




RESEARCH ARTICLE

The beta-adrenergic agonist zilpaterol hydrochloride may predispose feedlot cattle to cardiac remodeling and dysfunction [version 1; referees: awaiting peer review]

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Abstract

Background: The aim of this study was to address producer concerns that the β_2 -adrenergic agonist zilpaterol hydrochloride, a bovine growth promotant, predisposes cattle to cardiac disease and death. Our objectives were to evaluate the effect of zilpaterol on cardiac function, morphology, and risk of myocardial injury.

Methods: A prospective, case-control study was conducted on one feedlot in northern Colorado using convenience sampling of Angus-based steers ($n = 80$). Pulmonary arterial pressures (mean, systolic, and diastolic) were measured. Plasma cardiac troponin I was measured in a sub-sample of steers that were followed to slaughter ($n = 31$). The carcass, left ventricle plus inter-ventricular septum, and right ventricle were weighed.

Results: Relative to controls, steers fed zilpaterol hydrochloride had an adjusted left ventricle and septum that was 185 g heavier (95 % CI: 19, 350 g; $P = 0.03$), a diastolic pulmonary arterial pressure that was 10 mm Hg greater (95 % CI: 3, 17 mm Hg; $P = 0.004$), and a greater concentration of cardiac troponin I ($P = 0.01$), a biomarker of myocardial injury. Furthermore, left ventricular mass tended to be positively and deleteriously associated with diastolic pulmonary arterial pressure in steers fed zilpaterol ($P = 0.08$) but not controls ($P = 0.28$).

Conclusions: Our findings suggest that zilpaterol hydrochloride induced sufficient left ventricular hypertrophy to cause impaired left ventricular relaxation or diastolic dysfunction and myocardial injury. In conclusion, these results support concerns that, in the feedlot studied, zilpaterol hydrochloride predisposes cattle to cardiac disease.

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REVIEW

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Introduction

In the United States, two β -adrenergic agonists (β AA) are approved for the purpose of growth promotion in cattle fed in confinement for slaughter: ractopamine hydrochloride¹, a predominantly β_1 AA, and zilpaterol hydrochloride², a predominantly β_2 AA. In 2011, approximately 57% of cattle in U.S. feedlots were fed a β AA³. Beta-adrenergic agonists are synthetic, structural, and functional analogs of the endogenously produced compound epinephrine (adrenaline). They have the favorable effect of inducing skeletal muscle hypertrophy while decreasing adiposity⁴.

Chronic β -adrenoreceptor stimulation, however, may also cause left ventricular hypertrophy⁵, a strong, independent risk factor for death in humans^{6–8}. Moreover, a large observational study concluded that 40 to 50% of deaths among feedlot cattle treated with the β_2 adrenergic receptor-selective agonist zilpaterol hydrochloride (Zilmax®, Merck Animal Health, Summit, NJ, USA) were attributable to the drug⁹. The etiology of this increased mortality risk has not been investigated, but anecdotal reports suggest that cattle fed β_2 AA are at increased risk of heart failure. This is biologically plausible; mortality associated with chronic use of β_2 AA use in humans has been primarily attributed to myocardial disease^{10,11}.

The aim of this study was to address the concerns that zilpaterol hydrochloride may predispose cattle to heart failure. An in-situ, prospective, case-control study was performed at one feedlot in northern Colorado, U.S.A., to evaluate the effect of zilpaterol hydrochloride on bovine cardiopulmonary physiology, cardiac morphology, and the risk of myocardial injury.

Methods

Ethical considerations

The Colorado State University Animal Care and Use Committee approved of this project (Protocol 13-4451A). Permission to conduct the study at the feedlot and abattoir was granted by the owners prior to the start of sampling. All efforts were taken to ameliorate animal suffering by minimizing the time that steers were restrained for the purposes of this study.

