

# Pulmonary Arterial Pressure Testing for High Mountain Disease in Cattle

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## **History of high mountain disease and pulmonary arterial pressure testing**

In 1915, Glover and Newsom described a group of cattle in the high-altitude areas of Colorado that developed an accumulation of edematous fluid in the dependent tissues covering the parasternal muscles (known as the brisket region); hence, the term “brisket disease” [1–4]. Brisket disease is also known as high mountain disease (HMD), high altitude disease, dropsy, or big brisket to the rancher and is a very common condition seen in cattle raised in high-altitude regions (> 5000 ft [1524 m]) of Colorado, Wyoming, New Mexico, and Utah, with Colorado being the main region of interest [5–13]. Extensive epidemiologic and clinical studies of affected cattle by these and other researchers have demonstrated that this condition is a result of pulmonary arterial hypertension induced by pulmonary hypoxia occurring at high altitude [1–7,14–19]. Hypoxia-induced pulmonary arterial hyperplasia reduces the diameter of the pulmonary arterioles, resulting in pulmonary hypertension and subsequent right ventricular (RV) hypertrophy. The disease eventually progresses to RV congestive/dilatory cardiac failure [1].

HMD is characterized by the presence of ventral edema in the brisket region secondary to increased vascular hydrostatic pressure (intravascular hypertension) and the loss of fluid into the extravascular spaces. An animal suffering from HMD develops ventral and intrathoracic edema, pulmonary edema, plural effusion, passive liver congestion, perirenal and mesenteric edema, and ascites. To the rancher, the signs and symptoms seen may include lethargy, weakness, collapse, diarrhea, bulging eyes, jugular distension

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and pulsation, peripheral ventral pitting edema (with the brisket region being most pronounced), and death.

Cattle losses from this disease alone can result in 3% to 5% of the calf crop, but can be much higher. For example, one ranch in the high country of Colorado experienced a loss of 165 head of yearling cattle out of the 660 (25%) taken to a high-altitude mountain range. The disease has been a concern in the mountain regions since cattle began to take the place of sheep some 100 years ago. It became such a significant economic factor that in 1913, the Colorado Cattlemen's Association initiated the first investigative work by asking George Glover and Isaac Newsom to investigate the disease and determine the inciting factors involved [1]. It was of concern that some cattle seemed to be more prone to the effects of the disease, whereas others showed no effect. It was at this time that Glover and Newsome began looking into the pathophysiology of HMD [1].

The pioneering work done by Glover and Newsom concluded that altitude was the primary causative factor of HMD [2–4]. These studies demonstrated that the disease was more prevalent in lowland cattle that were brought to the high country either for grazing or for breeding purposes. They also found that when ranchers used their own bulls raised or based in high elevation, the incidence seemed to decrease, possibly giving rise to the first thought of a heritable condition. Glover and Newsome were also the first to realize that the cause of morbidity and mortality was cardiac failure. Based on these observations, they concluded that drugs would not cure this disease, but recommended to the ranchers that selective breeding and natural selection would be the most beneficial management practices for producing cattle adapted to high altitude [1].

Further investigation showed that the cardiac failure associated with HMD was specifically related to RV hypertrophy and right-sided congestive cardiac failure [14]. Specific architectural and histologic changes in pulmonary vasculature associated with HMD were described in the 1960s [15,17–20]. The primary vascular changes observed in response to hypoxia include increased arteriolar constriction, hypertrophy of the arteriole smooth muscle layer (medial hypertrophy), thickening of the vascular adventitia, decreased diameter of the lumen of pulmonary arteries, and pruning of the small pulmonary arteries and arterioles [15,17–19,21–28]. These pulmonary vascular changes occur secondary to hypoxia and lead to pulmonary hypertension, RV hypertrophy, congestive right heart failure, and death.

In the 1960s, landmark experiments began to provide a better understanding of this economically costly disease. Alexander, Jensen, Grover, Reeves, and Will were the first to measure pulmonary arterial pressure (PAP) in cattle [1,5]. By measuring PAP, they were able to establish a direct relationship between hypoxia and the increase in pulmonary vascular resistance, pulmonary arterial hypertrophy, and RV hypertrophy progressing to RV congestive failure. They concluded that the magnitude or degree of

pulmonary hypertension (represented by the PAP measurement) was directly related to the degree of pulmonary arterial hypertrophy. By 1962, these investigators had determined that cattle under chronic hypoxic conditions in the high-altitude mountain pastures of Colorado displayed a significant and progressive increase in PAP, and that the degree of the PAP measurement was directly related to the degree of medial hypertrophy of the small pulmonary arteries [1,5].

### **The bovine pulmonary response to hypoxia**

Pulmonary vascular shunting is seen in all animals under hypoxic conditions. Shunting of pulmonary blood flow is seen in cattle to a much greater degree than in other species [29]. The vasoconstriction mechanism of shunting is a means of distributing pulmonary blood flow away from poorly oxygenated lung tissue to more oxygen-rich areas. This exaggerated shunting mechanism, the anatomic pattern of the bovine lobulated lung, and the small lung-size/body-weight ratio all contribute to a severe loss of functional pulmonary capacity. Pulmonary vascular shunting is initially mediated through pulmonary arteriole constriction in the acute stages of hypoxia. Hypertrophy and thickening of the medial layers of the pulmonary arterioles (medial hypertrophy) and adventitial tissues occur with chronic hypoxic exposure (see Refs. [15,17–19,21,24,25,27,28]). Vascular remodeling with loss of peripheral pulmonary arteries (rarefaction or pruning) also contributes to increased pulmonary resistance. As indicated earlier, the ensuing pulmonary arterial hypertension results in cor pulmonale (heart disease secondary to pulmonary hypertension) and RV hypertrophy, followed by RV dilation and right-sided congestive heart failure.

It appears that this maladaptive response of vasoconstriction, shunting, arterial medial and adventitial hypertrophy, and vascular pruning resulting in pulmonary hypertension is characteristic of cattle and is a highly heritable characteristic in this species. Some cattle appear to be more naturally resistant to this process, whereas other animals develop these pathologic changes very rapidly and die of HMD in a short period of time.

