

Research Paper



Clinical, Blood Gas, Electrolyte, and Acid–Base Changes Following Experimental Myocardial Infarction in Sheep : Characterization of a Translational Large-Animal Model

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Citation Mokhber-Dezfouli M, Najd Ghahremani A, Dehghan MM, Pedram MS, Sabetzadeh N, Barzegar F. Clinical, Blood Gas, Electrolyte, and Acid–Base Changes Following Experimental Myocardial Infarction in Sheep : Characterization of a Translational Large-Animal Model. *Journal of Translational Regenerative Medicine*. 2027; 2:e254884. <http://dx.doi.org/10.32598/JTRM.2.1029>

doi <http://dx.doi.org/10.32598/JTRM.2.1029>

ABSTRACT

Background: Myocardial infarction (MI), commonly known as a heart attack, is a major manifestation of cardiovascular disease and a leading cause of death. Characterizing the pathophysiological consequences of MI in an appropriate animal model is essential for translational research. Therefore, this study investigated changes in clinical signs, arterial blood gases, electrolyte concentrations, and acid–base parameters 24 hours after experimentally induced MI in sheep to further characterize this large-animal model for translational research.

Methods: Six healthy male sheep were included in this experimental study. After confirmation of health status, myocardial infarction (MI) was induced through left lateral thoracotomy and ligation of a lateral branch of the left anterior descending (LAD) coronary artery. Clinical cardiovascular, respiratory, and general findings were recorded and scored, and arterial blood was collected from the auricular artery for blood gas and electrolyte analysis before surgery and 24 hours after MI induction.

Results: Compared with baseline, heart rate and respiratory rate increased significantly 24 hours after MI induction. Significant changes were also observed in heart rhythm, heartbeat intensity, heart and respiratory sounds, mucous membrane appearance, appetite, and general physical condition. Tachycardia, tachypnea, reduced heartbeat intensity, irregular cardiac rhythm, additional heart sounds, predominantly crackles on respiratory auscultation, mucosal hyperemia, reduced appetite, and depressed or withdrawn behavior were observed. Arterial blood analysis showed significant decreases in PO_2 , $SatO_2$, base excess (BE), and K^+ , as well as significant increases in PCO_2 , Na^+ , Cl^- , and anion gap.

Conclusion: Experimental MI in sheep is associated with significant cardiopulmonary and biochemical changes 24 hours after induction. The reduced BE and increased anion gap indicate a shift toward increased metabolic acid burden, accompanied by a significant rise in arterial PCO_2 . Since arterial pH remained unchanged, these findings should not be interpreted as overt mixed metabolic and respiratory acidemia.

Keywords: Sheep, Myocardial infarction (MI), Arterial blood gas, Electrolytes, Acid-base balance, Clinical signs

Article info:

Received: 10 Aug 2026

Accepted: 28 Dec 2026

Publish: 02 Jan 2027

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Highlights

- Sheep are a clinically relevant large-animal model for translational cardiovascular research.
- Significant changes in clinical signs, arterial blood gases, electrolytes, and acid-base variables were observed 24 hours after MI induction in sheep.
- The post-MI acid-base profile was characterized by decreased BE and increased anion gap, accompanied by increased arterial PCO₂, with no significant change in arterial pH.

Plain Language Summary

The sheep heart shares important physiological features with the human heart, making sheep useful for studying myocardial infarction (MI). In six healthy sheep, MI was induced surgically by ligating a branch of a major coronary artery. Clinical findings and arterial blood samples were evaluated before surgery and again 24 hours later. After infarction, the sheep developed faster and more irregular heartbeats, faster breathing, crackling lung sounds, and reduced appetite. Blood oxygen levels decreased, while carbon dioxide increased. Changes in base excess (BE) and the anion gap indicated a shift in acid-base balance, although arterial pH did not significantly change. These findings help characterize the early systemic response to MI in a translational large-animal model.

