interval between injections, and the control group (CTR, n = 8), which received two intravenous doses of saline solution. Body temperature was measured using intravaginal digital thermometers for 8 hours after the first and 12 hours after the second injection. Blood samples were collected at 0, 4, 8, 24, 28, 32, and 72 hours in relation to the first challenge, for hematological analysis and evaluation of energy and lipid metabolism, protein profile, hepatic enzymes, minerals, and inflammatory markers. Data were analyzed using a repeated measures model including group, time, and group x time interaction, with significance declared at P ≤ 0.05. LPS administration induced an increase in body temperature, a leukocytosis characterized by neutrophilia and monocytosis and a decrease in paraoxonase-1 (PON1). These findings demonstrate that experimental, acute endotoxemia induces alterations predominantly associated with the acute inflammatory response in feedlot beef heifers.

Keywords: acute phase response; endotoxemia; immunometabolism; leukocytosis; PON1.

Resumo: Bovinos de corte em sistemas de confinamento podem desenvolver doenças associadas à liberação de endotoxinas como, por exemplo, o lipopolissacarídeo (LPS). No entanto, poucos estudos avaliaram a endotoxemia aguda experimental em novilhas de corte. Este estudo teve como objetivo avaliar os efeitos da inflamação induzida por LPS sobre os parâmetros bioquímicos e do leucograma em novilhas de corte confinadas. Dezesseis novilhas de corte foram distribuídas aleatoriamente em dois grupos: o grupo LPS (n = 8), que recebeu duas doses intravenosas de 0,5 µg/kg de peso corporal de LPS de *Escherichia coli* (O111:B4), administradas com um intervalo de 24 horas entre as injeções, e o grupo controle (CTR, n = 8), que recebeu duas doses intravenosas de solução salina. A temperatura corporal foi medida utilizando termômetros digitais intravaginais por 8 horas após a primeira e 12 horas após a segunda injeção. Amostras de sangue foram coletadas em 0, 4, 8, 24, 28, 32 e 72 horas em relação ao primeiro desafio, para análise hematológica e avaliação do metabolismo energético e lipídico,

Copyright ©. This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original article is properly cited.

perfil proteico, enzimas hepáticas, minerais e marcadores inflamatórios. Os dados foram analisados utilizando um modelo de medidas repetidas, incluindo grupo, tempo e a interação grupo x tempo, considerando significância quando P < 0,05. A administração de LPS induziu aumento na temperatura corporal, leucocitose, caracterizada por neutrofilia e monocitose, e redução da paraoxonase-1 (PON1). Esses achados demonstram que a endotoxemia aguda experimental induz alterações predominantemente associadas à resposta inflamatória aguda em novilhas de corte confinadas.

Palavras-chave: fase de resposta aguda; endotoxemia; imunometabolimo; leucocitose; PON1.

1. Introduction

Animal confinement systems have become a popular method for increasing efficiency and production in livestock. However, these intensive systems, commonly used in beef and dairy production, rely on high-concentrate diets. Despite these diets being a strategy to increase performance, when there is inadequate feeding management or insufficient adaptation, it often leads to a reduction in rumen pH, causing acidosis [1, 2], rumenitis, and the death of gram-negative bacteria, which increases lipopolysaccharide (LPS) concentrations in the gastrointestinal tract [3, 4].

Gastrointestinal LPS is the primary source of endotoxin absorption into the bloodstream [5]. This absorption occurs when cell junctions and intestinal mucosal transporters are disrupted, as during transcytosis mediated by lipid transporters [6]. Additionally, LPS can be absorbed through the ruminal wall when the rumen epithelium is damaged, a common occurrence in ruminal acidosis [1, 7]. In addition to ruminal acidosis, infectious diseases such as mastitis, metritis, endometritis, and pneumonia are other common sources of LPS, as gram-negative bacteria are the main cause of these diseases [8-10].

Regardless of the source, LPS is transported to the hepatic portal system. When blood levels of LPS exceed the liver's detoxification capacity, the endotoxin can enter peripheral circulation [11]. Immune cells, such as leukocytes, recognize LPS via toll-like receptor 4 (TLR4) and trigger an immune response by releasing pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-1 (IL-1), and tumor necrosis factor alpha (TNF-α) [12-14]. These cytokines decrease the production of negative acute-phase proteins, such as paraoxonase-1 (PON1) [15], causing pyrexia and altering metabolic processes depending on the LPS source [13, 16, 17]. These metabolic alterations include peripheral insulin resistance [17, 18], elevated glucagon levels [13], and skeletal muscle and adipose tissue catabolism [17-19]. PON1 is an enzyme associated with protection against oxidative stress, and reduced PON1 activity may indicate inflammatory or disease conditions. However, studies evaluating PON1 in cattle are still limited, particularly in beef cattle [15].

In addition to altering systemic metabolism and acute-phase protein synthesis, LPS-induced inflammation also promotes metabolic reprogramming in immune cells. During the immune response, immune cells shift their energy metabolism from oxidative phosphorylation to anaerobic glycolysis, a phenomenon known as the Warburg effect [20]. This metabolic shift rapidly provides ATP and metabolic intermediates required for the biosynthesis of inflammatory proteins. Consequently, nutrients and energy are redirected toward the immune system [16, 21], reducing the energy available for meat and milk production, and negatively affecting animal performance.

