Effect of a 7.2% Hypertonic Saline Solution Infusion on Arterial Blood Pressure, Serum Sodium Concentration and Osmotic Pressure in Normovolemic Heifers

Kazuyuki SUZUKI, Tadaharu AJITO and Shigehiro IWABUCHI

Central Research Laboratories, Nippon Zenyaku Kogyo Co., Ltd., 1–1 Aza, Tairanoue, Sasagawa, Asakamachi, Koriyama-city, Fukushima-prefecture 963–0196, Japan

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ABSTRACT. The effects of an intravenous (iv) infusion of a small volume (5 ml/kg) or large volume (15 ml/kg) of hypertonic saline solution (HSS; 7.2%, 2,400 mOsmol/kg·H_2O) and those of an iv infusion of 5 ml/kg isotonic saline solution (ISS; 300 mOsmol/kg·H_2O) on plasma volume, arterial blood pressure, serum sodium concentrations and osmotic pressure were investigated in conscious heifers. Nine heifers (3 heifers/group) were monitored for 120 min after the initiation of fluid replacement. The relative plasma volume (rPV) in the 5 ml/kg HSS and 15 ml/kg HSS progressively increased to 137.7 ± 2.4% at t=5 min and 145.2 ± 5.4% at t=15 min, respectively. The expanding plasma volume in the 5 ml/kg HSS group remained at an up to 10% higher level until 120 min, but not in the 15 ml/kg HSS group. The 5 ml/kg HSS infusion induced transit high-osmotic (305.3 ± 4.0 mOsmol/kg·H_2O) and sodium levels (155.7 ± 3.5 mM/*l*) at t=5 min. However, the 15 ml/kg HSS infusion induced constant high-osmotic level (321.7–336.7 mOsmol/kg·H_2O) and hypernatremia (162.8-170.0 mM/*l*) from t=10 min to the rest of the experiment period. In the ISS and 5 ml/kg HSS groups, no changes in PaO_2 were observed. The 15 ml/kg HSS infusion induced a significant decrease in the partial pressure of oxygen at the t=30 min compared to the t=0 min values. On the basis of these findings, a small volume (5 ml/kg) HSS infusion can be rapidly and safely administered to cattle for expanding the plasma volume without inducing hypernatremia. A 5 ml/kg HSS infusion is thus recommended for the initial field resuscitation of cattle. — KEY WORDS: heifer, hypernatremia, hypertonic saline solution, plasma volume, serum osmotic pressure.

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Hypertonic saline solution (HSS) has been used clinically for the treatment of severe blood loss in human being as early as 1919 [14]. The intravenous (iv) administration of a small volume (3-5 ml/kg) of 7.2%-HSS (2,400 mOsmol/kg·H_2O) has been successfully used to resuscitate sheep [18], horse [1, 2], dogs [8, 13, 17, 22], cats [10], calves [3-6, 19] and cows [20, 21] with experimentally induced hemorrhage, endotoxic or septic shock.

The administration of HSS causes greater increases in plasma volume. The administration of HSS to hemorrhagic- or endotoxic-shocked animals results in increased cardiac output, cardiac index, myocardial stroke work efficiency [1, 10, 11, 15], and oxygen delivery [16]. In addition, mean arterial pressure (MAP) is restored, and peripheral and pulmonary vascular resistance is reduced [1, 10, 11, 15, 16]. These beneficial effects of HSS administration most likely result from an increase in preload, a decrease in afterload, or both. Another proposed mechanism is a pulmonary-mediated vascular response reflex by vagus innovation [2, 8, 15, 22].

HSS may be valuable in the initial management of endotoxemic calves and cattle, because of its rapid resuscitative effects and low cost. However, HSS has caused considerable increases in serum sodium and chloride concentrations as well as osmolality when administered to cattle. Cerebral edema may occur as a consequence of rapid NaCl administration, and sodium concentrations greater than 160 mM/*l* are diagnosed as salt poisoning [19]. Therefore, the rapid infusion of HSS should be tested for safety before recommended for the treatment of cattle.

The experiments reported here are aimed to determine whether a small volume of HSS (5 ml/kg, iv) can be administered to cattle without producing clinical signs, severe biochemical changes, arterial pressure or arterial blood gas changes with hypernatremia.