Introduction

Cardiovascular diseases are a leading cause of mortality worldwide and impose substantial economic, social, and health burdens [1]. Myocardial infarction (MI), commonly known as a heart attack, is a major manifestation of cardiovascular disease and an important cause of death [2]. Although MI has been recognized mainly as a fatal event diagnosed at autopsy, major advances have been made in understanding its pathophysiology, diagnosis, and treatment [3]. MI results from prolonged reduction or interruption of coronary blood flow, leading to irreversible myocardial injury. The infarcted region undergoes necrosis, microvascular damage, and edema, followed by reparative scar formation [4]. Replacement of damaged myocardium by scar tissue can impair ventricular function and increase the workload on the remaining viable myocardium [5].

Developing an animal model that adequately reproduces MI pathophysiology is challenging. Large animal models are particularly valuable when their cardiac anatomy and physiology are similar to those of human models. Sheep are suitable to be used in preclinical cardiovascular research because several features of myocardial structure and function, including the predominant beta-myosin heavy-chain isoform, cardiomyocyte contraction-relaxation kinetics, calcium handling, heart rate, and systemic blood pressure, resemble those in humans [6, 7]. Consequently, ovine models have been used to

study MI and to evaluate cardiac responses and potential therapies under conditions that may offer greater translational relevance than small animal models [8].

Experimental MI can be induced using several approaches, including coronary artery occlusion, balloon-based techniques, pharmacological induction, coronary embolization, and cryoinjury, each with specific advantages and limitations [9]. Surgical coronary artery ligation requires thoracotomy but offers direct visualization of the target vessel and ischemic territory, reproducibility, and a pathophysiological sequence of ischemia that resembles coronary occlusion in humans. Accordingly, coronary ligation remains a widely used method to induce experimental MI [10].

MI is evaluated using electrocardiographic (ECG) imaging methods [11], such as echocardiography and magnetic resonance imaging [12], and cardiac biomarkers such as troponins [13]. Clinical assessment also provides important information about the systemic consequences of acute cardiac injury. Arterial blood gas analysis can help evaluate cardiopulmonary status and the clinical course of patients with cardiovascular disease [14]. In heart failure, use of arterial blood gas analysis is associated with reduced hospital readmission based on observational data [15]. Electrolyte disturbances are common in acute MI and may be associated with adverse outcomes and mortality [16]. Characterizing these physiological changes in translational animal models may therefore improve understanding of the systemic response to MI.

Characterizing the pathophysiological consequences of MI in an appropriate animal model is important for translational research. Because cardiovascular dysfunction can secondarily affect respiratory function, tissue oxygenation, acid-base status, and electrolyte balance, simultaneous evaluation of clinical findings, arterial blood gases, and electrolytes may provide a more integrated assessment of the early response to MI.

To our knowledge, comprehensive evaluation of clinical signs together with arterial blood gases, electrolytes, and acid-base variables is limited in ovine MI models. The present study therefore investigated changes in these parameters 24 hours after experimental MI induced by ligation of a lateral branch of the left anterior descending (LAD) artery in sheep, to further characterize this translational large-animal model.

Materials and Methods

Study design and samples

We included 6 healthy male sheep with a mean body weight of 32.33 ± 0.71 kg from the Faculty of Veterinary Medicine, University of Tehran, Iran. Housing and feeding conditions were standardized throughout the study. Animals received two daily portions of a total mixed ration containing high-quality hay, stubble, silage, and concentrate, with free access to drinking water. Before enrollment, all animals underwent clinical and paraclinical assessment, including blood and fecal testing and echocardiography, to confirm their health status. The sheep were transferred to the surgical unit 48 hours before MI induction to allow acclimatization and reduce transportation-related stress. Food and water were withheld for 12 hours before anesthesia and surgery to reduce the risk of bloat.

Myocardial infarction induction

To maintain aseptic conditions and reduce the risk of postoperative infection, the wool over the surgical field was first clipped. Anesthesia was then induced with 30 mg/kg ketamine 10% (Alfasan, the Netherlands) and 2 mg/kg diazepam 2% (Interchemie, the Netherlands). Anesthesia was maintained with inhaled isoflurane (Terrell) at a minimum alveolar concentration of approximately 1%. The trachea was intubated with an 8-mm endotracheal tube, and the animals were mechanically ventilated using the intermittent positive-pressure ventilation (IPPV) method. Heating pads were used during surgery and recovery to help maintain body temperature.

