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Impaired alveolar-arterial oxygen transfer is associated with reduced milk yield in primiparous post-partum dairy heifers at moderate altitude

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Domestic cattle have limited cardiopulmonary reserve for their body size and oxygen requirements. Therefore, it is plausible that impaired alveolar-arterial gas exchange may be detrimental to energetically expensive traits such as milk production which, like all aerobic processes, requires oxygen. The degree of alveolar-arterial oxygen transfer impairment can be determined by estimating the alveolar-arterial oxygen (A-a O_2) pressure gradient from arterial blood-gas tensions. The degree of oxygen transfer impairment is proportional to the A-a O_2 pressure gradient: the higher the A-a O_2 pressure gradient the less oxygen is transferred to the blood for a given ventilation rate. In this study two cohorts of Holstein-Friesian heifers were followed on one northern Colorado dairy farm. Arterial blood-gas analyses were performed up to 9 d post-calving. Heifers were grouped into quartiles based on A-a O_2 pressure gradient so that relative comparisons could be made. Heifers in the lowest (Q_1) and highest (Q_4) quartile had the least and greatest impairment of alveolar-arterial oxygen transfer, respectively. We hypothesised that milk yield over 60 d would be greatest for heifers in Q_1 and would decrease with quartile increments. Hyperventilation, as indicated by hypocapnia, was notable. Despite hypoxia, haematocrit was low. Alveolar-arterial O_2 pressure gradient was associated with milk production ($P = 0{\cdot}03$) when controlling for cohort, treatment for disease and calving difficulty score. Heifers in Q_1 produced 1992 kg (95% CI = 1858, 2127 kg) of milk when controlling for all other variables. Relative to heifers in Q_1, heifers in Q_2, Q_3 and Q_4 produced 130 kg (95% CI = 313, − 52 kg; P = 0·45), 285 kg (95% CI = 474, 96 kg; P = 0·004) and 169 kg (95% CI = 395, − 57 kg; P = 0.14) less milk, respectively. In conclusion, efficacy of alveolar-arterial oxygen transfer was associated with milk yield in dairy heifers on one farm at moderate altitude.

Keywords: Alveolar-arterial oxygen pressure gradient, health, heifers, milk production.

The Holstein–Friesian breed can be traced back 2000 years to a coastal province in the Netherlands (Houghton, 1897). The breed now represents 90% of all dairy cows in the US dairy industry (USDA, 2007) and the average cow produces close to 10 000 kg of milk per year (USDA, 2008), which is over 4-times more milk than the average cow in 1955 (Crowley & Niedermeier, 1981). The net energy required for milk production is linearly related to the amount of milk produced when controlling for fat, protein and lactose content (NRC, 2001). Therefore, the original Holstein-Friesian breed had a lower oxygen demand in an oxygen-rich environment; air inspired in the Netherlands contains 17% more oxygen than at 1600 m above sea level, the altitude at which this study was conducted.

Typically, mammalian lungs have sufficient physiological reserve so that even under periods of high oxygen demand the transfer of oxygen from alveoli into the pulmonary circulation is rarely limiting (Wagner et al. 1986; Calbet & Lundby, 2009). However, domestic cattle are not a 'typical' mammalian species; they have a small lung volume and gaseous exchange surface area for their body size and oxygen requirements (Veit & Farrell, 1978). When administered 100% O_2 cattle attain a substantially lower arterial oxygen tension than other mammalian species (Kainer & Will, 1981). In order to maintain oxygen delivery to peripheral tissues mammals can adapt to chronic hypoxia

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through various mechanisms, such as increased haematocrit, increased cardiac output and increased oxygen extraction at the tissue level. However, cattle show a limited adaptive response to chronic hypoxia (Will et al. 1962; Neary et al. 2013). Given the limited reserve of the bovine cardio-pulmonary system, impairment of alveolar-arterial oxygen transfer, and consequently a reduction in blood-oxygen content, may have a detrimental impact on productivity. If so, the relationship between alveolar-arterial oxygen transfer efficacy and productivity would be most apparent under conditions of low atmospheric oxygen tension found at increasing altitudes.