### **Clinical and pathologic signs of high mountain disease**

The cardinal clinical sign of HMD in cattle is pitting edema observed primarily in the brisket region. The pitting edema is a result of increased hydrostatic pressure due to RV cardiac failure and venous hypertension. Additional signs of venous hypertension include distended and turgid jugular veins. Palpation and observation of the subcutaneous abdominal veins often determines that these are also distended and turgid. Intermandibular edema, ventral abdominal edema, and limb edema may also be observed, but they are less common than brisket edema.

Affected animals are generally lethargic and may have a decreased appetite. In the terminal stages of the disease, the animal is often anorexic, recumbent, and unable to rise. The body temperature is generally normal, unless other underlying illness or environmental conditions cause heat stress.

Thoracic auscultation may reveal a decreased intensity of breath sounds in the ventral thorax if pleural effusion is present. The heart and respiratory rates are generally elevated. Heart sounds may be muffled if pleural effusion is present. Cardiac dysrhythmia is rarely observed. A cardiac murmur may be auscultable if RV enlargement has resulted in right atrioventricular or pulmonic valve insufficiency. Although jugular distension is a characteristic clinical sign, an abnormal jugular pulse may or may not be observed.

The most common clinical pathologic changes are increases in hepatic enzymes, particularly aspartate transaminase and L-iditol dehydrogenase (formerly sorbitol dehydrogenase). Clinically affected animals may be azotemic because of decreased renal perfusion secondary to heart failure. The complete blood count is generally normal unless there is other underlying inflammatory pathology in the lungs. Gross pathologic findings include edema of the subcutaneous and intrathoracic tissues and the abdominal mesentery. The liver is generally enlarged and has the characteristic nutmeg appearance of passive hepatic congestion. Excessive pleural, pericardial, and peritoneal fluid may have a low cellularity and low or normal protein, consistent with a transudate. The heart is grossly enlarged because of hypertrophy and dilation of the right ventricle. Pulmonary edema has also been observed at post mortem examination of animals dying from HMD, but it is more commonly associated with left heart failure.

HMD should be differentiated from other causes of right side congestive heart failure, including traumatic reticulopericarditis, other causes of pericarditis, cardiac lymphosarcoma, valvular endocarditis, viral or bacterial myocarditis, cardiomyopathy (nutritional, hereditary, or idiopathic), pulmonary artery obstruction from embolic pneumonia, or chronic hypoxia and cor pulmonale due to other primary pulmonary disease. HMD in calves is often mistaken for acute viral or bacterial pneumonia because the onset of clinical signs can be very rapid and brisket edema may not be readily observed in peracute right side congestive heart failure. Alternatively, acute viral or bacterial respiratory disease can exacerbate the pulmonary hypoxia of high altitude, resulting in a rapid onset of heart failure in susceptible calves or adult cattle.

### **Pulmonary arterial pressure testing**

PAP testing in cattle can be used to confirm the presence of pulmonary hypertension due to any cause, including HMD. The procedure is also useful in differentiating cor pulmonale from other causes of congestive heart failure. Although PAP testing has clinical usefulness for the individual

animal with signs of cor pulmonale, the most useful application in cattle is for screening animals susceptible to pulmonary hypertension, to make management and breeding decisions. With the right equipment and facilities, a veterinarian can PAP test large numbers of animals daily and provide a valuable service to clients raising cattle at high altitude. The fundamental procedure involves passing flexible catheter tubing through a large bore needle inserted into the jugular vein. The catheter is passed down the jugular vein, through the right atrium, into the right ventricle, and then into the pulmonary artery. Mean pulmonary artery pressure is measured by a pressure transducer connected to the catheter.

The equipment and materials needed to perform PAP testing in cattle are listed in [Box 1](#). A good cattle working facility and manual help is a strict requirement ([Fig. 1A](#)). A cattle chute equipped with a squeeze and scissor head catch is best. Other types of head catches tend to bind the head and neck, making passing of the catheter difficult. The animal is secured within the chute with a moderate amount of squeeze applied to reduce body movement. Monitoring the squeeze is very important because too little squeeze allows too much movement, making the procedure difficult. If too much

### **Box 1. Facilities and equipment used to perform a PAP measurement**

- Cattle chute with a head catch and body squeeze
- Adequate help for handling cattle efficiently and safely
- Halter to secure the head in place (rather than nose tongs)
- Electric power or generator
- Datascope/oscilloscope capable of invasive blood pressure monitoring; many electrocardiogram machines or anesthesia vital sign monitors are acceptable for this use
- Pressure transducer to convert fluid pressure to an electric signal
- Catheter/polyethylene tubing (1.19-mm internal diameter by 1.7-mm external diameter), 120 cm (48 in) long
- 13- or 12-gauge 3.5-in needle that the catheter is passed through (the authors prefer 13-gauge)
- Disinfectants (chlorhexidine, povidone iodine, and 70% isopropyl alcohol)
- Isotonic (0.9%) NaCl solution
- Latex gloves
- 12-mL syringes
- Three-way stop cocks
- Record system
- Multiple buckets of water and disinfectants for cleaning needles and tubing between animals

