A Case of Complete Resealing of Patent Foramen Ovale in a Cloned Red Angus Calf

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Abstract

Case Description: A 56kg (123.2lbs) one-day-old newborn purebred red Angus calf was evaluated because of a cardiac condition.

Clinical Findings: Radiography and ultrasonography revealed a loss of continuity of 18mm in the mid intra auricular area, in the region of the oval trench and it was diagnosed as patent foramen ovale. The right auricle was notably distended, with marked volume overload. There were eco dense structures floating inside the left auricle. Treatment and Outcome: Pharmacological treatment aimed to avoid overload of liquid flow in both the lung and the heart. Drugs administered were: furosemide (1mg/Kg every 12h), enalapril (0,5mg/kg every 12h) and sildenafil (0,5mg/kg every 12h). The goal of using sildenafil was to reduce the preload of the right ventricle and to diminish the risk of right cardiac failure and thus of acute respiratory crisis.

Clinical Relevance: Patent foramen ovale is common in newborn cloned calves and probably is under diagnosed in otherwise healthy looking newborn calves. The results of this paper show that foramen ovale can be pharmacologically treated in calves and that euthanasia of newborn animals carrying such pathology must be the last option, only when pharmacological approaches proved non-effective.

Keywords: Foramen ovale; Bovine clones; Respiratory frequency

Case Presentation

A female cloned calf weighting 56kg (123.2lbs) was produced. A possible heart failure of the cloned fetus was anticipated at day 265 by trans abdominal ultrasonography, detected as low fetal activity, low cardiac frequency and weak contraction movement of the heart during the ultrasound and examination of the recipient cow. However it was difficult to visualize the heart structures due to the big size of the fetus. Parturition was induced by the intramuscular administration of 25mg of dexamethasone phosphate, 36h before the programmed time for the cesarean. Caesarian section was performed at day 278, with the animal lying in right lateral decubitus position, under local anesthesia. Cloned calf was received after dissection of the umbilical cord and immediately checked for physiological constants (cardiac and respiratory frequencies and temperature (CF, RF, T °)).

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At birth, thoracic wall movements were superficial and the calf was considered to be in respiratory distress with persistent taquipnea (respiratory rate 120 breaths per minute and cardiac rate 110 beats per minute), and a compensatory tachycardia. This led to mechanical ventilation with intranasal oxygen, which was well tolerated, by the patient, and responded with decreased respiratory frequency (44 breaths per minute) and deepness of breathing. However twelve hours after birth, the respiratory frequency increased again over 100 breaths per minute, and remained so during the next 48hours. Auscultation yielded a holosystolic ejection murmur heard loudest over the left heart base and with pulmonary creep due to a relative pulmonic stenosis caused by volume overload through the right side of the heart. At the electrocardiograph evaluation, deep S waves were found for DI, DII and DIII, indicating changes associated with right atrial overload. Thorax X-ray showed cardiomegaly with right predominance and a vascular arterial pattern (not shown).

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results confirmed an augmentation of the right ventricle, due to volume overload and a normal left ventricle. At the global view, it was found a preserved architecture of the mitral apparatus, with a good aspect of the tissue of the mitral valve. The tricuspid apparatus was well conserved, with appropriate definition of valve structures. The atrium section displayed a loss of continuity of 18mm in the mid intra auricular area, in the region of the oval trench and it was diagnosed as patent foramen ovale. The right auricle was notably distended, with marked volume overload. There were echo dense structures floating inside the left auricle.

In the long axis view of the four chambers, the outflow charts of both the left and right ventricle appeared normal, with a diameter of the aortic bulb of 24.5mm. As a resume, the patient showed an interauricular communication (foramen ovale) of 18mm, an enlargement of the right atrium and was classified as having type II cardiomyopathy. These kinds of patients normally develop severe congestive and hypertensive pulmonary symptoms and surgical approach is the most indicated procedure in these cases, but this is a rather invasive and risky treatment that implies high costs as well. For that reason we decided to follow a pharmacological treatment aimed to avoid overload of liquid flow in both the lung and the heart.