Surgery and ligation of the left anterior descending artery

A left lateral thoracotomy was performed to access the heart. Each sheep was placed in right lateral recumbency, and the left thoracic wall was clipped and aseptically prepared. An approximately 10-cm incision was made in the third to fourth intercostal space, followed by dissection of the subcutaneous tissues and muscles. The intercostal space was opened with a Finochietto retractor to expose the heart. The pericardium was opened, and a lateral branch of the LAD artery was permanently ligated with 4-0 silk suture. Successful coronary occlusion was confirmed by visible pallor of the affected anterior myocardial surface, along with ECG changes consistent with acute ischemia. The pericardium was then closed with 4-0 Monocryl suture, and the thoracotomy incision was closed in layers. A thoracic drain was placed to evacuate accumulated air and fluid. Cardiovascular and respiratory status were continuously monitored during surgery and recovery. Intravenous 2% lidocaine (Caspian Tamin Co., Iran) was administered before occlusion of the LAD branch and again 15 minutes after occlusion to reduce the risk of ventricular fibrillation.

Care after surgery

After surgery, the animals received intensive monitoring until full recovery from anesthesia. Vital signs were assessed regularly, and accumulated air and fluid were drained through the thoracic tube as required to maintain negative intrathoracic pressure and facilitate ventilation. Penicillin-streptomycin (Interchemie, the Netherlands) was administered intramuscularly at 1 mL/10 kg every 24 hours for 4 days for infection prophylaxis, and oxy-tetracycline spray (Vetaque) was applied topically to the incision twice daily. Tramadol (Tehran Shimi Co., Iran) was administered intramuscularly at 4 mg/kg every 12 hours for analgesia.

Recording of clinical signs

Clinical signs were recorded before surgery and LAD branch occlusion and again 24 hours after induction of MI, and were grouped into three categories: cardiovascular signs, including heart rate, rhythm, heartbeat intensity, and changes in heart sounds; respiratory signs, including respiratory rate, changes in breath sounds, cough, and nasal discharge; and general signs, including body temperature, mucous membrane appearance, appetite, and overall physical condition. Qualitative variables were scored for each animal, and pre- and post-MI induction scores were compared statistically.

Arterial blood sampling and measurement of blood gases and electrolytes

Arterial blood samples were collected from the auricular artery before surgery and MI induction and again 24 hours after LAD branch occlusion. An insulin syringe was lightly heparinized, and 0.5-1.0 mL of arterial blood was obtained after clipping and disinfecting the external ear. Samples were analyzed immediately, with care to avoid air exposure and hemolysis, using an OPTI Medical CCA-TS blood gas analyzer. The measured variables included partial pressure of oxygen (PO_2), oxygen saturation ($SatO_2$), partial pressure of carbon dioxide (PCO_2), bicarbonate (HCO_3^-), pH, base excess (BE), potassium (K^+), sodium (Na^+), chloride (Cl^-), and anion gap.

Statistical analysis

Statistical analyses were performed in SPSS software, version 24. Normality of data distribution was assessed using the Kolmogorov-Smirnov test. Pre- and post-MI induction results were compared using paired t-tests or the Wilcoxon signed-rank test. Results are presented as mean, standard deviation (SD), and standard error (SE). A two-sided $P < 0.05$ was considered statistically significant.

Results

Confirmation of myocardial infarction induction

After occlusion of the lateral LAD branch, successful induction of MI was assessed based on macroscopic, ECG, and echocardiographic findings. The myocardial territory distal to the ligated branch became visibly pale. ECG assessment demonstrated ST-segment elevation and prolongation, together with changes in the QRS complex. Echocardiography showed reductions in fractional shortening (FS) and ejection fraction (EF) compared with baseline. Overall, these findings were considered consistent with successful induction of the experimental MI model.