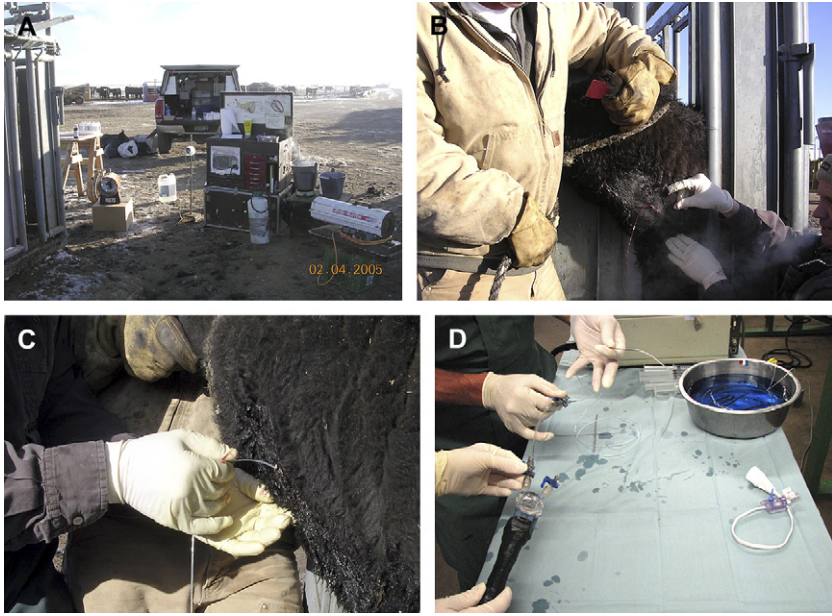


Fig. 1. Facilities, equipment, and catheter setup for performing PAP measurement in cattle. (A) Facilities and equipment setup for PAP testing in the field. (B) Proper restraint for venipuncture during the PAP testing procedure. (C) Threading the catheter through the venipuncture needle into the jugular vein during the PAP testing procedure. (D) PAP pressure transducer and catheter setup. Note the bowl of disinfectant on the table containing extra needles and catheters.

squeeze is applied, then often the catheter may not pass readily into the right ventricle and pulmonary artery because of increased thoracic pressure. Tying the head too tightly, with the neck pulled tightly against the head catch, may impede passage of the catheter and require the neck to be loosened during the procedure to allow the catheter to pass freely down the jugular vein. The use of hydraulic chutes makes the procedure much easier, but a good operator is required. Owners have described cattle with sore necks following the PAP testing procedure. This result is not caused by the PAP test itself or by the venipuncture, but rather is the result of either squeezing the neck too tightly in the hydraulic chute, neck strain caused by the use of a neck bender, or, in one case, cervical fracture. Most complications of the PAP test are chute related and are not caused by the actual test.

Once the animal is caught in the head catch, the head should be held or tied to expose the jugular furrow (see Fig. 1B). It is best to secure the head level with the point of the shoulder. If the head or nose is secured too high, the animal can manipulate its head and neck, thereby cutting the catheter within the jugular vein, resulting in a pulmonary foreign body emboli. A halter is preferred over any type of nose tongs because of the dyspnea caused by the intranasal equipment and the excitement level created with the nose tongs. Very few animals fight a well-fitted halter, which makes the process

much smoother. The halter is secured to the side of the chute, which allows for ease of vision of the jugular furrow (left or right). The proximal lateral aspect of the jugular furrow is scrubbed with chlorhexidine or alcohol solution (any type of disinfectant can be used). Surgical clipping and aseptic preparation is not generally performed for this procedure when testing large numbers of commercial cattle. The jugular vein is occluded at, or just rostral to, the thoracic inlet, causing jugular vein distension. The proximal jugular vein is then punctured with a 12- to 13-gauge 3.5-inch needle until blood flows freely from the needle (see Fig. 1B). The needle is then gently threaded down the jugular, leaving 1 cm of needle out of the skin to allow needle control. A 13-gauge needle is preferred over a 12-gauge needle because it creates a smaller hole and is easier to manipulate and thread into the jugular vein. A 12-gauge needle seems to cause an increase in post-PAP hematomas. Skin plugs within the needle that impede passage of the catheter through the needle have also been experienced with 12-gauge needles.

A polyethylene catheter (internal diameter 1.19 mm, outside diameter 1.7 mm, length 120 cm, Intradermic, Fischer Health Care) is then passed through the needle and into the jugular vein (see Fig. 1C). The catheter tubing is flushed with sterile isotonic saline (0.9% sodium chloride [NaCl]) before placing in the needle, and is flushed while the catheter is being gently advanced down the jugular vein. Flushing the catheter with isotonic saline while feeding down the jugular vein aids in the passage of the catheter. The total amount of saline that is injected into the animal during the procedure is generally less than 2 mL. The external end of the catheter is then connected to the pressure transducer (or equivalent) by way of a three-way stopcock after approximately 30 to 45 cm (1–1.5 ft) of the catheter has been passed into the jugular vein (see Fig. 1D). The transducer is placed at the level equal to the base of the heart, which is approximately just level with the point of the elbow. The transducer can be taped to a magnet and attached to the chute so that height adjustments can be made easily if cattle of different sizes are being tested. The transducer and catheter are again flushed to ensure no air has entered the system.

The catheter is then advanced to the distal jugular vein and the jugular pressure is evaluated. Jugular (central venous) pressure in the normal animal should be in the range of 6 to 12 mmHg at 5000 ft and above. The catheter is then passed into the right atrium, through the right atrioventricular valve, and into the right ventricle of the heart, where the second measurement is taken. An atrial spike is sometimes noted but is difficult to evaluate. The atrial spike is recognized as a very narrow, sharp spike on the pressure wave. In the normal animal at 5000 ft and above, the mean RV pressure is most often between 18 and 30 mmHg. The catheter is then advanced from the right ventricle through the pulmonary valve and into the pulmonary artery. The catheter is allowed to stay in this location until the pressure remains constant (approximately 10 seconds) and a mean PAP measurement can be obtained.

Identifying the location of the catheter within the animal's vasculature and determining the vascular pressure reading is accomplished by monitoring the pressure changes and the characteristics of the pressure wave form on an invasive blood pressure monitor (Fig. 2), which allows accurate assessment of the