Study site and sampling

Black-hided, Angus-based steers that were within 30 days of slaughter were studied in one feedlot located 1,440 m above sea level in northern Colorado (Table 1). The sample size was limited to 80 due to voluntary market withdrawal of the drug during the course of the study. Cattle were procured from the western U.S. through the auction market system and directly from producers. On arrival at the feedlot the cattle weighed approximately 300 kg. They were vaccinated against bacterial and viral pathogens, injected with an anthelmintic, implanted with a hormone growth promotant, and given an ear tag with a unique identification number. The cattle were harvested approximately 180 days after arrival and were managed per standardized protocols developed by specialists in the areas of feedlot animal health, nutrition, and husbandry. Steers were fed zilpaterol hydrochloride per the label directions: 7.6 g/ton zilpaterol (8.3 ppm on a 100% dry matter basis), to provide 60 to 90 mg zilpaterol hydrochloride per head per day. Steers were fed

Table 1. The number of cattle tested according to the date of testing in the year 2013.

Date	Control steers	Zilpaterol steers	Total
August 1 st	10	10	20
August 15 th	11	14	25
August 29 th	2	13	15
October 21 st	20	0	20
Total	43	37	80

zilpaterol for 21 days followed by a 7-day withdrawal period, rather than the minimum 3-day period required. Feed and water were always available.

Steers were chosen from each of 9 and 11 different pens, respectively. Control steers (CS) were selected that had the same, or a similar, slaughter date to zilpaterol treated steers (ZS). Steers were chosen from within each pen in such a way as to minimize animal disturbance. Steers were moved up to the chute individually, or in pairs, so that they spent minimal time within the curved alley. Steers were restrained in a chute for sampling and measurements. The ZS were studied at days 7 (n = 10), 8 (n = 6), 15 (n = 4), and 21 (n = 17) of β_2 AA exposure. In total, 35 apparently healthy CS and 28 apparently healthy ZS were sampled. Sixteen of the 80 steers studied, 8 ZS and 8 CS, were treated for respiratory disease at various times while at the feedlot. These animals were not included in the statistical analyses.

The sampling dates (Table 1) were determined by the schedule availability of investigators and feedlot personnel. Sampling was conducted between 8:00 am and 11:00am. In the original study design, approximately equal numbers of ZS and CS were to be sampled each day. This did not occur, however, for two reasons: first, zilpaterol hydrochloride was voluntarily withdrawn from the market on August 16th, 2013; and second, on August 29th sampling was called off by the feedlot manager after 2 ZS became highly stressed in the alley and refused to exit. Their rectal temperatures reached 42.2°C (108 °F) (Quick-temp Digital Thermometer, Agripro Enterprises, Iowa Falls, Iowa, USA). The steers were cooled with alcohol poured over the skin and, after approximately 1 hour, walked forwards out of the chute; consequently, only 11 healthy ZS, and 2 ZS and 2 CS that had been treated for respiratory disease, were studied on that day. Following the withdrawal of the drug from the market, only CS were available for further study.

Pulmonary arterial pressure (PAP) measurement

A full description of the equipment, materials, and facilities required for PAP testing is provided elsewhere¹². In brief, an 8.9 cm (3.5 inch) 12-gauge needle was inserted into the jugular vein through which flexible, saline-filled catheter/polyethylene tubing was threaded. The catheter tip was then fed through the right atrium and ventricle and into the pulmonary artery. A pressure

transducer connected the catheter to an oscilloscope (BM5Vet, Bionet America Inc., Tustin, CA, USA). The position of the catheter was determined from the pressure waveform on the oscilloscope. The jugular vein, right atrium, right ventricle, and pulmonary artery have distinct pressure waveforms¹². Mean, systolic, and diastolic pressures were recorded after the pulmonary pressure waveforms had stabilized. Diastolic PAP is hemodynamically influenced by left ventricular chamber pressures shortly prior to contraction, and therefore provides an indirect measure of end-diastolic left ventricular filling pressure¹³. Pulmonary arteriolar wedge pressure is a more direct measure of left ventricular end-diastolic pressure. Wedge pressures are, however, more difficult and time-consuming to obtain in cattle because the fluid-filled catheters used are not balloon-tipped; consequently, to minimize the time that cattle spent in the chute, arteriolar wedge pressures were not collected.