It is well established that the inflammatory response is associated with the release of anorexigenic compounds, which reduce feed intake through several pathways [22]. Consequently, inflammation may impair animal performance by reducing weight gain and feed efficiency, and by increasing the time required to reach slaughter weight, thereby negatively affecting production system productivity. Although some studies have evaluated the effects of inflammation in beef cattle, most have focused on productive performance, particularly weight gain, whereas few have

investigated its effects on inflammatory and oxidative stress biomarkers. Furthermore, while most studies evaluating LPS-induced inflammation have been conducted in rodent models, the metabolic and inflammatory responses may differ in ruminants. Therefore, this study aimed to evaluate the effects of LPS-induced inflammation on biochemical and leukogram parameters in feedlot beef cattle. We hypothesized that LPS-induced inflammation would alter leukogram parameters, leading to leukocytosis and reduced PON1 activity in feedlot beef cattle.

2. Material and methods

2.1 Experimental design

The experiment was approved by the Animal Ethics and Experimentation Committee of the Federal University of Pelotas (no. 9364-2018). The study was conducted on a commercial farm in São Lourenço do Sul, RS, Brazil. Sixteen healthy crossbreed beef heifers (Angus x Hereford), averaging 14 months of age, with body weight around 330 ± 16.9 kg, were housed in a feedlot.

The animals were selected 14 days before the start of the experimental period, when they were assigned to the experimental groups and had time to adapt to the diet and handling. Heifers were fed twice daily (7:00 am and 7:00 pm) with a total mixed ration (TMR) comprising maize silage, ground maize, and a mineral supplement with a forage-to-concentrate ratio of 60:40. However, the feed intake was not measured. Animals had unlimited access to fresh water. Diet chemical composition is given in Table 1.

Table 1. Chemical composition of the diet of beef heifers, submitted or not to challenge with LPS.

Chemical composition	Dry matter (%)
ADF[1]	25.74
NDF[2]	44.70
Lignin	4.40
Crude Protein	10.26
Degradable protein	9.57
Ethereal extract	5.35
Ashes	3.82
Calcium	0.22
Phosphorus	0.27

[1]Acid detergent fiber; [2] Neutral detergent fiber.

Heifers were randomly divided into two homogeneous groups: LPS group (LPS, n=8) was challenged with two intravenous (IV) 0.5 µg/kg of BW doses of *Escherichia coli* LPS (O111:B4, Sigma Aldrich®, Saint Louis, EUA) diluted in 2 mL saline solution with a 24-hour interval between administrations; while the control group (CTR, n=8) received two IV doses of 2 mL of saline solution in the same interval. The 0.5 µg/kg BW dose was chosen based on a previous study [13], which demonstrated that this concentration can induce an inflammatory response. The LPS solution was prepared prior to administration and maintained under refrigeration until use. Due to the low administration volume (2 mL), treatments were administered intravenously via direct jugular venipuncture. Following administration, animals were clinically monitored.

2.2 Blood collection, biochemical and leukogram analysis

Blood samples were collected by coccygeal venipuncture using a Vacutainer system (Vacutainer®, Becton Dickinson, Plymouth, UK). The samples were collected at 0 (before administration), 4, 8, 24, 28, 32, and 72 hours after the first administration. Because the second administration occurred 24 h after the first, the 28 h, 32 h, and 72 h sampling times corresponded to 4 h, 8 h, and 48 h after the second administration, respectively. Tubes containing clot activator

were used for serum collection, tubes containing sodium fluoride were used for plasma collection, and tubes containing EDTA were used for hematological analyses. Samples collected in clot activator and sodium fluoride tubes were centrifuged, aliquoted into microtubes, and stored at -20°C until further analysis.

Plasma aliquots were used to determine glucose and lactate concentrations. Serum concentrations of total protein, urea, albumin, cholesterol, high-density lipoprotein (HDL), phosphorus, calcium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were also analyzed. All analyses were performed using commercial kits (Labtest Diagnóstica®, Belo Horizonte, BR) and processed using an automatic biochemical analyzer (Labmax Plenno, Labtest Diagnóstica®, Belo Horizonte, BR). These analyses were run according to the manufacturer; intra-assay coefficients of variation (CV) ranged from 1.5 to 5.2 %, whereas inter-assay CV ranged from 2.3 to 8.7 %, depending on the metabolite. Serum globulin concentration was calculated by subtracting albumin from total protein concentrations, and the albumin:globulin ratio was subsequently determined, as described by Kaneko et al. [23].

PON1 activity was determined according to the protocol described by Browne et al. [24] and was performed using a spectrophotometer (Femto 200 plus®, São Paulo, BR). The intra- and inter-assay CV for PON1 analysis were below 5 % and 10 %, respectively.