MATERIALS AND METHODS

The experiment was performed on nine clinically healthy Holstein heifers weighing 260 ± 7.0 kg. The heifers were determined to be clinically healthy on the basis of physical findings, electrocardiograph and hematological profiles. A complete balanced growing diet consisting of pelleted concentrate ration and mixed grass hay and *ad libitum* access to fresh water were provided until the day before the experiment.

The day before the experiment, all heifers were anesthetized with an iv injection of xylazine (Seduluck-2%; Nippon Zenyaku Kogyo Co., Fukushima, Japan) at the dosage of 20 mg/100 kg body weight, for the insertion of an arterial catheter (Safelet Catheter NCKP-14-70; Nipro Co., Osaka, Japan) via the femoral artery. Approximately one hour before the initiation of fluid administration, 14-gauge iv catheters (IV catheter for animals; Nippon Zenyaku Kogyo) were implanted percutaneously into both jugular veins. The right jugular vein catheter was connected with an ordinary drip tube (15 drops equal one m*l*; Nippon Zenyaku Kogyo) [23] with a pump (ABP-101; Asahi Medical Co., Tokyo, Japan) to control the flow rate. The left jugular vein catheter was used for venous blood

sampling. The arterial catheter was connected to a Life Kit model DX-360 strain-gauge transducer (Nihon Kodhen Co., Tokyo) coupled to a BP-308 ETI galvanometric recorder (Nippon Colin Co., Aichi, Japan). The rectal temperature was also monitored by the galvenometric recorder throughout the experimental period.

The heifers were randomly assigned to a control or one of two experiment groups (3 heifers per each group): (1) in control group, heifers received fluid replacement with 5 ml/kg of isotonic saline solution (ISS), and (2) in the 5 ml/kg HSS and (3) in 15 ml/kg HSS groups, heifers were infused with 5 or 15 ml/kg of HSS, respectively. The time at ISS or HSS infusion started was designated as t=0 min. Immediately after the recording and blood sampling of the t=0 min values, the ISS or HSS solution was infused iv at a flow rate of 200 ml//min via the right jugular vein catheter. The animals of all three groups were then monitored for 120 min. Immediately before each blood sampling point, the heart rate (HR), arterial blood pressure and rectal temperature were recorded. Arterial blood samples were taken at t=0, 5, 15, 30, 60, 90 and 120 min. The arterial blood samples were collected anaerobically in a heparinized one-ml syringe, and the tips were capped. Immediately after sampling, the whole blood samples were measured for blood pH and gases by an automatic gas analyzer set at 37°C (model 248 pH/gas analyzer, Ciba-Corning Diagnostic, Essex, England), and the values were automatically corrected to correspond to the heifer's rectal temperature. Of the venous blood samples taken, some samples were measured for hemoglobin concentration (Hb) by a micro-cellcounter (Sysmex F-800, R.A.Systems Co., Nagano, Japan) and the hematocrit value (Ht). These samples were then stored in test tubes. After centrifugation, the serum samples were stored at −20°C until assay.

The relative changes in plasma volume (rPV) were calculated from the Hb and Ht, using the accepted formula [7]. The serum osmotic pressure was determined by the freezing point depression method, using a One-Ten Osmometer (Fiske Associate, Norwood, MA, U.S.A.). The serum sodium, potassium and chloride concentrations were analyzed by electrode methods using an automated $Na^+/K^+/Cl^-$ analyzer (model 644, Ciba-Corning Diagnostic). The serum calcium concentration was determined by the *o*-cresolphthalein chelation method with a video chemistry system (Video-Chemistry system model 600, Amco Co., Tokyo).

Data are expressed as mean ± S.D. The variables measured such as including heart rate, arterial blood pressure, rectal temperature, blood gas parameters, serum osmotic pressure, and serum electrolyte concentrations were compared at each sample collection interval among the groups, using ANOVA for repeated measures. The mean values for each dependent variable were compared with the t=0 min values within groups, using ANOVA for repeated measures. Significance was defined as $p<0.05$.