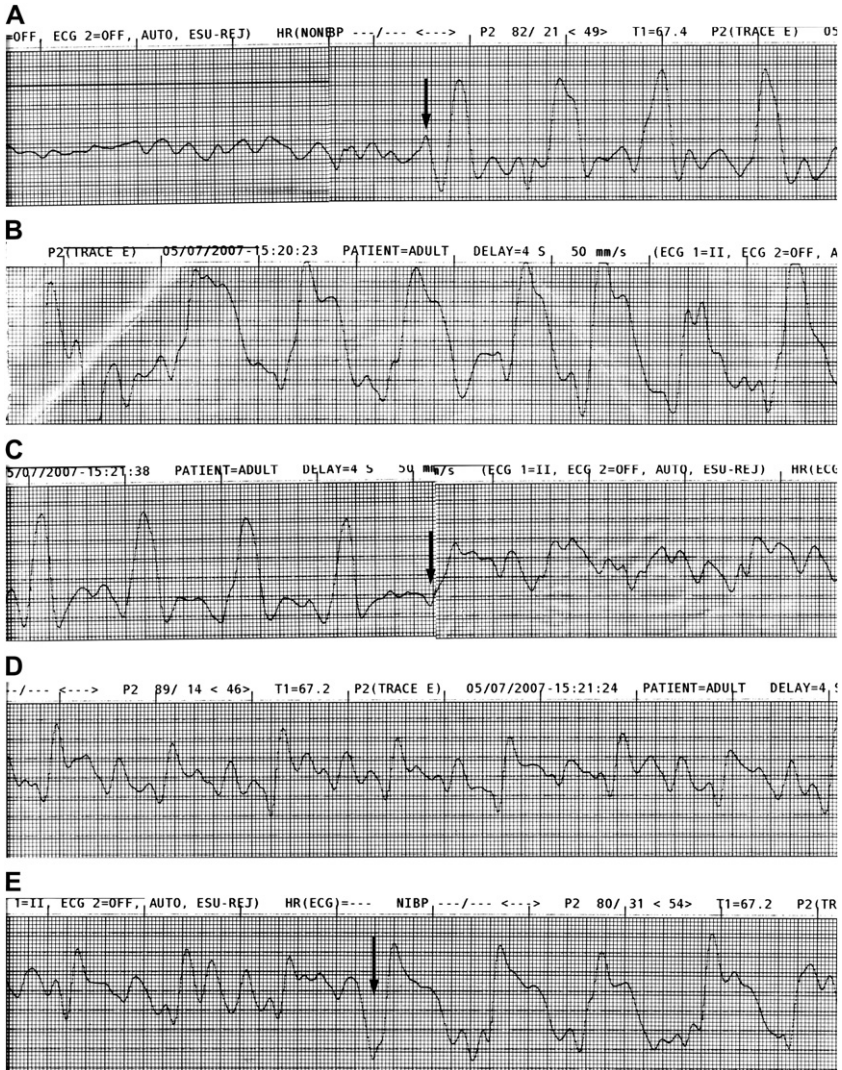


Fig. 2. Normal vascular pressure wave forms observed when PAP testing. Recognizing these wave characteristics will aid in accurately evaluating the placement of the catheter to achieve a reliable PAP measurement. (A) Normal jugular wave form with transition (arrow) to the right ventricle. (B) Normal RV wave form. (C) Normal right ventricle to pulmonary artery transition (arrow). (D) Normal pulmonary artery wave form. (E) Checking the transition (arrow) from the pulmonary artery to the right ventricle when withdrawing the catheter.

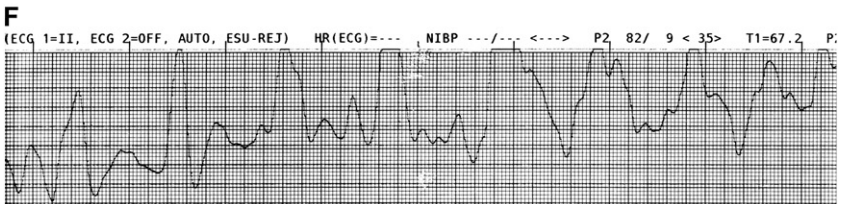
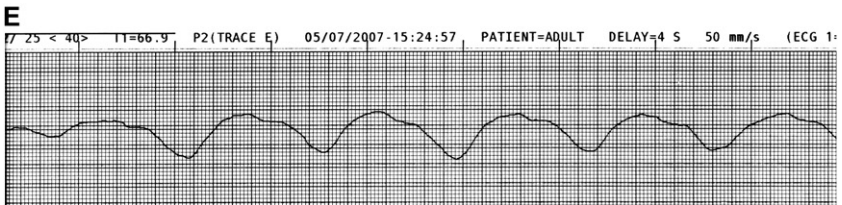
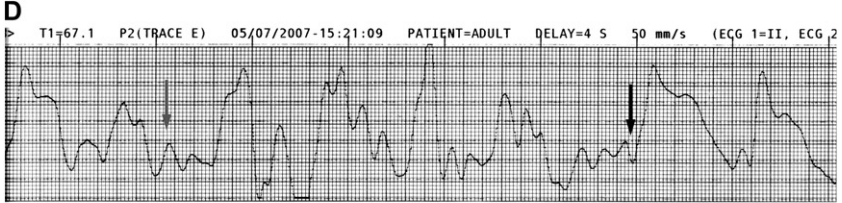
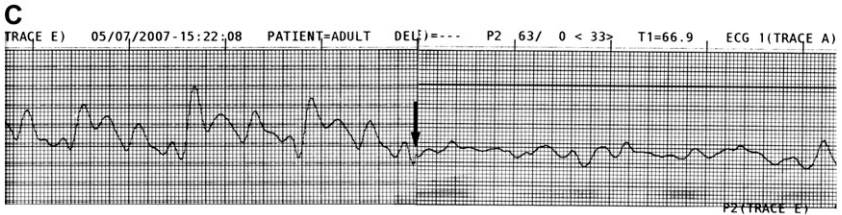
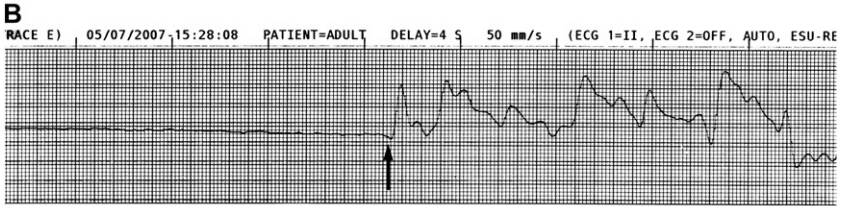
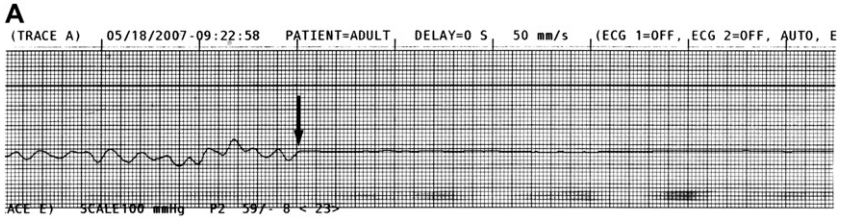