The leukogram was analyzed in the BC2800 VET automatic equipment (Mindray, Schenzhen, CHN). Leukocyte cell differential was determined through blood smears stained with Fast Panoptic (Laborclin, Pinhais, BR) and counted through an optical microscope [25].

2.3 Body temperature evaluation

Body temperature was continuously recorded using intravaginal digital data loggers (iButton®, Thermochron, Whitewater, USA), starting at the moment of the first injection (hour 0). Temperatures were logged automatically every 30 minutes. On the first day, data collection continued for up to 8 hours post-injection. On the second day, temperatures were recorded for up to 12 hours post-injection, until body temperature stabilization. In addition to temperature monitoring, animals were clinically evaluated at each sampling time point for heart rate, respiratory rate, ruminal motility, and behavioral indicators of discomfort or systemic illness.

2.4 Statistical analysis

Data were analyzed through repeated measures ANOVA in randomized design, considering groups (LPS and CTR), time (0, 4, 8, 24, 28, 32, and 72 hours), interaction between group and time, and random (individual) effects. These analyses were performed by NCSS 2005 (NCSS. Number Cruncher Statistical Systems. Kaysville, Utah) using the following model:

$Yijkl = \mu + Mj + Tk + MTjk + cl(bi) + eijkl,$

Where: Yijkl is the dependent continuous variable; μ is the overall mean; Mj is the group fixed effect (j = LPS vs Control); Tk is the time fixed effect (0,4, 8, 24, 28, 32, and 72); MTjk in the group interaction between group and time; cl(bi) is the individual random effect; and eijkl is the residual error. Statistical significance was considered at $P \leq 0.05$, and a trend was considered when $0.05 < P \leq 0.10$.

3. Results

The LPS challenge increased body temperature (Figures 1 and 2). After the first administration, animals in the LPS group had higher body temperatures than those in the CTR group ($P = 0.05$). The challenged group presented body temperatures above the physiological

range (38.5-39.5°C) after LPS injection. In the second LPS administration (Figure 2), an acute temperature elevation was observed two hours after injection, returning to the normal range in the subsequent 60 minutes (P < 0.05).

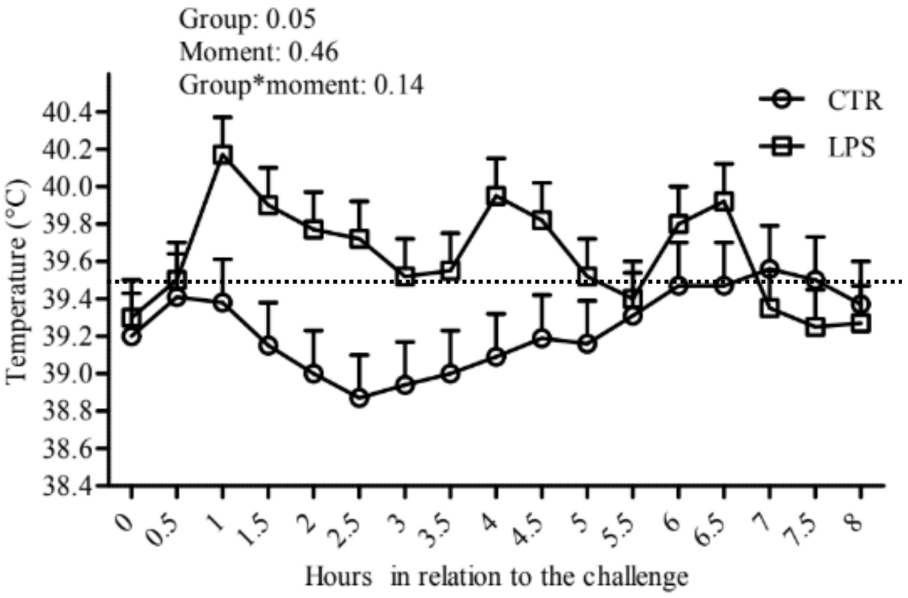

Figure 1. Body temperature of beef heifers after the first challenge with lipopolysaccharide (LPS) (0.5 µg LPS / kg body weight) or saline solution (CTR). The dotted line indicates the upper physiological temperature limit (39.5°C).