RESULTS

Figure 1 shows the sequential changes in rPV and serum osmotic pressure in the heifers given resuscitation fluids. The rPV in the ISS group remained constant at a level between 96.8 ± 3.4 and 103.0 ± 2.7% during the experimental period. In contrast, the rPV in the 5 ml/kg and 15 ml/kg HSS groups showed progressive increases to 137.7 ± 2.4% at t=5 min and 145.2 ± 5.4% at t=15 min, respectively. The expanding plasma volume in the 5 ml/kg-group remained at an up to 10% higher level until 120 min, but did not in the 15 ml/kg HSS group. The serum osmotic pressure was not altered by the ISS infusion and remained constant throughout the experimental period. The 5 ml/kg HSS infusion induced transit hyperosmolality at t=5 min (305.3 ± 4.0 mOsmol/kg·H_2O), and the serum osmotic pressure remained under the 300 mOsmol/kg·H_2O level for the rest of the experiment. In contrast, the serum osmotic pressure in the 15 ml/kg HSS group was significantly increased during the HSS infusion and remained constant at a level between 336.7 ± 2.5 and 326.3 ± 3.8 mOsmol/kg·H_2O ($p<0.05$).

Figure 2 shows the sequenial changes in the serum sodium, potassium and chloride concentrations in the heifers

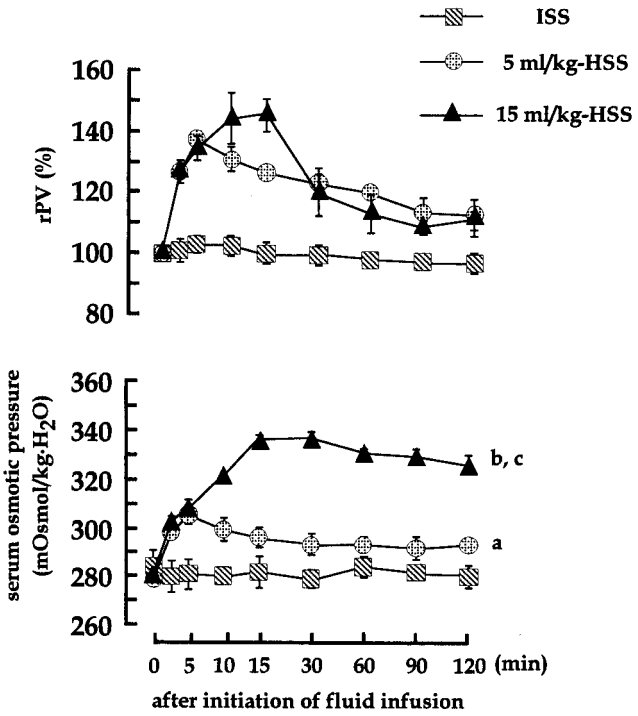

Fig. 1. Sequential changes in relative plasma volume (rPV) and serum osmotic pressure caused by fluid infusion in the heifers. The rPV values were calculated from Hb and Ht, using Greenleaf's formulas [7]. Levels of significance ($p<0.05$) indicated: a: ISS versus 5 ml/kg-HSS, b: ISS versus 15ml/kg-HSS and c: 5 ml/kg- versus 15 ml/kg-HSS.

given resuscitation fluids. In the ISS group, the serum sodium and chloride concentrations were not altered by the ISS infusion. The 5 ml/kg HSS infusion induced transient high sodium (155.7 ± 3.5) and chloride (115.3 ± 0.6 mM/*l*) levels at t=5 min, which then recovered to 147.0 ± 3.1 and 105.3 ± 1.5 mM/*l*, respectively, at t=120 min ($p<0.05$). In contrast, the 15 ml/kg HSS infusion induced constant hypernatremia (162.8–170.0 mM/*l*) and hyperchloremia (126.3–136.0 mM/*l*) from t=10 to the end of the experiment. The serum potassium concentration was not altered by the ISS infusion. In contrast, the HSS infusion induced significant decrease in serum potassium concentration in the 5 ml/kg (3.4 ± 0.1 mM/*l*; t=5 min) and 15 ml/kg HSS groups (3.4 ± 0.2 mM/*l*; t=5 min), which then recovered to the t=0 values ($p<0.05$).

Figure 3 shows the sequential changes in the HR and systolic arterial pressure (SAP) in the heifers given resuscitation fluids. In the ISS group, the HR was not altered by the ISS infusion. The 15 ml/kg HSS group showed a progressive and significant acceleration of the HR ($p<0.05$), reaching the value of 108.7 ± 14.2 beats/min at t=5 min. This acceleration was significantly higher than those in the other two groups ($p<0.05$). In contrast, in the 5 ml/kg HSS group, the HR was transiently accelerated at t=5 min (96.7 ± 8.6 beats/min.) but the HR at t=15 min had returned to the t=0 min value and remained there for the rest of the experiment.