location of the tip of the catheter at all times. Entry into the pulmonary artery is recognized by a change in the pressure wave form characterized by an increase in the diastolic pressure of the pulmonary artery over the diastolic pressure of the right ventricle. In the normal animal, the mean PAP at altitudes between 5000 and 6500 ft should be between 34 and 44 mmHg. Cattle displaying signs of pulmonary artery hypertension can have PAP results in the range of 48 to 213 mmHg. The PAP and the RV pressure may be normal to subnormal in cattle with end-stage congestive right heart failure because of the failing myocardial muscle. Subclinical or clinically affected animals with ventricular septal defect or atrial septal defect may be recognized because they often have PAPs in the hundreds in all three parameters (mean, systolic, and diastolic). Any animal with a PAP measurement over 50 mmHg should be ausculted for cardiac murmurs and evaluated for possible congenital cardiac defects.

After the PAP is recorded, the catheter is slowly pulled back through the pulmonary valve into the right ventricle. A drop in the mean, and particularly the diastolic, pressure should be noted along with a distinct change in the pressure wave form as the catheter moves from the pulmonary artery into the right ventricle (see Fig. 2E). The drop in mean pressure should be approximately 6 to 10 mmHg. If this drop in mean ventricular pressure is not noted, the catheter placement should be re-evaluated. If the pressures remain unchanged, the animal should be ausculted for the presence of mitral or pulmonary valve murmurs suggesting valvular damage. Various abnormal wave forms can help determine problems with the testing procedure (Fig. 3).

To remove the catheter, the needle is pulled from the neck first and then the catheter is pulled, not from the needle but from the skin. Extreme caution must be used to not sever the catheter with the needle and allow the catheter to enter into the vascular system. Several animals were evaluated between 1980 and 1984 where catheters of varying length were accidentally severed during the procedure. The animals were given antibiotics at the time of the test and monitored over a period of 6 months to 3 years. The animals experienced no acute or chronic problems arising from the foreign body and were kept at high elevation. All pregnant animals calved out without complication. At slaughter, all of the catheters but two were found to be lodged in the right ventricle and main pulmonary artery. One catheter only was found in the pulmonary artery and one was found within the liver. Mild to moderate fibrosis was observed at the catheter location and the surrounding tissue. Fibrosis was most apparent at the papillary muscle.

After the needle and catheter have been removed from the animal and disconnected from the transducer, the needle and catheter are rinsed in disinfectant. The author (TNH) uses a protocol whereby the equipment is first rinsed in a povidone iodine solution followed by a chlorhexidine soap and water solution, then rinsed in a chlorhexidine solution, and finally allowed to sit in a hot chlorhexidine/isopropyl alcohol solution for at least 5 to 10 minutes between each animal. At least four to six needles



and catheters should be available for use at all times when PAP testing large groups of cattle. These solutions are changed after every 20 head unless gross contamination occurs, at which time they are changed immediately.

Variations in the test can be seen in the manner in which the cattle are handled. Electric cattle prods should be avoided if possible and used only for the purpose of advancing cattle down the working facilities, and then only as a last resort. The use of dogs for herding has been observed to result in elevated PAP measurements; therefore, the use of dogs during testing is strongly discouraged. A dramatic but very brief (5- to 10-second) rise in a PAP can be seen in those animals that become agitated during the testing process. By allowing the animal to regain composure, the PAP pressure in a normal animal will return to normal very quickly. When all goes well, each PAP measurement can be done in about 3 minutes.

### Interpretation of pulmonary arterial pressure measurements

The interpretation of the mean PAP of an individual animal depends on many factors (see later discussion). In general, cattle more than 12 months of age that have a PAP of less than 41 mmHg at an elevation greater than 1500 m (5000 ft) are likely to maintain an acceptable PAP at high altitude and serve as good breeding stock for high elevation (Table 1). Cattle of any age with a PAP greater than 49 mmHg at any altitude are at risk for developing HMD and should not be maintained or used in breeding programs at high altitude. It is difficult to predict the outcome of cattle with PAPs between 41 and 49 mmHg at high altitude; these animals should be used with caution at high elevation.



Fig. 3. Common pressure wave forms characteristic of problems that can occur with the procedure. (A) The catheter is in the jugular vein and then becomes kinked. Notice that when the catheter becomes kinked, the normal jugular pressure wave form is lost and becomes a flat line (*arrow*). (B) The PAP catheter is kinked in the pulmonary artery and then gently withdrawn to remove the kink; observe the return of a normal pulmonary artery wave form (*arrow*). (C) Pulmonary artery transition (*arrow*) to a normal wedge pressure (left atrial pressure). Note the loss in amplitude of the pressure wave form and a slightly lower pressure, indicative of transition to the wedge pressure. (D) The chute squeeze is too tight and prevents advancement of the catheter from the right ventricle into the pulmonary artery. The wave form is very erratic and unable to successfully transition fully from the right ventricle wave form to the pulmonary artery wave form (*gray arrow*) and then returns to the right ventricle wave form (*black arrow*). (E) Bubble or leak in the catheter system. The wave form is dampened, with a loss of sharpness. (F) In this figure, the transducer is actually being moved lower during the tracing, resulting in a drift of the wave form to higher pressures. Note that having the transducer placed too low can mimic the elevated pressure you would see in an animal with pulmonary hypertension. Alternatively, if the transducer is placed too high, you will get falsely lower values and may miss an animal with abnormally high PAP.