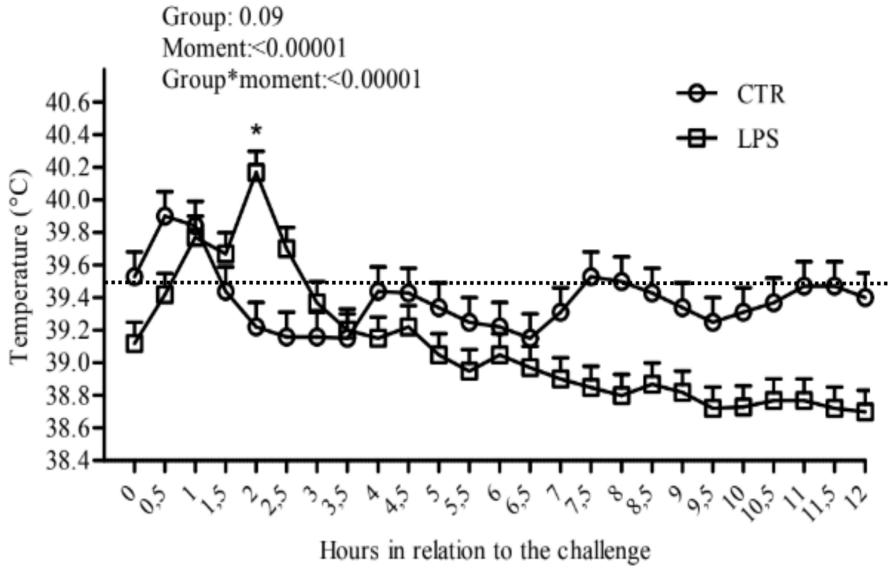

Figure 2. Body temperature of beef heifers after the second challenge with lipopolysaccharide (LPS) (0.5 µg LPS / kg body weight) or saline solution (CTR). *Statistical difference between control and LPS group P ≤ 0.05 at hour 2. The dotted line indicates the upper physiological temperature limit (39.5°C).

Regarding the leukogram, the LPS group had a higher leukocyte concentration compared to the CTR group (P = 0.02). Similarly, neutrophil (P < 0.01) and monocyte counts (P = 0.02) were higher in the LPS group. No differences were observed for lymphocytes, band neutrophils, or eosinophils between groups (P > 0.05; Table 2). No differences were observed between moments, and no interaction between group and moment was detected (P > 0.10).

Table 2. Leukocyte Parameters of Beef Heifers Challenged with Lipopolysaccharide (LPS) or Saline Solution (CTR).

Parameter	Groups				*P* -value		
	CTR		LPS				
	Mean	SE	Mean	SE	G	M	G*M
Total Leukocytes (x10³/µL)	9.51	0.21	12.68	0.79	0.02	0.17	0.76
Lymphocytes (x10³/µL)	6.19	0.26	6.15	0.54	0.44	0.70	0.93
Neutrophils (x10³/µL)	2.79	0.57	5.17	0.38	<0.01	0.46	0.25
Band Neutrophils (x10³/µL)	0.46	0.10	0.41	0.07	0.67	0.87	0.95
Eosinophils (x10³/µL)	0.30	0.09	0.32	0.05	0.58	0.68	0.66
Monocytes (x10³/µL)	0.52	0.10	1.04	0.13	0.02	0.32	0.91

G: group; M: moment of collect; G*M: interaction between group and moment; SE: Standard Error of the mean; different letters on the same line indicate statistical difference.

Table 3 shows the biochemical parameters evaluated in both groups. Animals challenged with LPS showed lower serum PON1 levels than the CTR group ($P < 0.01$). Furthermore, a tendency was observed for animals challenged with LPS to exhibit lower urea levels in serum ($P = 0.06$) and higher ALP levels ($P = 0.06$). Concerning other metabolites, no statistical differences or trends were observed between groups ($P > 0.10$). The parameters showing a significant effect of moment are presented in Supplementary Table 1. No interaction between group and moment was observed ($P > 0.10$).

Table 3. Biochemical Parameters of Beef Heifers Challenged with Lipopolysaccharide (LPS) or Saline Solution (CTR).

Parameter	Groups				*P* -value		
	CTR		LPS				
	Mean	SE	Mean	SE	G	M	G*M
Total protein (g/dL)	6.83	0.08	6.88	0.10	0.72	0.45	0.51
Albumin (g/dL)	2.52	0.06	2.46	0.05	0.44	<0.01	0.22
Globulin (g/dL)	4.31	0.10	4.41	0.09	0.45	<0.01	0.29
Albumin:globulin (g/dL)	0.61	0.02	0.57	0.01	0.19	<0.01	0.11
Urea (mg/dL)	22.35	0.72	20.39	0.75	0.06	<0.01	0.91
Paraoxonase-1 (U/mL)	99.95	1.82	88.18	3.10	<0.01	0.62	0.49
ALT (U/L)	27.70	1.32	27.05	0.96	0.69	0.01	0.97
AST (U/L)	77.66	4.14	79.00	2.96	0.79	0.36	0.72
ALP (U/L)	103.96	4.39	123.94	10.39	0.06	0.06	0.64
Cholesterol (mg/dL)	69.90	3.84	66.68	3.50	0.49	<0.01	0.54
HDL (mg/dL)	50.25	2.39	45.84	1.88	0.15	0.15	0.45
Glucose (mg/dL)	87.46	2.69	86.25	2.79	0.88	<0.01	0.12
Lactate (mmol/L)	0.35	0.03	0.30	0.02	0.18	<0.01	0.51
Phosphorus (mg/dL)	6.90	0.22	7.23	0.29	0.28	<0.01	0.11
Calcium (mg/dL)	9.20	0.12	9.09	0.14	0.45	<0.01	0.76

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; HDL: high-density lipoprotein; G: group; M: moment of collect; G*M: interaction between group and moment; SE: Standard Error of the mean.