An inductive approach was undertaken in order to evaluate patient’s response to the drugs. Firstly furosemide (1mg/Kg every 12h) was administered. The patient improved the frequency and depth of the respiratory pattern, and tolerated it very well. After, enalapril (0.5mg/kg every 12h) was given to the calf and lastly sildenafil (0.5mg/kg every 12h) was added to the treatment. The goal of using sildenafil was to reduce the preload of the right ventricle and to diminish the risk of right cardiac failure and thus of acute respiratory crisis (Figure 1A,1B).

During the first five days after treatment there was a significant increase of the CF (p=0.0357) while there was a trend of the RF to decrease (Figure 2A). After five days of treatment there was a significant reduction of both the respiratory and the cardiac frequencies (p= 0.001 and p= 0.0002 respectively) (Figure 2B) and both frequencies remained constant and within the range for a bovine calf. Also an acceptable improvement of the clinical condition and of the well being of the patient was observed coincident with a gradual reduction of the foramen ovale diameter (15mm at day five). After one month of treatment the foramen was completely closed and medication was withdrawn stepwise to avoid decompensating of the patient.

**Discussion**

Atrial septal defect and persistence of an open foramen ovale are relatively common congenital defects of calves [1,2]. These defects provide direct openings between the left and right atrium. A patent foramen ovale is commonly partially covered by a membrane. Normally the opening is closed after birth; however in some patients
the foramen does not close at all or it closes during a long time window. If the foramen ovale does not close in a timely appropriate fashion, the cardio-respiratory pathologies associated to it, can lead to death of the newborn calf in the first days or weeks of life. This condition is often observed in cloned animals, especially if they show overweight at birth, also known as large offspring syndrome, a common anomaly in cloned calves [3-7]. Although its precise causes are not clear, it is responsible of several complications of cloned newborn calves, this includes among others, respiratory and cardiac distress and higher neonatal mortality in the clones [8-10]. Considering that usually bovine clones are born with a cardiac and respiratory distress we used a pharmacological treatment to induce a spontaneous closure of the foramen by decreasing the pulmonary hypertension and the cardiovascular overloading. Alternative surgical procedures to those described here imply either implantation of a catheter or prosthesis in the discontinuous atrial zone. These are rather invasive and risky treatments that imply high costs as well; normally such patients are euthanized, instead in this work we hypothesized that it is possible to treat the foramen ovale in newborn cloned calves using a non-invasive protocol.

Most of the patent foramen ovale in humans closes within three months after birth. The rate of closing is inversely proportional to the wide of the opening [11]. In this way openings between 3-5mm close in 87% of the cases, between 5-8 mm in 80% and bigger than 8mm do not close at all. We are not aware of similar measurements in cattle. In this case foramen closed within a month. The patient is at the moment of writing of this manuscript more than one year old, completely healthy and without any signs of cardiac miss function. Another cloned calf produced from the same cell line did not show this kind of pathology, thus it is not likely to be a cell-dependent event, but rather an epigenetic effect of nuclear transfer. Here we report a case of foramen ovale sealing in type II cardiopath Red Angus female cloned calf. The results of this paper show that foramen ovale can be treated in cloned calves and that euthanasia of newborn animals carrying such pathology must be the last option, only when pharmacological approaches proved non effective.

**Footnotes**

a. doxapram hydrochloride; Cobilux, Montevideo, Uruguay
b. Cobactan® 2.5%; Intervet, Boxmeer, The Netherlands
c. Histamil 1%; Troy Laboratories, Sydney, Australia
d. Ket-10“ 10 mg/ml; Drag Pharma, Santiago de Chile, Chile
e. Calf’s Choice Total™ Silver Colostrum; The Saskatoon Colostrum Company Ltd. Saskatoon, Canada
f. MINDRAY DP-6600 Vet Transductor 5-8.5 MHz; National Ultrasound, Duluth, Georgia, United States Supported in part by INNOVA BIO BIO Grant No. 08 PCS5-352F10.

**References**