Table 1  
Evaluation of pulmonary arterial pressure scores

PAP	Interpretation
30–35 mmHg	This score is considered excellent and highly reliable.
36–39 mmHg	This score is considered excellent for any animal over the age of 12 months. If the animal is less than 12 months of age, the score is still fairly reliable, but retesting before breeding is suggested.
< 41 mmHg	Scores less than 41 mmHg are reliable measurements in all animals more than 12 months of age. It is recommended that yearling cattle have a PAP measurement less than 41 mmHg (depending on altitude of the test). The variation in scores 41 mmHg and above is inconsistent and difficult to predict in some cattle as they age. Any animal measuring 41 mmHg and greater should always be retested before use.
41–45 mmHg	This range is acceptable for older animals (ie, more than 16 months of age). Animals less than 16 months scoring in this range should be retested to predict the future PAP of the animal accurately.
45–48 mmHg	This range is acceptable only for older animals that have been in high elevations for an extended period of time. Animals with this score are more susceptible to environmental stresses leading to HMD and should be considered at some risk. Elevation of test site and where the animal lives must be evaluated closely for those in this PAP score range.
> 49 mmHg	Animals that score in this range must always be considered high-risk candidates for developing HMD, not only for themselves but also their offspring. Many animals that have scored in this range have died of HMD. An option for these animals is to move them to a lower elevation for use there. It is also recommended that offspring of these animals never return to high altitude.

These figures are based on cattle tested at or above 1800 m (6000) ft and 12 months of age or greater. If the animal does not meet these criteria then adjustments must be made, as discussed in this article.

### Problems encountered with pulmonary arterial pressure testing

Needle selection and needle care are important factors in successfully performing the PAP measurement and minimizing catheter-related complications. The needles must be maintained throughout the day; they must be cleaned regularly in muriatic acid and the hubs and barrels kept clear of debris. Often, small burs will form on the needle tips and they need to be filed and smoothed off. The needles dull very quickly after use in many animals. Sharpening them has not been successful; therefore, it is best to replace used needles with new needles when they become too dull for effective venipuncture. Prior to use of any new needle, it is recommended that

the inside cutting edge of the needle be dulled with a Dremel tool or round file to decrease the potential risk of shearing a catheter, resulting in a pulmonary emboli.

Jugular venipuncture can become a challenge if the animal is not appropriately positioned and restrained. In many cases, poor positioning and restraint of the animal can make good visualization of the jugular more difficult. If this situation occurs, it is recommended that the animal be repositioned to allow easy and safe access to the vein. It has also been observed that some animals may have abnormal anatomy, where one or both jugular veins are not apparent or are hypoplastic. If one jugular vein cannot be visualized or palpated, then a switch to the other side is recommended. This phenomenon has rarely been seen bilaterally, but is possible. PAP testing has not been able to be performed in some animals because of this syndrome.

The catheters tend to get kinked and bent, making them difficult to pass. They, too, must be maintained throughout the day, and thrown away as necessary. Once a catheter becomes rough, it tends to develop weak spots, making shearing a greater risk. Any damaged catheters should be thrown away and replaced with new ones. Multiple catheters are used; each catheter should be allowed to sit in the disinfectant for at least 5 to 10 minutes between use. Once the catheter enters the vascular system, possible complications include shearing of the catheter; the catheter getting entangled with the papillary muscle, chordae tendinae, or valve; and kinking or tying itself in a knot, making removal difficult. Keeping the catheter moving in a smooth, forward direction will help in passing it into the right ventricle. Moving the catheter into the main pulmonary artery is best done by short, smooth advancements coinciding with ventricular systole. In some cattle, movement of the catheter into the pulmonary artery is difficult, because of either an elevated PAP or anatomic issues not diagnosed at the time. Once the catheter has entered the pulmonary artery, knowledge of catheter location is important. Advancing the catheter too far may result in a pulmonary wedge pressure (left atrial pressure), resulting in a much lower reading than the true PAP measurement. A wedge pressure is identified on the screen as a slow decline in the wave amplitude and form and a slow drop in the pressures. Too little advancement may result in the catheter resting in the turbulent pulmonary valvular flow, increasing measured pressure. The catheter can be moved back and forth from the ventricle to the pulmonary artery a couple of times to assure correct location for the PAP measurement. Ideally, the end of the catheter should rest about one half of the way from the pulmonary valve to the first branch of the pulmonary artery.

Once in place, the catheter is left alone while the measurement is obtained. If the animal begins to move or get excited, the pressure can spike sharply, often into the hundreds. In a normal animal, this pressure spike returns to normal within seconds. If the animal does get excited and jumps, caution must be used to never let go of the needle because at this time the catheter can be sheared off by the tip of the needle.

Testing in the cold weather often encountered at altitude can be challenging. The author (TNH) has performed PAP testing at temperature ranges of from  $-40^{\circ}\text{C}$  to  $41^{\circ}\text{C}$  ( $-42^{\circ}\text{F}$ – $106^{\circ}\text{F}$ ). The use of blown heat (salamander heater) is often required to keep the electronic equipment warm and functioning and to keep the system from freezing. The freezing of the small catheter line is often a problem. When conditions such as this occur, it is recommended that the animals be retested on another day.

### **Factors affecting pulmonary arterial pressure in cattle**

Multiple factors contribute to the variation in PAP in cattle, including breed, gender, age, body condition, concurrent illness, environmental conditions, elevation, and genetics. Individual animal differences appear to have a strong genetic component and can be partially mitigated by identifying high-risk individuals and by selective breeding. To use and evaluate a PAP measurement accurately, these factors must be considered. The veterinarian, owner, buyer, and seller must be aware of these factors to understand how they play a role in correctly evaluating a PAP measurement.

#### *Breed*

Based on tests of more than 150,000 head of cattle, it appears that no one breed is resistant to the effects of high-altitude hypoxia. High-PAP animals ( $> 50$  mmHg) have been found in all breeds tested. Some breeds, and pedigrees within breeds, appear to be more naturally resistant to the effects of high altitude, lending support to the conclusion that specific genetic factors can be managed to decrease clinical cases of HMD.

It is important in the evaluation of any animal originating from a low altitude herd ( $< 5000$  ft elevation) to realize that it has a higher probability of experiencing high-altitude effects than those raised in higher elevations. This innate resistance to high altitude is secondary to the effects of natural selection and the culling processes by the rancher. By PAP testing all bulls and all replacement heifers, and culling all females that may give birth to an HMD calf, a rancher can develop a more naturally resistant herd. This type of selection is not possible for ranchers at low elevation because the animals must spend some time at high altitude to show the effects of high-altitude pulmonary hypertension. This consideration is important in testing or using animals originating from lowland herds or artificial insemination sires.