No significant differences were observed in the SAP, diastolic (DAP) or mean arterial pressures (MAP) between the ISS and 5 ml/kg HSS groups. The SAP, DAP and MAP in the ISS group remained constant at the t=0 min level. In contrast, the SAP in the 15 ml/kg HSS group showed a progressive increase to 165.7 ± 18.0 mmHg at t=3 min. Immediately after the initiation of fluid administration (t=1 min), there were transient decreases in SAP in the 5 ml/kg (from 140.7 ± 5.9 at t=0 min to 124.7 ± 18.6 mmHg at t=1 min) and 15 ml/kg HSS groups (from 150.0 ± 13.9 at t=0 min to 139.0 ± 6.9 mmHg at t=1 min).

The sequential changes of the arterial blood pH (pH), partial pressure of carbon dioxide ($PaCO_2$) and partial pressure of oxygen (PaO_2) are shown in Fig. 4. The pH in the ISS group remained constant at a level between 7.400 and 7.426 after t=0 min. The 5 ml/kg HSS infusion induced a transient and significant decrease in the pH at t=15 (7.367 ± 0.009), which then remained at that level for the rest of the experiment ($p<0.05$). The changes in pH in the 5 ml/kg HSS group was significantly lower than that in the ISS group ($p<0.05$). The 15 ml/kg HSS infusion induced metabolic acidosis from t=10 (7.335 ± 0.011) to 60 min (7.342 ± 0.024), which reached 7.310 ± 0.017 at the t=30 min ($p<0.05$). This decrease was significantly higher than those in the other two groups ($p<0.05$).

The $PaCO_2$ in the ISS and 5 ml/kg HSS groups were not significantly altered after t=0 min. The 15 ml/kg HSS infusion induced a significant increase in $PaCO_2$ from 46.1 ± 3.2 at t=0 min to 53.6 ± 5.1 mmHg at t=60 min ($p<0.05$). In the ISS and 5 ml/kg HSS groups, no changes in PaO_2 and

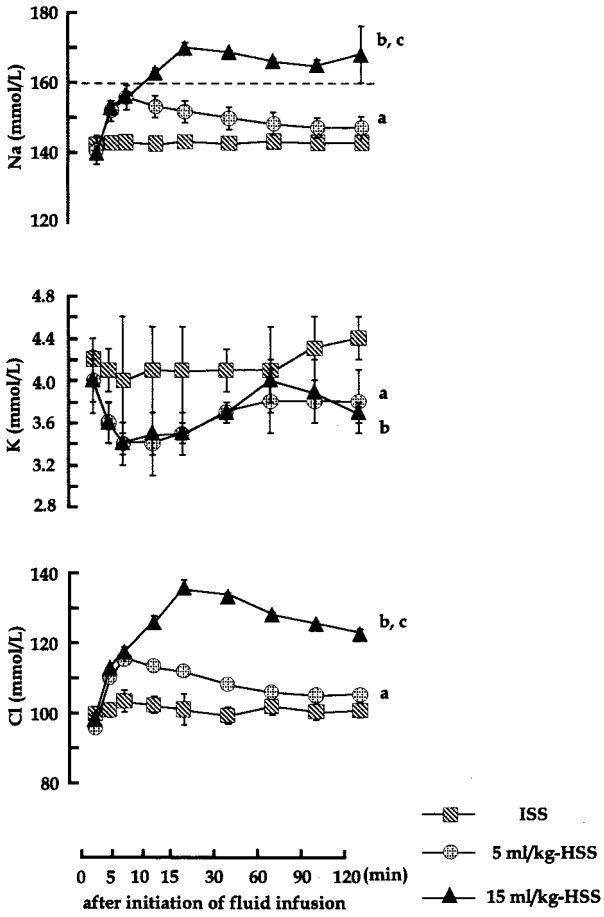

Fig. 2. Sequential changes in serum sodium (Na), potassium (K) and chloride concentrations (Cl) caused by fluid administration in the heifers. Levels of significance ($p<0.05$) indicated: a: ISS versus 5 ml/kg-HSS, b: ISS versus 15ml/kg-HSS and c: 5 ml/kg- versus 15 ml/kg-HSS.

O_2 saturation (O_2sat) were observed. The 15 ml/kg HSS infusion, in contrast, induced a progressive and significant decrease in PaO_2 compared to the t=0 min values ($p<0.05$), reaching 77.6 mmHg at t=30 min.