4. Discussion

The LPS-challenged group exhibited a prolonged febrile response following the first administration and a shorter febrile episode after the second administration. This biphasic pattern is consistent with the inflammatory mechanisms triggered by LPS, in which cytokines such as IL-1, IL-6, and TNF-α induce fever by acting on hypothalamic centers, and with compensatory mechanisms mediated by the hypothalamic-pituitary-adrenal axis, which promotes the release of vasopressin and other antipyretic mediators to modulate body temperature [26-29]. Moreover, the magnitude and duration of pyrexia are closely related to the LPS administrations [30-32]. Fever is a hallmark clinical sign in most infectious diseases and represents an evolutionarily conserved defense mechanism that impairs pathogen replication and enhances host immune responses [33, 34].

In addition to pyrexia, LPS administration induced leukocytosis characterized by neutrophilia and monocytosis, classical features of the acute-phase response to endotoxemia [35, 36]. Upon recognition of LPS by TLR4 on antigen-presenting cells, an inflammatory cascade is initiated, leading to the production of pro-inflammatory cytokines that stimulate bone marrow leukopoiesis and mobilize neutrophils and monocytes into circulation [37-40]. Neutrophils serve as the first line of defense by targeting invading pathogens, while monocytes contribute to tissue repair and modulation of the inflammatory response [41-43]. The hematological changes observed in this study reflect a robust activation of innate immune mechanisms designed to rapidly neutralize endotoxins and protect host tissues.

Corroborating the systemic inflammatory response, a significant decrease in serum PON1 activity was observed after LPS administration. PON1, a liver enzyme associated with HDL particles, protects cellular membranes and circulating lipids from oxidative stress, thus preventing apoptosis and preserving endothelial integrity [44-46]. During acute inflammation, hepatic synthesis of negative acute-phase proteins, such as PON1, is suppressed [47-49]. As PON1 activity is closely linked to lipid metabolism, reductions in PON1 are frequently accompanied by decreases in HDL and total cholesterol levels [8, 50-52]. However, in the present study, no differences in lipid metabolites were observed.

In terms of energy metabolism, despite the inflammatory challenge, no significant effect on blood glucose or lactate concentrations was observed, consistent with previous findings [13, 17]. Interestingly, urea levels tended to decrease after the LPS challenge. Although the mechanisms involved were not investigated in the present study, this response may be related to reduced feed intake associated with sickness behavior and fever induced by endotoxemia, resulting in lower nitrogen availability for hepatic urea synthesis. Furthermore, the inflammatory response may alter hepatic metabolism and impair urea cycle activity, thereby contributing to reduced circulating urea concentrations [53].

Regarding liver function, no significant differences in serum ALT and AST activities were detected between groups, suggesting that the hepatocytes maintained their capacity to detoxify circulating endotoxins during the short exposure period. However, ALP levels tended to be higher post-challenge, suggesting early hepatic stress [54]. In addition, no significant effects on blood calcium and phosphorus concentrations were observed following LPS administration, suggesting that the acute inflammatory stimulus did not severely disrupt mineral homeostasis.

Our results demonstrate that the LPS challenge triggered classical hallmarks of an acute-phase response, including pyrexia, leukocytosis, reduced PON1 activity, and alterations in lipid and protein metabolism, without causing significant disturbances in mineral balance or inducing

significant hepatic injury. These findings highlight the sensitivity of inflammatory biomarkers to short-term endotoxemic stimuli, and reinforce the capacity of confined beef heifers to maintain metabolic homeostasis under inflammatory challenges.

5. Conclusion

The administration of two doses of LPS, with a 24-hour interval, induced a systemic inflammatory response in confined beef heifers, characterized by fever, leukocytosis with neutrophilia and monocytosis, and a significant reduction in serum PON1 activity. These findings demonstrate that LPS-induced inflammation is a useful experimental model for evaluating biochemical and leukogram alterations associated with acute systemic inflammation in beef cattle.

Conflict of interest statement

The authors declare no conflict of interest.

Data availability statement

The complete dataset supporting the findings of this study is available upon request from the Research, Teaching and Extension Center in Livestock - Nupeec Hub Ufpel. The data are not publicly available due to confidentiality restrictions related to the origin of the animals, which were obtained from a partner slaughterhouse, in accordance with institutional agreements and ethical standards.

Author contributions

Conceptualization: Corrêa M.N., Brauner C.C. Data curation: Maffi A.S., Rincon J.A.A., Barbosa A.A., Silveira R. Formal analysis: Maffi A.S., Silveira R. Funding acquisition: Corrêa M.N., Del Pino F.A.B., Brauner C.C. Investigation: Maffi A.S., Rincon J.A.A., Barbosa A.A., Silveira R. Methodology: Corrêa M.N., Brauner C.C., Del Pino F.A.B., Rabassa V.R. Project administration: Corrêa M.N., Brauner C.C. Resources: Corrêa M.N., Del Pino F.A.B., Brauner C.C. Supervision: Komninou E.R., Rabassa V.R., Del Pino F.A.B., Corrêa M.N., Brauner C.C. Validation: Corrêa M.N., Brauner C.C. Writing (original draft): Maffi A.S. Visualization: Maffi A.S., Silveira R. Writing (review and editing): Silveira R., Komninou E.R., Rabassa V.R., Del Pino F.A.B.