#### *Gender*

No physiologic basis exists for a difference in PAP measurements between male and female cattle. The author (TNH) has observed differences in the percent of male and female cattle that have high PAP measurements in specific herds. These differences can often be attributed to husbandry practices and feeding management (see later discussion on body condition), or to

breeding practices and breeding management. Selection of low elevation seed stock that have not been confirmed to have a low PAP measurement at altitude can greatly influence the PAP measurements of replacement cattle and may result in a gender difference in PAP measurements.

### *Pregnancy*

It has been reported that pregnant cattle can have higher PAP measurements than nonpregnant cattle [30]. The increased PAP response is greater in animals that already have an elevated PAP. Animals with lower PAP before pregnancy had reduced arterial  $P_{CO_2}$  tension during pregnancy, suggesting a compensatory hyperventilatory mechanism that could help offset pulmonary hypoxia. The specific mechanism for the increased pulmonary vascular resistance during pregnancy in susceptible cows is not fully understood.

### *Age*

The effect of age on the PAP has been evaluated by retesting specific animals over time. Animals were tested at ages ranging from 8 weeks to 12 months and then retested at multiple age intervals up to 24 months [31]. This type of retesting has helped in determining what effect, if any, age has on PAP.

The age of the animal at the time of testing should always be considered when evaluating the PAP of an individual animal. The accuracy level of the PAP test is less predictable for those animals tested at 12 months of age or younger. The PAP of animals tested at ages less than 12 months showed much greater variation over time than those of older animals. Testing animals at 16 months of age and older appears to be the most consistent and accurate at predicting susceptibility to high-altitude-induced pulmonary hypertension.

PAP measurement in animals tested at less than 12 months of age accurately predicts high-PAP-testing animals, but is less accurate in predicting low-PAP-testing animals as they age. An elevated PAP measurement ( $>49$  mmHg), regardless of age or elevation of the test, is extremely accurate at predicting a high PAP measurement later in life. For example, if the animal has a PAP measurement of 49 mmHg or greater at any age or elevation, one may assume with a great degree of confidence that this animal is a high-risk candidate for high-altitude problems and should be used at high altitude with caution. The area of concern is in those animals with low PAPs that were tested at less than 12 months of age. It has been determined that low ( $<40$  mmHg) PAP measurement at this young age may not predict the PAP measurement as the animal ages. Some breed variation also appears to be a part of this inconsistency. Some breeds show a greater degree of inconsistency and variability than others.

In summary, special consideration should be made for those animals tested at 12 months of age or younger. Eighty percent of the animals

younger than 12 months of age that have a PAP between 30 and 40 mmHg will remain at acceptable PAP levels as they mature. However, mature PAP measurements for young animals that initially test between 41 to 49 mmHg have a high variability. Animals testing over 49 mmHg should always be considered at risk for HMD.

### *Concurrent illness*

Because the PAP measurement is actually a measure of pulmonary blood flow resistance, any cause of temporary or permanent pulmonary hypoxia can cause an increase in the PAP measurement [32,33]. Multiple infectious and noninfectious respiratory diseases, including bovine viral diarrhoea virus (BVDV), infectious bovine rhinotracheitis (IBR), parainfluenza type 3 (PI3), *Histophilus somni*, *Pasteurella multocida*, *Mannheimia hemolytica*, lung abscess, lung worm, migrating larva of intestinal parasites, asthma, or even traumatic reticuloperitonitis/pleuritis, can predispose animals to pulmonary hypertension. Hypoxia caused by these conditions can result in pulmonary hypertension and cor pulmonale syndrome, even at elevations lower than 1500 m (5000 ft). However, animals at altitude are much more susceptible to the synergistic effects of concurrent respiratory disease on pulmonary hypoxia and can readily develop acute heart failure in the face of acute respiratory disease.

If an elevated PAP measurement is thought to be secondary to a temporary pulmonary disease, then retesting the animal should be done when the respiratory condition is resolved. It should be noted that PAP scores of more than 50 to 55 mmHg, even when associated with transient respiratory disease, rarely return to an acceptable level. It appears that once the PAP measurement reaches this degree or higher, extensive pulmonary vascular damage has taken place and the animal does not return to a normal pulmonary pressure, making it a high-risk candidate for use in high-elevation situations. This situation is only true if the animal remains at high elevation. Those animals with elevated pressures that are moved to lower elevation often return to a normal PAP, but they are at extreme risk if ever moved again to high elevation. Even though this animal may not be genetically susceptible to high-altitude effects, the lung pathology has made them at risk for acquiring HMD.

Gram-negative sepsis may also cause elevation in PAP. Calves experimentally treated with endotoxin show increased pulmonary vascular resistance and elevated PAP [34–36]. The endotoxin-mediated pulmonary hypertension is mediated, at least in part, by prostaglandin F [37]. This effect can be inhibited by indomethacin. These studies suggest that naturally occurring gram-negative sepsis can affect PAP measurements, and thus, PAP values, from animals with concurrent bacterial infections; the tests should be repeated at a later date. In addition, gram-negative sepsis can potentiate pulmonary hypertension in susceptible cattle at high altitude



and could increase the risk of clinical HMD in individual animals. Treatment with flunixin meglumine may be clinically helpful in blocking the effect of endotoxin on pulmonary hypertension.

### *Elevation of the pulmonary arterial pressure test*

Clinically, the pulmonary hypertension seen at high altitude and the severity of clinical HMD appear to have a significant individual variability. Some cattle appear to be prone to developing congestive right heart failure, whereas others live at high altitude with a documented elevated PAP and never have a clinical problem. It is of major concern that even though these animals may not develop clinical HMD, they still pass the genetic predisposition to their offspring. These types of animals tend to be the most costly to the rancher who is not performing PAP testing. This variable expression of clinical disease and the variable penetrance of the gene makes PAP testing challenging at all elevations and becomes an even greater concern at lower elevations (<5000 ft).