Blood analysis

Cardiac troponin I analyses were performed on a single day using plasma samples that had been obtained from all steers that were followed to slaughter. The plasma had been stored at -80° C and thawed at room temperature prior to analysis (cTnI, i-STAT 1, Abaxis, Union City, CA).

Hot carcass weight (HCW) and ventricular weights

In the original study design, all cattle at the feedlot that died within the late feeding period were to be evaluated postmortem throughout the duration of the study. Due to an insufficient number of feedlot personnel, however, postmortem data were not collected. Cardiac dimension data were, therefore, collected at slaughter from the remaining 2 cohorts of steers: the 11 ZS studied on August 29th, 2013, and slaughtered on September 5th; and the 20 CS studied on October 21st and slaughtered on October 29th, 2013. Only steers that were healthy at the time of sampling and had not been treated for disease while at the feedlot were followed to slaughter.

The steers were slaughtered at a nearby USDA-approved facility. The individual animal identification number of every animal in the study remained with the carcass and heart throughout the slaughter process. This allowed the hot carcass weight (HCW, mass of the unchilled carcass after removal of the head, hide, and viscera) to be paired with cardiac mass. After inspection by a USDA veterinarian, the heart was removed from the processing line, placed in a plastic bag, and stored in ice.

The atria were dissected from the ventricles at the level of the atrioventricular valves and the ventricles subsequently divided into a left ventricle plus inter-ventricular septum (LVS) and right ventricular free wall (RV). The ventricles were weighed using

a scale with precision to 0.045 kg (0.1 lb). All cardiac tissue was dissected and weighed within 3-hours of slaughter.

Statistical analyses

Data were analyzed using statistical software (STATA version 12.1, Stata Corporation, College Station, Texas, USA). Statistics are provided as an adjusted average (mean or median) \pm 95% confidence interval of the average. The animal served as the experimental unit. Only steers that were apparently healthy at the time of testing and had not been treated for any disease while at the feedlot were included in statistical analyses. Steers that had been treated, or needed treatment, for disease were not included in any statistical analyses due to the small sample size.

Between-group statistical differences in PAP (3 variables) were assessed using quantile regression for nonparametric data while controlling for pen-level clustering ('qreg2' command)¹⁴. In subsequent analyses, pen-level clustering was not a concern because ZS and CS that were followed to slaughter belonged to the same 2-pens. Differences in right and left ventricular masses were assessed using linear regression analyses. A Wilcoxon rank-sum test (Mann-Whitney *U* test) was performed for evaluation of cardiac troponin I due to the non-parametric distribution of residual error about the mean ('ranksum' command). Finally, the effect of left ventricular mass per unit of HCW on diastolic PAP was evaluated, stratified by the feeding of zilpaterol. Left ventricular mass per unit of HCW was chosen as the dependent variable rather than LVS because of the potential collinearity between LVS and HCW. A linear regression analysis was performed for ZS and, due to lack of normality of the standardized residuals, quantile regression was performed for CS ('qreg' command). Evaluations of model fit included graphical and statistical assessments of residual error normality (Shapiro-Wilk test), heteroskedasticity (Breusch-Pagan/Cook-Weisberg test), and linearity.

Results

The results of this study indicate that, in the feedlot studied, steers fed the β A zilpaterol hydrochloride had greater left ventricular hypertrophy and plasma cardiac troponin I, a biomarker of myocardial injury, than controls. The mass of the left ventricle tended to be positively associated with diastolic PAP in ZS, but there was no association between left ventricular mass and diastolic PAP in CS.

Pulmonary arterial pressures

Diastolic PAP was 10 mm Hg greater in ZS than CS (95% CI: 3, 17 mm Hg; $P = 0.004$). Mean and systolic PAP were not statistically different ($P > 0.20$). Mean PAP was 47 mm Hg (95% CI: 44, 50 mm Hg) in both ZS and CS. Systolic PAP was 80 mm

Hg (95% CI: 76, 84 mm Hg) in CS and 82 mm Hg (95% CI: 73, 90 mm Hg) in ZS.