DISCUSSION

Several mechanisms concerning the beneficial effects of HSS administration have been proposed; one is the expansion of circulating blood volume [2, 3, 9, 12, 18]. HSS draws water from interstitial or intracellular fluid compartments, increasing plasma volume, and consequently improves the perfusion of peripheral tissues. A second possibility is that hypertonic electrolyte solutions have positive intropic effects [4, 15, 21, 22]. The increasing cardiac output is apparently mediated by a reflex arc involving the vagus nerve with receptors in the lungs [12, 15, 22]. In addition, HSS alters peripheral vascular capacitance [17].

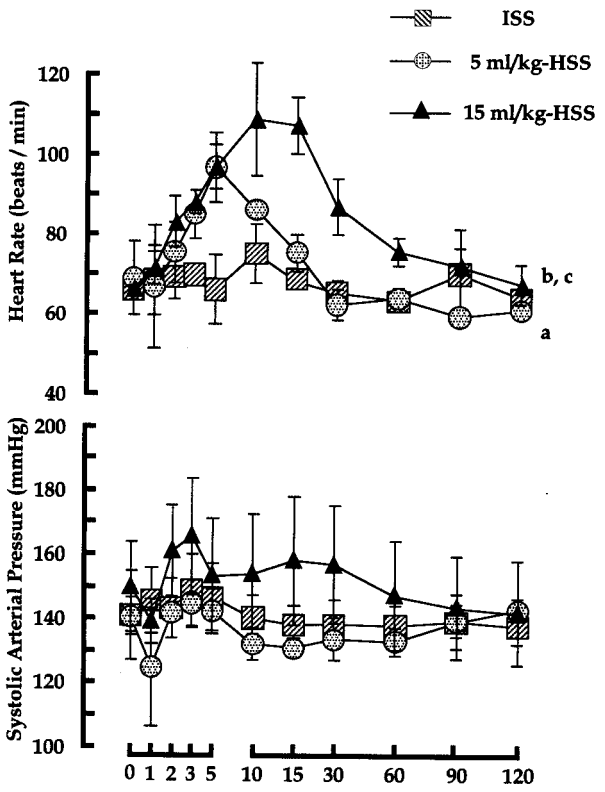

Fig. 3. Sequential changes in heart rate (HR) and systolic arterial pressure (SAP) caused by fluid infusion in the heifers. Levels of significance ($p<0.05$) indicated: a: ISS versus 5 ml/kg-HSS, b: ISS versus 15ml/kg-HSS and c: 5 ml/kg- versus 15 ml/kg-HSS.

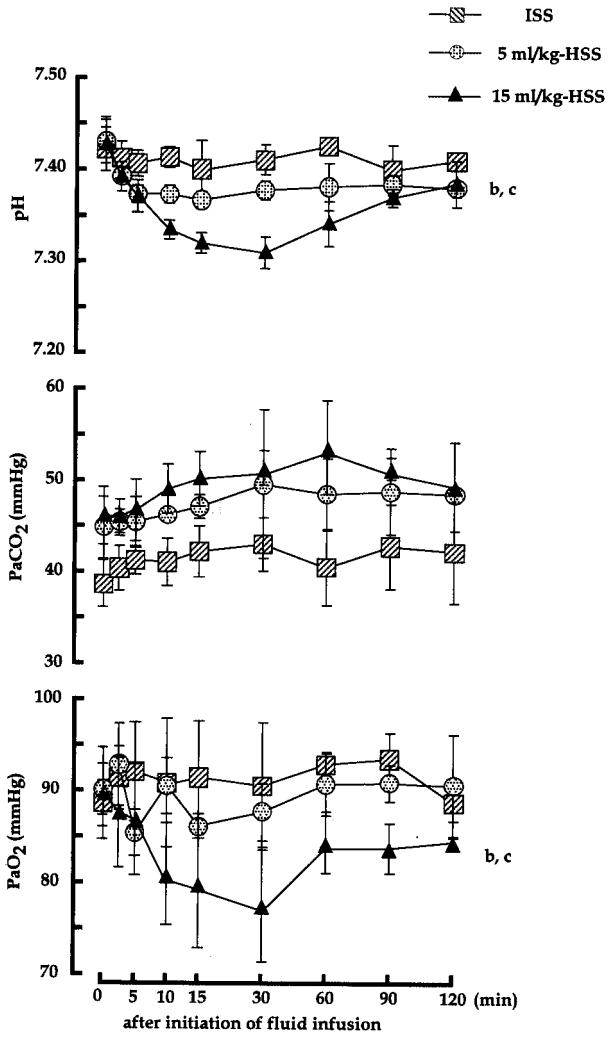

Fig. 4. Sequential changes in arterial blood pH (pH), partial pressures of carbon dioxide ($PaCO_2$) and oxigen (PaO_2) caused by fluid administration in the heifers. Levels of significance ($p<0.05$) indicated: a: ISS versus 5 ml/kg-HSS, b: ISS versus 15ml/kg-HSS and c: 5 ml/kg- versus 15 ml/kg-HSS.