In this study alveolar-arterial oxygen transfer efficacy was evaluated by estimating the alveolar-arterial oxygen (A-a O_2) pressure gradient from arterial blood-gas tensions (Bach, 2008). End-tidal CO_2 measurement is required for determination of the respiratory exchange ratio (RER), a component of the alveolar gas equation. However, end-tidal CO_2 measurement would have required use of cumbersome spirometric equipment, which would have been detrimental to routine farm operations. Therefore, in order to minimise our on-farm impact we used a RER of 0·9 based on prior studies of Holstein cattle (Gallivan et al. 1989, 1991). In the unlikely event that the A-a O_2 pressure gradients calculated in our study were incorrect due to an incorrect RER the relative values and therefore between-animal comparisons should still be correct even if the absolute values are not. By grouping heifers into quartiles based on their A-a O_2 pressure gradient relative comparisons could be made. Heifers in the lowest (Q_1) and highest (Q_4) quartile had the least and greatest impairment of alveolar-arterial oxygen transfer, respectively. Respiratory exchange ratios are influenced by factors such as diet and degree of fasting (Blaxter & Wainman, 1966; O'Kelly, 1985). In our study individual variation in RER was minimised by studying primiparous heifers on one farm that were fed the same diet and sampled at a consistent time of the day. We hypothesised that milk yield over 60 d would be greatest for heifers in Q_1 and would decrease with increments in quartile.

Materials and methods

Colorado State University Animal Care and Use Committee approved this study.

Study herd

Two cohorts of Holstein-Friesian heifers were followed on one northern Colorado dairy herd with approximately 1370 milking animals located at an altitude of 1600 m above sea-level. The cohorts represent a convenience sample of two groups of similarly aged heifers enrolled at two difference time points. The heifers enrolled in this study were born and raised on the farm until approximately 6 months old when they were transported 20 km to a heifer raising facility (1700 m above sea-level). The heifers returned to the farm approximately 2 months prior to their expected calving date. Heifers were sampled up to 9 d post calving.

Four weeks prior to calving the heifers were given an intranasal modified live respiratory disease vaccine offering protection against *Bovine herpes virus 1* (infectious bovine rhinotracheitis, IBR), *Bovine respiratory syncytial virus* (BRSV) and *Bovine parainfluenza virus 3* (BPIV-3) (INFORCE 3, Zoetis Animal Health, Florham Park NJ, USA) and an *Escherichia coli* J5 bacterin vaccine (Enviracor J-5, Zoetis Animal Health). At approximately 12 d in milk (DIM) the heifers were vaccinated with a modified live respiratory disease vaccine offering protection against IBR, *Bovine viral diarrhoea virus* (BVDV), BRSV, and BPIV-3 (Bovishield Gold FP 5, Zoetis Animal Health) and revaccinated with an *Escherichia coli* J5 bacterin vaccine. A calving difficulty score was recorded by the calving attendant; values ranged from 1, no assistance required, to 5, caesarean section delivery required. A score of 2 indicated that minimal manual assistance was provided and a score of 3 indicated a 'hard pull' by the calving attendant.

Heifers were housed according to calving and lactation status. Prior to calving heifers were located in a dry lot. Post-calving heifers were housed in a freestall barn with other primiparous heifers until approximately 30 DIM. Heifers were then moved to another freestall barn containing primiparous heifers until approximately 140 DIM when they were moved to another pen. Individual heifer milk yield was monitored daily (DairyPlan, GEA Farm Technologies, Inc., Naperville IL, USA).