Cattle treated for respiratory disease had greater pressures than healthy cattle. Mean PAP was 57 (95% CI: 36, 78 mm Hg) in CS and 61 (95% CI: 33, 89 mm Hg) in ZS. Systolic PAP was 95 mm Hg (95% CI: 60, 130 mm Hg) in CS and 93 mm Hg (95% CI: 52, 134 mm Hg) in ZS. Diastolic PAP was 20 mm Hg (95% CI: 4, 36 mm Hg) in CS and 37 (95% CI: 16, 58 mm Hg) in ZS.

Cardiac hypertrophy

Steers fed zilpaterol hydrochloride had hypertrophy of the LVS. Steers fed zilpaterol had an adjusted LVS mass that was 185 g (95% CI: 19, 350 g) heavier than CS ($P = 0.03$). Right ventricular mass did not differ between ZS and CS ($P = 0.33$). The HCW of ZS was 403 kg (95% CI: 376, 429 kg) and 418 kg (95% CI: 400, 437 kg) in CS ($P = 0.29$). The adjusted mean mass of the RV was 588 g (95% CI: 526, 650 g) in CS and

535 g (95% CI: 450, 619 g) in ZS. The adjusted mean mass of the LVS was 1.512 kg (95% CI: 1.419, 1.605 kg) in CS and 1.697 kg (95% CI: 1.570, 1.824 kg) in ZS.

The mass of the LVS per unit of HCW tended to be associated with diastolic PAP in ZS ($P = 0.08$) but not CS ($P = 0.28$) (Figure 1A). In ZS, a 0.1 kg increase in LVS per 100 kg of HCW was associated with a 9 mm Hg (95% CI: -1, 19 mm Hg) increase in diastolic PAP.

Cardiac troponin I (cTnI)

Plasma cardiac troponin I (cTnI) concentrations were significantly greater in ZS than CS ($P = 0.01$). The greatest concentrations were observed in the two steers with the most hypertrophied left ventricles (Figure 1B). In CS, the concentrations of cTnI ranged from 0.00 to 0.02 ng/mL; 5% (1 of 20 steers) had a cTnI concentration of 0.02 ng/mL. In ZS, the concentrations of cTnI ranged from 0.00 to 0.04 ng/mL; 36% (4 of 11 steers) had a cTnI concentrations