Clinical findings

Clinical findings before and 24 hours after surgery and LAD branch occlusion are summarized in Table 1. Mean heart rate increased significantly 24 hours after MI induction compared with baseline ($P < 0.001$). Cardiac rhythm became irregular, heartbeat intensity decreased, and additional heart sounds were detected. The corresponding clinical scores for heart rhythm, heartbeat intensity, and heart sounds also increased significantly after MI induction ($P < 0.05$).

Mean respiratory rate increased significantly 24 hours after induction ($P < 0.001$). Breath sounds were predominantly characterized by crackles, and some animals developed a wet cough; no nasal discharge was observed. The respiratory-sound score increased significantly after induction ($P = 0.014$), whereas changes in cough and nasal discharge were not statistically significant ($P > 0.05$).

Mean body temperature increased 24 hours after induction, and this change was statistically significant ($P = 0.003$). Mucous membranes, which were bright pink before surgery, became hyperemic and in some cases appeared cyanotic; the corresponding score increased significantly ($P = 0.014$). Appetite and general physical condition also worsened after MI induction, with some animals becoming anorexic, depressed, or withdrawn. Appetite and physical condition scores changed significantly compared with baseline ($P = 0.023$ for both).

Arterial blood gases and electrolytes

Table 2 shows arterial blood gas results before and 24 hours after surgery and MI induction. Mean PO_2 and $SatO_2$ decreased from 64.83 mm Hg and 98.0% at baseline to 50.0 mm Hg and 81.40%, respectively, at 24 hours ($P < 0.001$ for both). Mean PCO_2 increased from 26.33 to 39.33 mm Hg ($P = 0.002$). Mean HCO_3^- and pH were 22.43 mmol/L and 7.51, respectively, before surgery and 23.08 mmol/L and 7.52 at 24 hours. Neither HCO_3^- nor pH changed significantly ($P > 0.05$). In contrast, mean BE decreased significantly from 0.96 to -2.33 mmol/L ($P < 0.001$).

Table 3 summarizes arterial electrolyte results before and 24 hours after LAD branch occlusion. Mean K^+ decreased significantly from 4.2 to 3.62 mmol/L ($P = 0.038$). Mean Na^+ and Cl^- increased from 144 and 105.16 mmol/L at baseline to 152.16 and 115.5 mmol/L, respectively, at 24 hours ($P < 0.001$ and $P = 0.001$, respectively). Mean anion gap also increased significantly from 12.52 to 16.36 mmol/L ($P = 0.013$).

Discussion

MI remains a major cardiovascular disorder and an important cause of mortality worldwide [17]. Experimental models are essential for understanding the mechanisms and systemic consequences of ischemic myocardial injury and for evaluating potential therapies [18]. An appropriate animal model should reproduce clinically relevant structural and functional features of human disease and yield reproducible results [19]. In the present study, we reproducibly induced MI in sheep by surgically ligating

Table 1. Clinical findings before and 24 hours after MI induction in sheep

Clinical Findings	Clinical Symptoms	Phase	Mean	SD	SE	P
Cardiac	Heart rate	Before	82.5	2.34	0.95	<0.001
		After	113.66	5.95	2.43	
	Heart rhythm status	Before	0	0	0	0.014
		After	3	0	0	
	Heartbeat intensity	Before	0	0	0	0.014
		After	3	0	0	
	Heart sounds changes	Before	0	0	0	0.024
		After	2.5	0.54	0.22	
Respiratory	Respiratory rate	Before	26.83	4.49	1.83	<0.001
		After	46.16	7.8	3.18	
	Respiratory sounds change	Before	0	0	0	0.014
		After	3	0	0	
	Cough	Before	0	0	0	0.063
		After	1	0.89	0.36	
	Nasal discharge	Before	0	0	0	-
		After	0	0	0	
General	Body temperature	Before	38.68	0.19	0.07	0.003
		After	39.13	0.19	0.08	
	Mucous membrane status	Before	0	0	0	0.014
		After	3	0	0	
	Appetite status	Before	0	0	0	0.023
		After	2.66	0.51	0.21	
	Physical condition	Before	0	0	0	0.023
		After	2.66	0.51	0.21	

a lateral branch of the LAD artery. Coronary occlusion is a well-established approach in preclinical MI research [20]. Prolonged reduction in coronary blood flow causes myocardial ischemia and, if sustained, infarction [21]. Consistent with this process, LAD branch occlusion in the present study produced myocardial pallor, ECG abnormalities including ST-segment changes, and reductions in FS and EF on echocardiography.

