Brisket Disease in Western Nebraska Feedlot Cattle

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We received reports from feedlots in the high plains regions of Nebraska, Colorado, and Wyoming of an anecdotal increase in the percentage of cattle deaths with antemortem or postmortem signs of ventral or brisket edema.
We began an investigation to determine the cause of this syndrome.
Major Differential Diagnoses of Ventral Edema

- Ruptured urinary bladder/urethra
- Decreased lymphatic drainage
  - Lymphatic obstruction
- Decreased intravascular oncotic pressure (blood vessels)
  - Hypoproteinemia (e.g., secondary to glomerulonephritis, diarrhea, etc.)
- Vascular leakage
  - Inflammation
- Increased intravascular hydrostatic pressure
  - Right-sided congestive heart failure

This is the most likely pathogenetic process for brisket edema. The main cause of brisket edema is brisket disease.
Differential Diagnoses of Right Heart Failure

• **Cor pulmonale** (which is defined as right-sided heart failure occurring secondary to pulmonary disease; *pathogenesis involves pulmonary hypertension causing work overload*)
  - Pulmonary hypertension caused by low pulmonary arterial oxygen tension (*generalized hypoxia*—“brisket disease”, “high mountain disease”, “high altitude disease”) or other causes (e.g., *Crotalaria* toxicity)

- Chronic obstructive pulmonary disease (COPD) (*regional or generalized hypoxia*)
  - Chronic bronchopneumonia (e.g., bacterial)
  - Chronic bronchointerstitial pneumonia (e.g., viral)

• Cardiomyopathy
  - Toxic (ionophores, plants, etc)
  - Nutritional (e.g., vitamin E and/or selenium deficiency)
  - Hereditary cardiomyopathies (e.g., Holstein-Friesian cattle, Red Holstein-Simmental crosses, Polled and Horned Herefords, Japanese black calves)

• Infectious/inflammatory disease of the heart
  - Vegetative endocarditis (e.g., bacterial)
  - Pericarditis
  - Bacterial myocarditis
Brisket Disease
(High Altitude Disease, High Mountain Disease)

- Seen in cattle raised in high-altitude regions (>5000 ft [1524 m] of Colorado, Wyoming, New Mexico, and Utah)
- Is cor pulmonale (right-sided heart failure caused by chronic pulmonary arterial hypertension) due to generalized hypoxia
- Hypoxia-induced pulmonary arterial hypertension causes work overload of the right ventricle
- This eventually results in congestive/dilatory cardiac failure
Gases move across the blood–gas interface (alveolar-capillary membrane) by diffusion, following the Fick law. PAO$_2$, partial pressure of oxygen, alveolar; PACO$_2$, partial pressure of carbon dioxide, alveolar.

Fick law: the volume of gas diffusing per minute ($V_{gas}$) across a membrane is directly proportional to the membrane surface area (As), the diffusion coefficient of the gas (D), and the partial pressure difference ($\Delta$P) of the gas, and is inversely proportional to membrane thickness (T):

$$V_{gas} = \frac{(As \times D \times \Delta P)}{T}$$

Oxygen Tension Changes with Altitude

Boyle’s law states that at constant temperature, the absolute pressure and the volume of a gas are inversely proportional.

Sea level (0 ft)
PB = 101 kPa
PAO₂ = 13.3 kPa

Western Nebraska Feedlot (4500 ft)
PB = 86 kPa (645 mm Hg)
PAO₂ = 10.4 kPa

Mt. Everest
Pb = 253 mm Hg
PAO₂ = 53 mm Hg
FIo₂ = 0.21

Mt. Everest
Pb = 380 mm Hg
PAO₂ = 80 mm Hg
FIo₂ = 0.21

Andes
Pb = 640 mm Hg
PAO₂ = 134 mm Hg
FIo₂ = 0.21

Denver
Pb = 760 mm Hg
PAO₂ = 160 mm Hg
FIo₂ = 0.21

The height of the column of mercury that is supported by air pressure decreases with increasing altitude, which is a result of a fall in barometric pressure (P_b).