Generative AI use statement

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to assist with translation into English, language editing, improvement of clarity and readability, and refinement of responses to peer reviewers. After using this tool, the authors reviewed and edited the content appropriately. The authors assume full responsibility for the content of the publication.

References

1. Rodríguez-Lecompte JC, Kroeker AD, Ceballos-Márquez A, Li S, Plaizier J, Gomez, DE. Evaluation of the systemic innate immune response and metabolic alterations of nonlactating cows with diet-induced subacute ruminal acidosis. J. Dairy Sci. 2014; 97:7777-7787. Available at: https://doi.org/10.3168/jds.2014-8319

2. Zhao C, Liu G, Li X et al. Inflammatory mechanism of Rumenitis in dairy cows with subacute ruminal acidosis. BMC Vet. Res. 2018; 14(135). Available at: https://doi.org/10.1186/s12917-018-1463-7

3. Gozho GN, Krause DO, Plaizier JC. Ruminal Lipopolysaccharide Concentration and Inflammatory Response During Grain-Induced Subacute Ruminal Acidosis in Dairy Cows. J. Dairy Sci. 2007; 90:856-866. Available at: https://doi.org/10.3168/jds.S0022-0302(07)71569-2

4. Plaizier JC, Mesgaran MD, Derakhshani H, et al. Review: Enhancing gastrointestinal health in dairy cows. Anim. 2018; 12(s2):s399-s418. Available at: https://doi.org/10.1017/S1751731118001921

3. Munford R.S. Endotoxemia-menace, marker, or mistake? J. Leukoc. Biol. 2016; 100:687-698. Available at: https://doi.org/10.1189/jlb.3RU0316-151R

4. Eckel EF, Ametaj BN. Invited review: Role of bacterial endotoxins in the etiopathogenesis of periparturient diseases of transition dairy cows. J. Dairy Sci. 2016; 99:5967-5990. Available at: https://doi.org/10.1017/S1751731118001921

5. Yáñez-Ruiz DR, Abecia L, Newbold CJ. Manipulating rumen microbiome and fermentation through interventions during early life: a review. Front. Microbiol. 2015; 6. Available at: https://doi.org/10.3389/fmicb.2015.01133

6. Santos JE, Cerri RL, Ballou M, et al. Effect of timing of first clinical mastitis occurrence on lactational and reproductive performance of Holstein dairy cows. Anim. Reprod. Sci. 2004; 80:31-45. Available at: https://doi.org/10.1016/S0378-4320(03)00133-7

7. Huzzey JM, Veira DM, Weary DM, et al. Prepartum Behavior and Dry Matter Intake Identify Dairy Cows at Risk for Metritis. J. Dairy Sci. 2007; 90:3220-3233. Available at: https://doi.org/10.3168/jds.2006-807

8. Sheldon IM, Owens SE. Postpartum uterine infection and endometritis in dairy cattle. Anim. Reprod. 2017; 14:622-629. Available at: https://doi.org/10.21451/1984-3143-AR1006

9. Yao Z, Mates JM, Cheplowitz, AM., et al. Blood-Borne Lipopolysaccharide Is Rapidly Eliminated by Liver Sinusoidal Endothelial Cells via High-Density Lipoprotein. J. Immunol. 2016; 197(6):2390-2399. Available at: https://doi.org/10.4049/jimmunol.1600702

10. Hoeben B, Burvenich C, Trevisi E, et al. Role of endotoxin and TNF- α in the pathogenesis of experimentally induced coliform mastitis in periparturient cows. J. Dairy Res. 2000; 67:503-514. Available at: https://doi.org/10.1017/s0022029900004489

11. Waldron MR, Nishida T, Nonnecke BJ, et al. Effect of Lipopolysaccharide on Indices of Peripheral and Hepatic Metabolism in Lactating Cows. J. Dairy Sci. 2003; 86:3447-3459. Available at: https://doi.org/10.3168/jds.S0022-0302(03)73949-6

12. Lecchi C, Avallone G, Giurovich M, et al. Extra hepatic expression of the acute phase protein alpha 1-acid glycoprotein in normal bovine tissues. Vet. J. 2009; 180:256-258. Available at: https://doi.org/10.1016/j.tvjl.2007.12.027

13. Hamar P. A New Role of Acute Phase Proteins: Local Production Is an Ancient, General Stress-Response System of Mammalian Cells. Int. J. Mol. Sci. 2022; 23(6):2972. Available at: https://doi.org/10.3390/ijms23062972

14. Kvidera SK, Horst EA, Abuajamieh M, et al. Glucose requirements of an activated immune system in lactating Holstein cows. J. Dairy Sci. 2017; 100:2360-2374. Available at: https://doi.org/10.3168/jds.2016-12001

15. Horst EA, Kvidera SK, Dickson MJ, et al. Effects of continuous and increasing lipopolysaccharide infusion on basal and stimulated metabolism in lactating Holstein cows. J. Dairy Sci. 2019; 102:3584-3597. Available at: https://doi.org/10.3168/jds.2018-15627