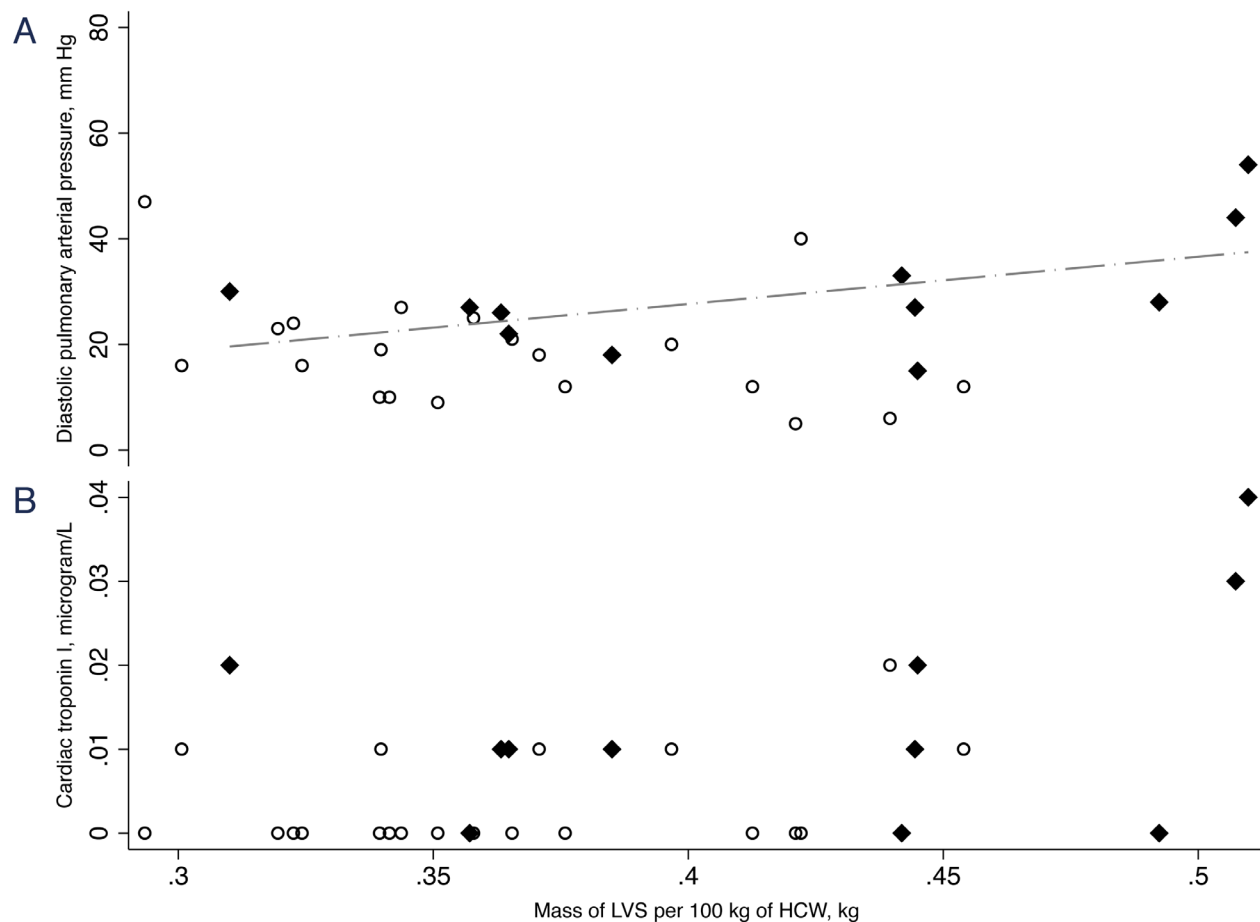


Figure 1. The relationship between A) diastolic pulmonary arterial pressure (PAP) and B) plasma cardiac troponin I with mass of the left ventricle plus inter-ventricular septum (LVS) per 100 kg of hot carcass weight (HCW). Left ventricular hypertrophy in steers fed zilpaterol hydrochloride tended to be positively associated with diastolic PAP. Cardiac troponin I concentrations were significantly greater in steers fed zilpaterol hydrochloride. The two steers with the greatest left ventricular hypertrophy had the greatest diastolic pulmonary arterial pressures (A) and the greatest cardiac troponin I concentrations (B).

of 0.02 ng/mL or greater. The complete results are as follows: among the 20 CS sampled, 14 (70%) had a cTnI of 0.00 ng/mL, 5 (25%) had a cTnI of 0.01 ng/mL, and 1 (5%) had a cTnI of 0.02 ng/mL; among the 11 ZS sampled, 3 (27%) had a cTnI of 0.00 ng/mL, 4 (36%) had a cTnI of 0.01 ng/mL, 2 (18%) had a cTnI of 0.02 ng/mL, 1 (9%) had a cTnI of 0.03 ng/mL, and 1 (9%) had a cTnI of 0.04 ng/mL.

Discussion

The findings of this study indicate that, in the feedlot studied, the β_2 AA zilpaterol hydrochloride is associated with left ventricular hypertrophy and myocardial injury. Furthermore, the tendency in our study for left ventricular mass to be positively and deleteriously associated with diastolic PAP in steers fed zilpaterol hydrochloride suggests that β AA-induced left ventricular hypertrophy likely caused diastolic dysfunction.