Because the fractional concentration of inspired O₂ (FIo₂) does not change with altitude, the decrease in PO₂ with altitude is caused entirely by a decrease in P_B.
Low oxygen tension in the alveoli (alveolar hypoxia) is the major mechanism regulating blood flow within normal lungs.

A. With regional hypoxia, precapillary constriction diverts blood flow away from poorly ventilated regions, with little change in pulmonary arterial pressure.

Hypoxia-induced vasoconstriction is unique to the lungs

B. In generalized hypoxia, which can occur with high altitude or with certain lung diseases, precapillary constriction occurs throughout the lungs and there is a marked increase in pulmonary arterial pressure.

Case Definition

• Cattle exhibiting one or more of the following antemortem signs:
  – Brisket edema
  – Jugular pulse
  – Dyspnea
  – Cyanosis

• Postmortem lesions:
  – Heart enlargement
  – Pleural or pericardial effusion
  – Pulmonary edema
Materials and Methods

Either fresh intact heart (preferred) or 3-mm-thick slices through entire wall, formalin-fixed

3-mm-thick tissue slices, formalin-fixed

Feedlot personnel performed necropsies and submitted specimens to lab
Results

• **Signalment**: 8/8 were purebred Angus cattle; 7 steers, 1 heifer

• **History**: 7/8 native to ranch; 1/8 from Wyoming; cattle died or realized 137-183 days after entering feedlot (mean, 167 days)

• **Necropsy/ Gross pathology**:
  — Right ventricular hypertrophy — 2/2
  — Brisket edema, ventral edema — 6/6
  — “Chronic lung lesions” — 2/8
  — Nutmeg liver — 8/8
Evidence of Right Ventricular Hypertrophy

**Case Animals**

<table>
<thead>
<tr>
<th>Heart Weight/Body Weight</th>
<th>(LV + Septum)/RV</th>
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<tbody>
<tr>
<td>0.59%</td>
<td>1.0</td>
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<tr>
<td>0.55%</td>
<td>1.375</td>
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</table>

**Normal Reference Values**

<table>
<thead>
<tr>
<th>Heart Weight/Body Weight</th>
<th>(LV + Septum)/RV</th>
</tr>
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<tbody>
<tr>
<td>0.48%</td>
<td>2.8-4.0</td>
</tr>
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</table>
Results

Histopathology:

Lung:

- Hypertrophy & hyperplasia of endothelial cells and medial myocytes in pulmonary arteries & arterioles — 8/8
- Adventitial proliferation (arteries) — 1/8
- Calcification of elastin (arteries) — 2/8
- Thrombi — 3/8
- Hemorrhage — 8/8
- Calcification of alveolar septa — 2/8
- Mild multifocal bronchiolitis obliterans — 1/8
Results

Histopathology:

Heart:
—right atrium & ventricle: interstitial fibrosis associated with scattered foci of myocyte necrosis; cardiac myocyte hypertrophy—8/8

Liver:
— Severe chronic passive congestion —8/8

Kidney:
— minimal chronic interstitial inflammation —6/8
— thrombus, arcuate artery—1/8
Normal arteriole

endothelial hypertrophy & hyperplasia

Medial myocyte hypertrophy & hyperplasia
medial myocyte necrosis

medial myocyte hyperplasia

obstructed lumen
medial myocyte necrosis
intimal hyperplasia
calcification of elastin
cardiac myocyte hypertrophy

perimysial fibrosis
cardiac myocyte necrosis

perimysial fibrosis
Anitschkow cell proliferation and fibrosis
necrotic cardiac myocyte
Discussion

• Lesions seen in the present study are diagnostic of brisket disease (high altitude disease) as previously reported in the literature.

• Although previously reported, pulmonary vascular lesions in cattle with brisket disease have not been completely described.