Blood collection

Blood was collected from the coccygeal artery using a 22 gauge, 2·54-cm hypodermic needle. The bovine coccygeal artery is a suitable source for blood-gas analysis (Collie, 1991; Nagy et al. 2002). Syringes were heparinised with approximately 0·25 ml of sodium heparin. The plunger of each syringe was pulled back to the 3-ml mark coating the inner chamber surface with heparin and then evacuated several times so that only the needle hub contained heparin. Approximately 2·5 ml of blood was collected in a 3-ml syringe. Dilution of blood by heparin <10% is sufficient to minimise pre-analytical error (Hutchison et al. 1983). The sample was discarded if during collection the flow of arterial blood was interrupted. Air bubbles within the blood were immediately expelled and the first several drops of blood discarded before analysis. Blood-gas analysis was performed using a handheld analyser (VetScan i-STAT 1, Abaxis, Union City CA, USA). Variables analysed as part of the study included: pH, oxygen tension (pO_2), carbon dioxide (pCO_2) and haematocrit. Blood-gas tensions are temperature dependent. Blood-gas tensions were therefore corrected to 37 °C so that comparisons among individuals differing in body temperature could be made (CLSI, 2001). Blood samples were collected between 6·00 and 8·00 and analysed immediately.

Alveolar-arterial oxygen gradient

An A-a O_2 pressure gradient is a measure of alveolar-arterial oxygen transfer and was estimated using the following formulae (Bach, 2008):

$$A - a\ O_2\ \text{pressure gradient} = p_AO_2 - pO_2$$

$$p_AO_2 = FiO_2(BP - pH_2O) - (pCO_2/RER)$$

where p_AO_2 = alveolar O_2 tension (mm Hg); pO_2 = arterial O_2 tension (mm Hg); pCO_2 = arterial CO_2 tension (mm Hg); RER = respiratory exchange ratio (0·9 (Gallivan et al. 1989, 1991)); FiO_2 = fraction of inspired O_2 (0·21); BP = barometric pressure (mm Hg); and pH_2O = water vapour pressure at body temperature (51 mm Hg at 38·5 °C).

Arterial pO_2 is not a reliable indicator of alveolar-arterial oxygen transfer impairment as it varies with ventilation rate and altitude. An A-a O_2 pressure gradient is the estimated difference in oxygen tension between the alveoli of the lung and arterial blood when corrected for ventilation rate. An A-a O_2 pressure gradient of 0 mm Hg is the lowest possible value and indicates that there is no impairment to oxygen transfer between the alveoli of the lungs and pulmonary circulation.

Statistical analysis

Statistical analyses were performed using STATA version 12 (Stata Corporation, College Station, Texas, USA). Descriptive statistics are given as mean ± SD unless otherwise indicated.

Student's *t* test was performed to determine whether the arterial blood-gas variables differed between heifers treated for any disease prior to sampling and heifers not treated for any disease prior to sampling. Bonferroni correction was applied in order to achieve a family-wise type I error risk of 0·05.

Heifers were grouped into quartiles based on A-a O_2 pressure gradient. The lowest quartile of A-a O_2 pressure gradients (Q_1) served as the baseline reference. A linear regression analysis was performed to determine the association between the outcome variable milk yield and the explanatory variable A-a O_2 pressure gradient when controlling for cohort, calving difficulty score, treatment for at least one disease prior to calving and treatment for at least one disease between calving and 60 DIM.

Results

A total of 80 heifers were sampled (Table 1). Cohort 1 had a wider calving interval (71 d) than cohort 2 (29 d) (Table 1). At the time of sampling body condition scores ranged from 3·25 to 4·0 (mode = 3·5). Sampling was performed 4·13 ± 2·37 d post calving and ranged from the day of calving up to 9 d post calving. A calving difficulty score of 1 (n = 55) was most common followed by scores of 2 (n = 19) and 3 (n = 6). Rectal temperatures among heifers ranged from 38·2 to 39·7 °C. The mean temperature was 38·7 ± 0·3 °C.

