Natural History of Pulmonary Hypertension: Adaptive versus Maladaptive Physiologic Responses in Beef Cattle Exposed to Chronic Hypoxia

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Introduction

1. Humans with group 3 PH characterized by alveolar hypoxia exhibit diversity in disease progression outcomes.
2. Similarly, certain breeds and individuals among beef cattle, including the American Angus demonstrate variable susceptibility to hypoxia-induced pulmonary vasocoonstriction, progressive remodeling of the pulmonary vasculature, pulmonary hypertension (PH) and right heart failure (HF).
3. Despite selection of breeding stock with low PH susceptibility, failure to thrive (≥47 mm Hg). Mean PAP values were re
4. Clinical and experimental evidence coupled with gross and microscopic cardipulmonary lesions suggest inflammation plays a significant role in the pathogenesis of pulmonary vascular remodeling, PH and right HF in cattle and recapitulates features of Group 3 PH in humans.

Hypothesis

1. The extent of pulmonary inflammation predicts the magnitude of fibroproliferative remodeling in the pulmonary vascular tree and the perivascular adventitia of the right ventricle.

Methods

Roose Ranch, Saratoga, WY 710 ft/218 m

The steers in Figure 1 exhibit transient transcutaneous oxygen tension of right heart failure, traditionally referred to as “Edematous Disease.” “Dray” or “High Country Dray” owing to prominent brisket, ventral and submandibular edema.

Three Hemodynamic Responses to Chronic Hypoxia

1. Atrial right heart catherection and procedures described by Holt and Callan (2007) were used to obtain the mean pulmonary arterial pressures (mPAP) in Angus steers born and raised at the Roose Ranch. Steers (n = 10 each) were selected at weaning (age 6 mos) with low mPAP (≤38 mm Hg) or high mPAP (≥47 mm Hg). Mean mPAP values were re-tested at 12–15 mos of age and animals were slaughtered at 15 mos. The total heart weight, isolated right ventricle (RV) and left ventricle (LV) plus associated septum, main pulmonary artery, aorta), fixed in 10% buffered formalin and processed for histopathology.

Cardiac Histopathology Indicates PH Progression

1. Pulmonary Histopathology Indicates PH Progression Influenced by Inflammation

1. Low mPAP Steers with No Cardiac Pathologic Alterations
2. Normal right ventricular myocardium
3. Intestinal fibrosis is not present in the right ventricle
4. Right ventricular myocardium with normal cardiomyocytes

High mPAP Steers with Cardiac Lesions

1. Cytologic vasculization in the right ventricle
2. Myocardial fibrosis in the right ventricular myocardium
3. Replacement fibrosis in the right ventricular myocardium
4. Masson’s Trichrome highlighting replacement fibrosis
5. Masson’s Trichrome demonstrating thickened adventitial matrix surrounding mural arteries
6. Masson’s Trichrome demonstrating extravasated cardiacocytes

Maladaptive lesions in the left ventricle were not present (Not Shown)

1. The average number of cardiomyocytes was determined by counting the number of cells in 10 high power (400X) fields for each ventricle. In order for a cardiomyocyte to be counted, the entire cross sectional area of the cell had to be contained within the boundaries of a 250 x 250 micron field.

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1. Similar to humans, there is variation among beef breeds and individual steers to alveolar hypoxia
2. Variation in hemodynamics and vascular remodeling is directly correlated to the extent of pulmonary inflammation
3. BALT expands in pulmonary hypertension and may influence pulmonary vascular remodeling and PH
4. Steers with the most severe pulmonary vascular remodeling, PH and right HF have evidence of pulmonary venocclusive disease, a novel finding in this species.

Conclusion

Beef cattle raised in chronic hypoxic environments provide a natural model of Group 3 PH where pulmonary inflammation and venous remodeling predict disease severity and outcomes and may provide novel therapeutic targets for the treatment of PH in humans and beef cattle.

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