• Relationship of brisket disease with pulmonary arterial aneurysms, hemorrhage and embolism also has not been well documented.
Discussion

• Lesions seen in the present study were very similar to those described in a preliminary report last year by O’Toole et al. AAVLD Annual Conference Proceedings, p. 51, Oct. 2008.

• This report involved Holstein heifers 6-12 months old in dairy herds on the Colorado Front Range (altitude >1600 m [>5249 ft]) which had right-sided heart failure secondary to pulmonary vascular lesions indicative of pulmonary hypertension.
Yes — In 1975, Hibbs reported 19 cases of unexplained brisket edema in feedlot cattle.

Location? — Western Nebraska (<5,000 ft).

(Neb. Vet. Ext. Newsletter Vol. 4, No. 10 pg. 82)
Conclusions

- Results of our investigation indicate that brisket disease caused by hypoxia-induced pulmonary hypertension at altitudes lower than 5,000 ft is responsible for the anecdotal increase in deaths.

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<thead>
<tr>
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<th>Sea Level (0 ft)</th>
<th>4500 ft</th>
<th>5000 ft</th>
</tr>
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<tbody>
<tr>
<td>PB*</td>
<td>101</td>
<td>86</td>
<td>85</td>
</tr>
<tr>
<td>PAO₂**</td>
<td>13.3</td>
<td>10.4</td>
<td>10</td>
</tr>
<tr>
<td>Difference in PAO₂ compared to sea level</td>
<td>↓21.8%</td>
<td>↓24.8%</td>
<td></td>
</tr>
</tbody>
</table>

*Barometric pressure in kPa.
**Partial pressure of oxygen in alveoli in kPa.
Is there an increased susceptibility of some cattle to brisket disease?

First, we know that pulmonary vascular shunting is seen in cattle to a much greater degree than in other species.

Species vary with regard to the extent of their vascular shunting responses to alveolar hypoxia:

• Cattle and pigs are hyper-responders
• Humans are intermediate responders
• Dogs and sheep are hypo-responders
Factors potentially predisposing to brisket disease

Age:
- Young cattle are more susceptible than older

Growth rate:
- Rapid growth increases susceptibility

Obesity (“highly conditioned”):
- Excess adipose tissue causes increased intra-abdominal pressure which, along with forestomach engorgement and recumbency can lead to hypoventilation and alveolar hypoxia

Lack of conditioning to altitude:
- Cattle moved from low to high altitudes increases incidence (0.5-5% vs. 10-40%)

Concurrent pneumonia or heart disease:
- e.g., bronchopneumonia, interstitial pneumonia, endocarditis, etc.

Cold environmental temperatures:
- temps <0°C have increased pulmonary arterial pressures (PAP) by 25 to 55%

Feeding ionophores:
- Preliminary data in one study found an association between ionophore feeding at recommended dosages and increased PAP
Is there a genetic predisposition to brisket disease in Angus cattle?

• Shirley et al. conducted studies concerning inheritance of pulmonary arterial pressure (PAP) in Angus cattle and its correlation with growth (J. Anim. Sci. 2008.86:815-819.).

• These authors concluded that PAP is moderately heritable in spring-born Angus cattle acclimatized and tested at high altitude, and proposed selecting breeding stock based on low PAP scores.
What might explain a genetic predisposition to hypoxia-induced pulmonary hypertension?

• Plausible explanations involve factors that regulate the vasoconstrictor response, e.g., plasminogen activator inhibitor (PAI), endothelial NO synthase, and hypoxia-inducible factor-1.

• Polymorphisms induced in the endothelial nitric oxide (NO) synthase gene resulted in mice that were more reactive to mild hypoxia and developed pulmonary hypertension more quickly than mice lacking the polymorphisms (Steudel et al. 1997. Circ. Res. 81:34-41)
Hypoxia-inducible Factor (HIF)

One possible scenario to explain a genetic predisposition to brisket disease:

Hypoxia → HIF-1 activates genes of the HRE

Increased expression of PAI-1

Increased proliferation of smooth muscle cells in pulmonary artery vasculature
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