Table 1. The date, number of heifers sampled (*n*), and age when sampled according to cohort (mean ± SD)

Cohort	Date sampled	*n*	Age when sampled, d
1	30/4/12–10/7/12	42	708 ± 57
2	13/3/13–11/4/13	38	666 ± 81
Total		80	

Health events

Prior to calving 18 heifers (18/80, 23%) were treated at least once for bovine respiratory disease (BRD): 17 heifers were treated only once and 1 heifer was treated on 3 occasions. The median age at first treatment was 264 d and ranged from 33 to 497 d. Of the 18 calves treated for BRD, 10 were also treated for other conditions including: miscellaneous illness (n = 6), diarrhoea (n = 2), lameness (n = 1) and bloat (n = 1). Another 17 heifers were treated for diseases other than, but not in addition to, BRD: miscellaneous illness (n = 13), bloat (n = 3) and lameness (n = 1).

Seven heifers (9%) were treated for BRD between calving and 60 DIM. None of these 7 heifers had been treated for BRD prior to calving. Only one heifer was treated for BRD between calving and blood sampling. Three of the 7 heifers treated for BRD were also treated for other diseases: gastrointestinal disease (n = 1), metritis (n = 1) and left displaced abomasum (LDA) (n = 1). Twenty-nine heifers (36%) were treated for non-respiratory diseases between calving and 60 DIM. Eight of these heifers were treated between calving and blood sampling. Non-respiratory diseases included: metritis (n = 5), mastitis (n = 4), udder oedema (n = 4), LDA (n = 2), gastrointestinal disease (n = 2) and ketosis (n = 2). Five of the 15 heifers treated for metritis were also treated for the following diseases within 60 DIM: gastrointestinal disease (n = 2), ketosis (n = 1), injury (n = 1) and re-treatment for metritis (n = 1). Eight of the 29 heifers treated for non-respiratory diseases were treated between calving and blood sampling mostly for metritis (n = 4) but also ketosis (n = 2), udder oedema (n = 1) and mastitis (n = 1).

Arterial blood-gas analysis

Arterial blood-gas statistics did not differ between heifers treated and heifers not treated for any disease between calving and blood sampling (Table 2). Compared with a study conducted on 7 healthy Holstein cows ranging in age from 2 to 5 years at an altitude of approximately 300 m (Gallivan et al. 1989) the heifers in our study were more hypoxic despite hyperventilating, as indicated by hypocapnia. The minimum and maximum A-a O_2 pressure gradients were − 2·5 mm Hg and 35·0 mm Hg, respectively (Table 3). Relative to heifers with low A-a O_2 pressure gradients heifers with high A-a O_2 pressure gradients had low arterial O_2 and CO_2 tensions but haematocrit did not differ (Table 3). Alveolar-arterial O_2 pressure gradient was not significantly

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Table 2. Arterial blood-gas variables and haematocrit for all heifers, heifers not treated for any disease and, heifers treated for any disease between calving and blood sampling (mean ± SD)

	All heifers		Heifers not treated for any disease		Heifers treated for any disease		
Variable	*n*		*n*		*n*		*P* value†
pH	80	7·50 ± 0·04	71	7·50 ± 0·03	9	7·50 ± 0·04	>0·5
pCO_2, mm Hg	80	34·9 ± 2·8	71	34·9 ± 2·7	9	34·7 ± 3·5	>0·5
pO_2, mm Hg	80	72·5 ± 6·2	71	72·7 ± 6·3	9	71·4 ± 5·2	>0·5
A-a O_2,‡ mm Hg	80	10·3 ± 7·5	71	10·1 ± 7·7	9	11·6 ± 5·3	>0·5
Haematocrit, %	26	26·5 ± 2·5	25	26·5 ± 2·5	1	26	>0·5

† Heifers not treated for any disease *vs.* heifers treated for any disease
‡ Alveolar-arterial oxygen pressure gradient

Table 3. Alveolar-arterial oxygen pressure gradient, haematocrit, arterial O_2 and CO_2 tensions by quartile (mean ± SD)