To our knowledge, few studies have comprehensively characterized clinical signs, arterial blood gases, electro-

lytes, and acid-base variables during the early phase after experimental MI in sheep. The present study therefore adds an integrated description of cardiopulmonary and biochemical changes 24 hours after MI induction. Clinical examination demonstrated tachycardia, tachypnea, irregular cardiac rhythm, reduced heartbeat intensity, altered cardiac and respiratory sounds, mucosal hyperemia, reduced appetite, and depressed or withdrawn behavior. Several findings resemble systemic manifestations reported in human MI [22]. The observed tachycardia is also consistent with previous experimental MI

Table 2. Arterial blood gas variables before and 24 hours after MI induction in sheep

Parameters	Phase	Mean	SD	SE	P
PO ₂ (mm Hg)	Before	64.83	3.86	1.57	<0.001
	After	50	5.86	2.39	
SatO ₂ (%)	Before	98	0.70	0.31	<0.001
	After	81.4	2.07	0.92	
PCO ₂ (mm Hg)	Before	26.33	2.58	1.05	0.002
	After	39.33	4.13	1.68	
HCO ₃ ⁻ (mmol/L)	Before	22.43	1.22	0.49	0.261
	After	23.08	0.9	0.37	
pH	Before	7.51	0.03	0.01	0.75
	After	7.52	0.09	0.04	
BE (mmol/L)	Before	0.96	0.38	0.15	<0.001
	After	-2.33	0.81	0.33	

studies in dogs [23]. The findings support the utility of sheep as a translational large animal model while highlighting the value of careful clinical phenotyping.

Arterial blood gas analysis can provide useful information in patients who develop cardiopulmonary complications during MI [24]. In the present study, MI induction was followed by reduced PO₂ and SatO₂, increased PCO₂, and decreased BE. Hypoxemia has also been described in human MI [25]. Coronary occlusion disrupts aerobic metabolism in ischemic myocardium, leading to adenosine triphosphate depletion, metabolite accumulation, impaired ventricular contractility, reduced cardiac

output, and potentially reduced tissue perfusion [26]. A decrease in BE may reflect increased metabolic acid burden [2, 27]. In the present study, the significant reduction in BE along with an increased anion gap is therefore compatible with a shift toward metabolic acid accumulation 24 hours after LAD branch occlusion.

PCO₂ also increased significantly after MI induction. However, arterial pH remained essentially unchanged (7.51 at baseline and 7.52 at 24 hours), and HCO₃⁻ did not change significantly. Accordingly, the present data do not demonstrate overt mixed metabolic and respiratory acidemia. Rather, they show an acid-base disturbance

Table 3. Arterial blood electrolyte variables before and 24 hours after surgery and MI induction in sheep

Parameters	Phase	Mean	SD	SE	P
K ⁺ (mmol/L)	Before	4.2	0.14	0.06	0.038
	After	3.62	0.4	0.18	
Na ⁺ (mmol/L)	Before	144	2.89	1.18	<0.001
	After	152.16	3.25	1.32	
Cl ⁻ (mmol/L)	Before	105.16	2.13	0.87	0.001
	After	115.5	4.63	1.89	
Anion gap (mmol/L)	Before	12.52	0.35	0.15	0.013
	After	16.36	1.87	0.84	

characterized by decreased BE and increased anion gap, accompanied by increased PCO_2 , with no significant decline in arterial pH. Previous human studies have reported heterogeneous acid-base patterns in acute MI and acute heart failure, including mixed disorders in patients with severe cardiopulmonary compromise [28, 29]. Differences from previous canine experimental data, including reports of hypocapnia or minimal blood-gas change, may reflect interspecies differences, model characteristics, and perioperative factors [23]. These findings indicate that arterial blood gas and acid-base assessment can provide complementary physiological information in experimental MI models. Their role in clinical diagnosis or prognosis should, however, be interpreted alongside established cardiac assessment methods rather than as stand-alone diagnostic measures.