16. Bradford BJ, Mamedova LK, Minton JE, et al. Daily Injection of Tumor Necrosis Factor-α Increases Hepatic Triglycerides and Alters Transcript Abundance of Metabolic Genes in Lactating Dairy Cattle. J. Nutr. 2009; 139:1451-1456. Available at: https://doi.org/10.3945/jn.109.108233

17. Mcguinness OP. Defective Glucose Homeostasis During Infection. Annu. Rev. Nutr. 2005; 25;9-35. Available at: https://doi.org/10.1146/annurev.nutr.24.012003.132159

18. Palsson-mcdermott EM. The Warburg effect then and now: From cancer to inflammatory diseases. Bioessays. 2013; 35:1-9. Available at: https://doi.org/10.1002/bies.201300084

19. Johnson MD, Plantinga TS, Van de Vosse E, et al. Cytokine Gene Polymorphisms and the Outcome of Invasive Candidiasis: A Prospective Cohort Study. Clin. Infect. Dis. 2012; 54:502-510. Available at: https://doi.org/10.1093/cid/cir827

20. Gouvêa VN, Cooke R, Marques RS. Impacts of stress-induced inflammation on feed intake of beef cattle. Front. Anim. Sci. 2022; 3:962748. Available at: https://doi.org/10.3389/fanim.2022.962748

21. Kaneko JJ, Harvey JW, Bruss ML, editors. Clinical biochemistry of domestic animals. 6th ed. San Diego: Academic Press; 2008.

22. Browne RW, Koury ST, Marion S, Wilding G, Muti P, Trevisan M. Accuracy and biological variation of human serum paraoxonase 1 activity and polymorphism (Q192R) by kinetic enzyme assay. Clin Chem. 2007; 53(2):310-7. Available at: https://doi.org/10.1373/clinchem.2006.074559

23. Thrall M. Hematologia e bioquímica clínica veterinária. ROCA, São Paulo. 2007.

24. Giusti-Paiva A, Branco LGS, de Castro M, et al. Role of nitric oxide in thermoregulation during septic shock: involvement of vasopressin. Pflügers Arch. 2003; 447:175-180. Available at: https://doi.org/10.1007/s00424-003-1164-2

25. Roth J, Rummel C, Barth SW, et al. Molecular Aspects of Fever and Hyperthermia. Immunol. Allergy Clin. North Am. 2009; 29:229-245. Available at: https://doi.org/10.1016/j.iac.2009.02.005

26. Xiao HB, Wang CR, Liu ZK, Wang JY. LPS induces pro-inflammatory response in mastitis mice and mammary epithelial cells: Possible involvement of NF-κB signaling and OPN. Pathol Biol (Paris). 2015; 63(1):11-16. Available at: https://doi.org/10.1016/j.patbio.2014.10.005

27. Peñailillo AK, Sepulveda MA, Palma CJ, et al. Haematological and blood biochemical changes induced by the administration of low doses of *Escherichia coli* lipopolysaccharide in rabbits. Arch. Med. Vet. 2016; 48:315-320. Available at: https://doi.org/10.4067/S0301-732X2016000300012

28. Steiger M, Senn M, Altreuther G, et al. Effect of a prolonged low-dose lipopolysaccharide infusion on feed intake and metabolism in heifers. J. Anim. Sci. 1999; 77:2523-2532. Available at: https://doi.org/10.2527/1999.7792523x

29. Rudaya AY, Steiner AA, Robbins JR, et al. Thermoregulatory responses to lipopolysaccharide in the mouse: dependence on the dose and ambient temperature. American Am. J. Physiol. Regul. Integr. Comp. Physiol. 2005; 289(5):R1244-R1252. Available at: https://doi.org/10.1152/ajpregu.00370.2005

30. Grabbe N, Kaspers B, Ott D, et al. Neurons and astrocytes of the chicken hypothalamus directly respond to lipopolysaccharide and chicken interleukin-6. J Comp Physiol B. 2020; 190:75-85. Available at: https://doi.org/10.1007/s00360-019-01249-1

31. Ning LT, Dong GZ, Ao C, et al. Effects of continuous low dose infusion of lipopolysaccharide on inflammatory responses, milk production and milk quality in dairy cows. J. Anim. Physiol. Anim. Nutr. 2018; 102(1):e262-e269. Available at: https://doi.org/10.1111/jpn.12737

32. Brandão AP, Cooke RF, Schubach KM, Marques RS. Physiologic and innate immunity responses to bacterial lipopolysaccharide administration in beef heifers supplemented with OmniGen-AF. Anim. 2019; 13(1):153-160. Available at: https://doi.org/10.1017/S1751731118001441

33. Pils MC, Pisano F, Fasnacht N, et al. Monocytes/macrophages and/or neutrophils are the target of IL10 in the LPS endotoxemia model. Eur. J. Immunol. 2010; 40(2):443-448. Available at: https://doi.org/10.1002/eji.200939592