Quartile	Alveolar-arterial O_2 pressure gradient (mm Hg)	Haematocrit (%)	Arterial O_2 tension (mm Hg)	Arterial CO_2 tension (mm Hg)
Q_1	$-2·5 < Q_1 \leqslant 4·9$	26 ± 2	78·9 ± 2·7	36·9 ± 1·9
Q_2	$4·9 < Q_2 \leqslant 10·2$	26 ± 1	75·6 ± 2·5	35·0 ± 2·1
Q_3	$10·2 < Q_3 \leqslant 14·3$	27 ± 1	70·5 ± 2·8	35·5 ± 2·6
Q_4	$14·3 < Q_1 \leqslant 35·0$	27 ± 1	65·7 ± 5·5	32·3 ± 2·4

correlated with haematocrit ($r = 0·18$, $P = 0·38$) but it was significantly correlated with arterial O_2 tension ($r = -0·92$, $P < 0·001$) and arterial CO_2 tension ($r = -0·60$, $P < 0·001$). The interpretation of these results indicates that heifers with high A-a O_2 pressure gradients had greater alveolar ventilation but lower arterial oxygen tensions than heifers with low A-a O_2 pressure gradients.

Milk production

Mean milk yield to 60 DIM was 1854 ± 293 kg. Alveolar-arterial O_2 pressure gradient was associated with milk production ($P = 0·03$) when controlling for cohort, treatment for at least one disease prior to calving, treatment for at least one disease between calving and 60 DIM and calving difficulty score in heifers not treated for any disease between calving and arterial blood-gas analysis. Heifers in Q_1 produced 1992 kg (95% CI = 1858, 2127 kg) of milk when all other variables were held at their mean values. Relative to heifers in Q_1 heifers in Q_2, Q_3 and Q_4 produced 130 kg (95% CI = 313, −52 kg; $P = 0·45$), 285 kg (95% CI =474, 96 Kg; $P = 0·004$) and 169 kg (95% CI = −395, −57 kg; $P = 0·14$) less milk, respectively.

Discussion

Numerous physiological and environmental factors have been described that impact milk production in dairy cattle such as milking frequency and dietary factors (Patton et al. 2006), disease (Green et al. 2002) and heat stress (West, 2003). However, despite the detrimental impact of BRD on lifetime milk production (Cobo-Abreu et al. 1979), little attention has been afforded to oxygen, the defining component of aerobic respiration: ATP generation through glycolysis coupled to oxidative phosphorylation. The impact of respiratory disease on productivity has largely been attributed to factors other than an impairment of lung function per se.

Oxygen transfer impairment is proportional to the A-a O_2 pressure gradient: the higher the A-a O_2 pressure gradient the less oxygen is transferred to the blood for a given ventilation rate. Impairment of the gaseous exchange ability of the lungs following pathogen challenge results in a rapid drop in arterial oxygen tension and an increase in the A-a O_2 pressure gradient (Lekeux et al. 1985; Slocombe et al. 1989; Ostermann et al. 2013).

In this study, we found that A-a O_2 pressure gradient in post-partum primiparous heifers was significantly associated with milk yield over 60 d. An A-a O_2 pressure gradient >10 mm Hg is an indicator of poor O_2 transfer efficacy due to ventilation-perfusion mismatching, diffusion impairment or right-to-left vascular shunt (Lekeux, 1993). Airway obstruction, consolidation of alveoli, pulmonary vasoconstriction, pulmonary inflammation and interstitial oedema are all potential causes of reduced A-a O_2 transfer, which are reflected by an increased A-a O_2 pressure gradient. Alveolar-arterial oxygen transfer can be influenced by pathophysiology originating from extrapulmonary sites, such as endotoxaemia (Olson & Brown, 1985). Therefore, estimation of the A-a O_2 pressure gradient reflects the ability of the lung to oxygenate blood whatever the cause, or causes, of variation

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in the efficacy of alveolar-arterial oxygen transfer might be when controlling for ventilation rate.

A limitation of our study is that only a small sample of heifers on one farm was studied ($n=80$). However, to our knowledge this is the first study of its kind: a quantitative evaluation of the relationship between bovine A-a O_2 transfer and productivity. Therefore, we did not have sufficient prior information to perform statistical power calculations.