Electrolyte measurement may also help characterize the systemic response to acute MI. In the present study, K^+ decreased, whereas Na^+ , Cl^- , and anion gap increased after MI induction. Anion gap represents the difference between measured cations and anions and can provide information about unmeasured anions and metabolic acid accumulation [27]. Previous human studies have reported variable electrolyte patterns after MI, including reduced potassium and changes in sodium, calcium, and magnesium [30, 31].

Other clinical studies have described hypokalemia and hyponatremia more frequently than hypernatremia and hyperkalemia after acute MI [32], and some electrolyte disturbances have been associated with short-term mortality [16]. Walim and Yatiraj [33] also reported changes in sodium and potassium after MI and discussed potential contributions from ischemia, membrane permeability, and catecholamine responses. The electrolyte profile observed in the present ovine model therefore should be interpreted as a model-specific early response rather than assumed to directly reproduce the pattern seen in every human MI population.

Experimental canine studies have also yielded different electrolyte findings. Jennings et al. [34] reported decreased potassium together with increased sodium and chloride after surgically induced MI, broadly consistent with the present study results, whereas Kumar et al. [23] found no significant changes in potassium, sodium, or chloride. This discrepancy may reflect differences in species, infarct model, timing of sampling, and perioperative management.

This study had several limitations. The sample size was small, though it is common in complex large animal sur-

gical studies, and no sham-operated control group was included. Consequently, some postoperative cardiopulmonary and biochemical changes cannot be attributed exclusively to MI because anesthesia, thoracotomy, mechanical ventilation, postoperative pain, and perioperative treatments may also have contributed. In addition, quantitative EF and FS values were not available in this study. These limitations should be considered when interpreting the translational implications of the findings.

Conclusion

In this ovine model study, experimental MI induced by ligation of a lateral LAD branch was followed within 24 hours by significant changes in clinical findings, arterial blood gases, electrolytes, and acid-base variables. The animals developed hypoxemia, electrolyte disturbances, decreased BE, increased anion gap, and increased arterial PCO_2 , while arterial pH remained unchanged. Thus, the data support an early acid-base disturbance with increased metabolic acid burden and altered ventilation rather than overt mixed metabolic and respiratory acidemia. Together with the observed clinical, ECG, echocardiographic, and macroscopic changes, the findings further characterize the early systemic response to experimental MI in sheep and may inform future translational large-animal studies.

Ethical Considerations

Compliance with ethical guidelines

All procedures involving animal care and handling were approved by the Animal Ethics Committee of the Faculty of Veterinary Medicine, [University of Tehran](#), and were conducted in accordance with applicable international standards (Code: IR.UT.VETMED.REC.1402.031).

Funding

This study was funded by the [Iranian National Science Foundation \(INSF\)](#), [Vice Presidency for Science, Technology and Knowledge-Based Economy](#) (Grant No.: 96006067).

Authors' contributions

Conceptualization and supervision: Marzieh Makhber-Dezfouli and Sirous Sadeghian Chaleshtori; Methodology: Abolfazl Najd Ghahremani, Mir Sepehr Pedram, Neda Sabetzadeh, and Fatemeh Barzegar; Investigation: Abolfazl Najd Ghahremani, Neda Sabetzadeh, Fatemeh Barzegar, and Javad Abbasi;

Software and validation: Mohammad Mehdi Dehghan; Formal Analysis and data curation: Mohammad Mehdi Dehghan and Sirous Sadeghian Chaleshtori; Writing the original draft: Abolfazl Najd Ghahremani; Review and editing: Marzieh Mokhber-Dezfouli, Mohammad Mehdi Dehghan, and Sirous Sadeghian Chaleshtori; Project administration: Sirous Sadeghian Chaleshtori; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors would like to thank the [Iranian National Science Foundation \(INSF\)](#), [Vice Presidency for Science, Technology and Knowledge-Based Economy](#), for financial support.

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