Left ventricular hypertrophy is a product of chronic β -adreno-receptor activation and is a major risk factor for cardiovascular morbidity and mortality in humans and animals^{5,15}. Two major sequelae of ventricular hypertrophy pertinent to our study are diastolic dysfunction¹⁶ and myocardial ischemia¹⁷. Diastolic dysfunction is defined as failure of the myofibrils to return to their resting length and ventricular filling is slow or incomplete unless atrial pressure increases¹⁶. A hallmark of diastolic dysfunction is an increase in left ventricular end-diastolic pressure¹⁶. End-diastolic pressure is positively correlated with diastolic PAP, even when pulmonary vascular resistance or heart rate is elevated^{13,18}; consequently, the positive association between left ventricular mass and diastolic pulmonary arterial pressure in steers fed zilpaterol, but not controls, suggests that the myocardial hypertrophic effects of zilpaterol induced diastolic dysfunction. This is not unreasonable: the myocardial hypertrophic action of β AA, such as isoprenaline, are used for the study of diastolic dysfunction in animal models of heart failure^{19–21}.

Hypertrophy also predisposes to myocardial ischemia¹⁷. This may explain why steers fed zilpaterol had significantly greater cardiac troponin I concentrations than controls, the latter having concentrations similar to those reported in healthy cows²². Intriguingly, the two steers with the greatest cardiac troponin I concentrations also had the greatest left ventricular hypertrophy. This may have been coincidental, but the research literature suggests otherwise. Left ventricular hypertrophy in humans is a strong predictor of death from cardiovascular disease⁶. Without histological evaluation of the myocardial tissue, however, we cannot say if the statistical difference observed was biologically relevant.

Myocardial injury has, to our knowledge, not been previously associated with zilpaterol in cattle. A recent study of 30-Angus steers found no histologic evidence of apoptosis associated with the β AA zilpaterol and ractopamine²³. Myocardial necrosis and fibrosis have, however, been reported in association with β AA in other species^{24,25}. The myocardial injury observed in association with zilpaterol in our study could have been

exacerbated by poor air quality since the inhalation of particulate matter may exacerbate cardiopulmonary injury induced by β AA^{26,27}. This may, in part, explain the seasonal variation observed in mortality risk associated with zilpaterol hydrochloride⁹.

The health implications of diastolic dysfunction in cattle fed β AA may be extensive: diastolic dysfunction in humans increases the risk of pulmonary edema²⁸ and all-cause mortality^{29,30}. Given that the findings of our study suggest that β_2 AA-induced left ventricular hypertrophy caused diastolic dysfunction, and that an increased in all-cause mortality has been associated with the feeding of β AA to cattle⁹, studies to evaluate the effect of β AA on cardiac function and morphology are needed. Suitable echocardiographic measures of diastolic ventricular function include transmitral filling velocity, ventricular relaxation velocity, and pulmonary vein flow. Pulmonary arteriolar wedge pressures would provide a more accurate measure of left ventricular end-diastolic pressure than diastolic PAP. Balloon floatation catheters are superior to the saline-filled polyethylene tubing typically used for PAP measurement¹² because arteriolar occlusion is necessary for accurate wedge pressure measurement.

A limitation of our study design is that it was necessary to forfeit external validity to maintain internal validity. This allowed us to successfully address the aim of this study. To achieve internal validity, cattle were not randomized into treatment groups because, in the feedlot studied, the feeding of zilpaterol was at the discretion of the feedlot manager. Concerned that zilpaterol may increase the risk of death, particularly among cattle with a history of disease, the feedlot manager only fed zilpaterol to cattle in pens with a low incidence of morbidity and mortality. Given that respiratory disease predisposes cattle to heart failure³¹, any confounding, if present, should have biased the results towards the null. Large, randomized studies are necessary to validate our findings because our results cannot be extrapolated to other feedlots and the number of cattle studied was small.

In conclusion, our results raise concerns that, in the feedlot studied, zilpaterol hydrochloride predisposes cattle to cardiac disease. Healthy cattle fed the β AA zilpaterol hydrochloride had left ventricular hypertrophy that was positively associated with diastolic PAP and myocardial injury.

Data availability

All raw data underlying this study is available from Harvard Dataverse under a CC0 Public Domain Dedication: <http://dx.doi.org/10.7910/DVN/4IKGIN>³²

Competing interests

No competing interests were disclosed.

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