The mean A-a O_2 pressure gradients in our study were over 10 mm Hg indicating that approximately half of the heifers sampled had A-a O_2 pressure gradients that were abnormally high. The lowest A-a O_2 pressure gradient obtained in this study was $-2{\cdot}5$ mm Hg, which is physiologically impossible. However, because we used a respiratory exchange ratio of 0·9 based on prior studies of Holstein cattle (Gallivan et al. 1989, 1991) a minimum estimated A-a O_2 pressure gradient less than 0 mm Hg was not unexpected; the diet of cattle in our study and therefore, the true respiratory exchange ratio was likely to be slightly different. However, the relative values and therefore the quartile-quartile comparisons should still be correct. Given that the lowest A-a O_2 pressure gradient was $-2{\cdot}5$ mm Hg it is likely that the true mean A-a O_2 pressure gradient was approximately 2·5 mm Hg higher than reported.

In mammals, only 20–30% of oxygen delivered to the systemic circulation is utilised (McLellan & Walsh, 2004). Therefore, it may be surprising that oxygen availability could be limiting given the large reserve of oxygen within the circulation. However, Fick's Law of Diffusion states that the diffusion rate of a gas is proportional to the pressure gradient. A high A-a O_2 pressure gradient may reduce the oxygen gradient, or 'driving pressure', between the capillary bed and the peripheral tissue. For instance, two heifers with the same alveolar ventilation rate but differing in their A-a O_2 pressure gradients by 20 mm Hg would have arteriolar oxygen tensions differing by 20 mm Hg, all other things being equal. The smaller the pressure difference between the arteriolar oxygen tension and the peripheral tissue the smaller the driving pressure. Within mammary tissue, limited oxygen availability could plausibly result in reduced ATP availability for the production, packaging and secretion of milk components.

Fick's Law of Diffusion also states that the diffusion rate of a gas is inversely proportional to the distance needed for the gas to travel. Mammary alveolar cells most distant from a capillary network may be particularly prone to hypoxia due to large diffusion distances. Studies in rodents show that flow rates and haematocrit within the mammary capillary network vary considerably between capillaries with some capillaries inactive for periods of over 2 h (Prosser et al. 1996). Under-perfused areas within bovine mammary tissue could rapidly consume the limited oxygen available.

In the latest national survey Colorado had the highest average milk production per cow (USDA, 2008) demonstrating that dairy cows can be highly productive at this altitude. Animals can compensate for a reduction in atmospheric oxygen tension by hyperventilating, thereby elevating arterial oxygen tension. However, hyperventilation is associated with diminishing returns: the energetic cost associated with ventilatory effort increases quadratically with ventilation rate in humans (Coast et al. 1993) and respiratory alkalosis impairs oxyhaemoglobin dissociation (Bohr effect) at the level of the capillary beds (Hayashi et al. 1999). Respiratory alkalosis was notable in all heifers, reflecting the moderate altitude at which this study was conducted.

The ratio of oxygen consumption to lung volume and alveolar surface area in the bovine is substantially greater than other mammalian species (Veit & Farrell, 1978). Through continued genetic and technological developments milk production of US dairy cattle is expected to increase by 200 kg/year from an average of 9945 kg/cow per year in 2013 to 11 740 kg/cow per year in 2022 (USDA, 2013). This will place greater demand on the cardiopulmonary system, particularly on cattle at higher altitudes. If so, maintaining optimal cardiopulmonary function will become increasing important. Perhaps it is no coincidence that a study of beef cattle found that lung tissue expressed as a proportion of slaughter weight is significantly correlated ($r=0{\cdot}79$) with a breed's mean milk yield (Jenkins et al. 1986).

According to the US Geological Survey there are 6 US states with a mean altitude of 1500 m or higher: CO, ID, NV, NM, UT and WY. In 2013, these 6 States account for 12·6% (1·16 million) of all milking cows in the USA (9·22 million) (NASS, 2013). Therefore, there is a need to further understand the importance of oxygen on the health and productivity of cattle.

In conclusion, efficacy of alveolar-arterial oxygen transfer was associated with milk yield in primiparous dairy heifers on one farm at moderate elevation in northern Colorado. We speculate that lung function is an important determinant of bovine productivity.

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