34. Radzyukevich YV, Kosyakova NI, Prokhorenko IR. Participation of monocyte subpopulations in progression of experimental endotoxemia (EE) and systemic inflammation. J. Immunol. Res. 2021; (1):1762584. Available at: https://doi.org/10.1155/2021/1762584

35. Chávez-Sánchez L, Madrid-Miller A, Chávez-Rueda K, et al. Activation of TLR2 and TLR4 by minimally modified low-density lipoprotein in human macrophages and monocytes triggers the inflammatory response. Hum. Immunol. 2010; 71(8):737-744. Available at: https://doi.org/10.1016/j.humimm.2010.05.005

36. Nijland R, Hofland T, Van Strijp JA. Recognition of LPS by TLR4: potential for anti-inflammatory therapies. Mar. Drugs. 2014; 12(7):4260-4273. Available at: https://doi.org/10.3390/md12074260

37. Kushner I, Mackiewicz A. The acute phase response: an overview. In: Acute Phase Proteins Molecular Biology, Biochemistry, and Clinical Applications. crc Press. 2020; p. 3-19.

38. Zamyatina A, Heine H. Lipopolysaccharide recognition in the crossroads of TLR4 and caspase-4/11 mediated inflammatory pathways. Front. Immunol. 2020; 11:585146. Available at: https://doi.org/10.3389/fimmu.2020.585146

39. Selders GS, Fetz AE, Radic MZ, Bowlin GL. An overview of the role of neutrophils in innate immunity, inflammation and host-biomaterial integration. Regen. Biomater. 2017; 4(1):55-68. Available at: https://doi.org/10.1093/rb/rbw041

40. Fine N, Tasevski N, McCulloch CA, et al. The neutrophil: constant defender and first responder. Front. Immunol. 2020; 11:571085. Available at: https://doi.org/10.3389/fimmu.2020.571085

41. Kraus RF, Gruber MA. Neutrophils-from bone marrow to first-line defense of the innate immune system. Front. Immunol. 2021; 12:767175. Available at: https://doi.org/10.3389/fimmu.2021.767175

42. Oda MN, Bielicki JK, Ho TT, et al. Paraoxonase 1 overexpression in mice and its effect on high-density lipoproteins. Biochem. Biophys. Res. Commun. 2002; 290(3):921-927. Available at: https://doi.org/10.1006/bbrc.2001.6295

43. Sentí M, Tomás M, Fitó M, et al. Antioxidant paraoxonase 1 activity in the metabolic syndrome. J. Clin. Endocrinol. Metab. 2003; 88(11):5422-5426. Available at: https://doi.org/10.1210/jc.2003-030648

44. Kulka M. A review of paraoxonase 1 properties and diagnostic applications. Pol. J. Vet. Sci. 2016; 19(1):225-232. Available at: https://doi.org/10.1515/pjvs-2016-0028

45. Tietge UJF, Maugeais C, Cain W, et al. Overexpression of Secretory Phospholipase A 2 Causes Rapid Catabolism and Altered Tissue Uptake of High Density Lipoprotein Cholesteryl Ester and Apolipoprotein A-I. J. Biol. Chem. 2000; 275:10077-10084. Available at: https://doi.org/10.1074/jbc.275.14.10077

46. Curcic S, Holzer M, Frei R, et al. Neutrophil effector responses are suppressed by secretory phospholipase A2 modified HDL. Biochim. Biophys. Acta - Mol. Cell Biol. Lipids. Available at: https://doi.org/10.1016/j.bbalip.2014.11.010

47. Kükürt A, Gelen V. Paraoxonase 1 in cattle health and disease. In Cattle Diseases-Molecular and Biochemical Approach. IntechOpen. 2023. Available at: https://doi.org/10.5772/intechopen.110844

48. Diez-Fraile A, Meyer E, Duchateau L, Burvenich C. L-selectin and β2-integrin expression on circulating bovine polymorphonuclear leukocytes during endotoxin mastitis. J. Dairy Sci. 2003; 86:2334-2342. Available at: https://doi.org/10.3168/jds.S0022-0302(03)73826-0

49. Catapano AL, Pirillo A, Bonacina F, Norata GD. HDL in innate and adaptive immunity. Cardiovasc. Res. 2014; 103(3):372-383. Available at: https://doi.org/10.1093/cvr/cvu150

50. Cervellati C, Vigna GB, Trentini A, et al. Paraoxonase-1 activities in individuals with different HDL circulating levels: Implication in reverse cholesterol transport and early vascular damage. Atherosclerosis. 2019; 285:64-70. Available at: https://doi.org/10.1016/j.atherosclerosis.2019.04.218

51. Cruzat V, Rogero MM, Keane KN, et al. Glutamine: Metabolism and Immune Function, Supplementation and Clinical Translation. Nutrients, 2018; 10(11):1564. Available at: https://doi.org/10.3390/nu10111564

52. Fernandez NJ, Kidney BA. Alkaline phosphatase: beyond the liver. Vet. Clin. Pathol. 2007; 36(3):223-233. Available at: https://doi.org/10.1111/j.1939-165X.2007.tb00216.x