HSS has been shown to successfully restore cardiovascular function when used in dogs and cats with hemorrhagic/hypovolemic shock [5, 8–10, 13, 15, 22]. Smith *et al*. [18] reported that about 4 ml/kg of HSS rapidly increased the plasma volume by about 10 to 12 ml//kg, in bled sheep. In the present study, the plasma volume and serum osmotic pressure in the heifers that received ISS remained constant at the pre-treatment levels. In contrast, the rPV in the 5 ml//kg and 15 ml//kg HSS infusion groups increased markedly after the completion of the HSS infusion, reaching the values of 137.7 ± 2.4% at t=5 min and 145.2 ± 5.4% at t=15 min, respectively. Assuming that the plasma volume is equal to 5% of body weight, the 5 ml//kg and 15 ml//kg HSS increased the plasma volume by about 18.5 and 22.6 ml//kg, respectively. In this study, the expanding plasma volume in the 5 ml//kg HSS group remained at an up to 10% higher level until 120 min, but this did not occur in the 15 ml//kg HSS group. The expanding plasma volume in the 15 ml//kg group demonstrated a maximal value at the end of the HSS infusion, but it did not remain at the up to 10% higher level after the end of the HSS infusion.

HSS generates an osmotic plasma expansion and increased plasma volume. Since sodium is largely confined to the extracellular compartment, HSS expands the extracellular fluid space by extracting water from the cell. However, a rapid increase in the serum sodium concentration will cause salt poisoning. The diagnosis of salt poisoning is usually based on an increased serum or cerebrospinal sodium concentration or osmolality. Cerebrospinal or serum sodium concentrations greater than 160 mM/*l* are diagnostic for salt poisoning [19]. Here, the administration of 5 ml//kg HSS caused increase in the serum sodium concentration to a mean value of 155.7 ± 3.5 mM/*l*. This value (lower than 160 mM/*l*) is the highest limited of the reference range for the serum sodium concentration and was not likely to put the heifers at risk for adverese effect, cf hypernatremia. However, the serum sodium concentration in the 15 ml//kg HSS group reached, the maximal concentration 170.0 ± 1.5 mM/*l*, at the end of the HSS infusion. The serum sodium

level in the 15 m*l*/kg HSS group then remained constant at a level between 165.0 ± 1.5 and 168.7 ± 0.7 mM/*l*. These values (greater than 160 mM/*l*) were likely to have put the heifers at risk for hypernatremia. Immediately after the initiation of the fluid administration (t=1 min), SAP in the 5 m*l*/kg and 15 m*l*/kg HSS groups were progressively decreased, but transient and returned to the pre-infusion levels at t=2 min. This phenomenon may have been caused by the vagus nerve reflex. Several workers [15, 22] demonstrated that the beneficial response to an HSS infusion is apparently mediated by a reflex arc involving the vagus nerve, with receptors in the lungs.

In this study, no changes in PaO_2 and O_2sat were observed in the ISS and 5 m*l*/kg HSS groups, whereas the 15 m*l*/kg HSS infusion caused a progressive decrease in PaO_2, reaching 77.6 ± 6.3 mmHg at t=30 min. The HR in the 15 m*l*/kg HSS group progressively and significantly accelerated, reaching 108.7 ± 14.2 beats/min; such an accelerating HR may induce a decrease in stroke volume. This pulmonary response, therefore, may be caused by a decrease in pulmonary circulation.

Although increases in the sodium, chloride and serum osmotic pressure caused by the 5 m*l*/kg HSS infusions, the changes were not of sufficient magnitude to be of risk to the heifers. In contrast, the 3-fold volume of HSS (15 m*l*/kg) induced constant hypernatremia (>160 mM/*l*) from t=10 min to the end of the experiment (t=120 min). Therefore, the HSS used in the other group (5 ml/kg, 7.2% HSS) was found to be safe for use in cattle, when the infusion is given through a jugular vein at the flow rate of 200 m*l*/min.

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