The hypoxic conditions needed to stimulate a pulmonary response are not seen until approximately 5000 ft. It is for this reason that PAP measurements taken at low elevations (<5000 ft) are not used as a positive selection tool but only to identify those animals that are sensitive to hypoxic conditions and hypertensive at these lower elevations. Cattle moved from low elevations to high elevations should remain at the altitude for a period of 3 weeks or more to PAP test accurately for adaptation to high altitude. Hypoxic pulmonary changes have been seen immediately in cattle as they have been moved to high altitude. However, to test most accurately those that are to be used for breeding, a longer stay at high altitude before PAP testing is recommended.

In practicality, it is important for the rancher to know at what elevation the PAP measurement was performed because it has been shown that the PAP measurement increases as the animal is moved or travels to higher elevations. It is not uncommon to see clinical HMD in animals that have a PAP measurement of greater than 49 mmHg. Based on repeated PAP testing of animals at different altitudes, it has been observed that the PAP measurement increases 1 to 2 mmHg per 1000-ft rise in elevation (SD + 3). Therefore, a rancher can predict what a purchased animal's PAP measurement might be at the elevation of their ranch if the PAP measurement was taken at a lower altitude. For simple guidelines to the rancher and veterinarian, an animal should be tested at an elevation of at least 5000 ft. The higher the elevation, the more accurate and reliable test results will be.

### *Environmental conditions*

Cold environmental temperature can cause pulmonary hypertension in cattle [38–40]. Temperatures less than 0 °C have been shown to increase PAP by 25% to 55% [39]. Animals with elevated PAP before cold exposure

showed greater increases in PAP than normal animals. Animals exposed to cold environments showed decreased arterial  $PO_2$  and increased arterial  $Pco_2$ , indicating that hypoventilation-induced hypoxia is, in part, responsible for the pulmonary hypertension observed at cold temperatures. Increased pulmonary blood flow also contributed to the pulmonary hypertension.

Ingestion of the swainsonine contained in locoweed (certain species of *Astragalus* and *Oxytropis*) increases the incidence and severity of HMD in calves at high altitude [41,42]. Calves fed swainsonine or swainsonine-containing locoweed demonstrated clinical signs including brisket and intermandibular edema, and pathologic findings of congestion of the liver, RV hypertrophy, pleural effusion, and ascites. All calves exposed also showed microscopic lesions consistent with swainsonine toxicity, including neurovisceral cytoplasmic foamy vacuolation and cerebellar neuroaxonal dystrophy. No specific data indicate that swainsonine causes pulmonary hypertension and elevation of PAP. It is possible that the effect of swainsonine exposure on development of HMD is due to direct cardiotoxic effects in conjunction with hypoxia-induced pulmonary hypertension.

Ionophores fed to cattle at high altitude may increase the risk of pulmonary hypertension. In a small pilot study, an ionophore was fed to calves at the labeled dose for 6 weeks in a Colorado feedlot at an elevation of 1500 m (5000 ft). No other changes were made in the cattle's diet or environment. The PAP results at the end of the 6-week feeding trial resulted in 44% being over 50 mmHg and 71% being 45 mmHg or greater. A repeat PAP measurement was taken 1 month after removal of the ionophore and showed a mean decrease in the PAP of 6 mmHg. Further work is needed to evaluate the potential effect of ionophores on pulmonary hypertension when fed to cattle at high altitude.

### Genetics

Evidence is strong that the susceptibility of cattle to hypoxia-induced pulmonary hypertension is inherited [9,10,43–45]. The genetics of susceptibility to hypoxia-induced pulmonary hypertension in cattle appears to be complex. One study suggested a model of an autosomal gene with reduced penetrance [44]. In this study, it was postulated that the variable penetrance could be due to an abnormality in the Y chromosome.

### Economics and management of high mountain disease

HMD is one of the top causes of morbidity and mortality in cattle raised at high altitude and also accounts for significant loss in growth and reproductive performance. An estimated 1.5 million cattle are raised at high elevation in Colorado, Wyoming, Utah, and New Mexico. Based on discussion with ranchers in these areas, it is estimated that HMD accounts for a 5%

annual death loss, on average. These figures suggest an annual loss of as many as 75,000 head of cattle annually at a value of more than \$60 million.

As an example, a purebred beef herd (214 head) in Nebraska (elevation 853 m [2800 ft]) was purchased and moved to a ranch in Colorado at 2400 m (8000 ft). Within 2 months of arrival, six pregnant cows had died of HMD, at a loss of \$20,400. At that time it was decided to PAP test the herd. After PAP testing, seven cows were immediately taken to lower elevation because of early clinical signs of HMD, with a loss of \$17,500. After PAP testing, 68 animals (32%) were considered to be at high risk for developing HMD or as genetic carriers. These 68 animals were valued at \$171,000. These animals were sold at a loss of \$68,000.

In another herd, 125 head were purchased and moved from an elevation of 1150 m (3800 ft) to 2900 m (9500 ft). Within 60 days of arrival, two cows and 23 calves ranging from 2 weeks to 2 months of age had died of HMD. At this time, the remaining adult herd (84 cows and 4 bulls) was PAP tested. Thirty-four percent of the cows PAP tested at extreme risk ( $> 50$  mmHg, with most being  $> 70$  mmHg). At the time of testing, three cows and nine more calves were identified with high PAP and were showing clinical signs of HMD. All these animals were treated and moved to lower elevation the next day. Of the four bulls, one was showing clinical signs of HMD, one had a PAP of 86 mmHg, and the two others had PAPs of less than 45 mmHg. These bulls had already bred the cows in the herd and, thus, the next year's calves are at risk of being susceptible to HMD. The financial loss for just the animals with clinical signs was estimated to be \$38,000.

Another example is a high-quality seed stock herd of 900 breeding cows raised at 7800 ft. This herd performs annual PAP tests to identify HMD-resistant and susceptible cattle for marketing purposes, but does not selectively breed to eliminate the problem. This herd expects an annual loss of 15% due to animals that develop clinical HMD or are determined to be at high risk, based on PAP measurements. However, the rancher tests cattle at 8 months of age so that he can identify extremely high-risk animals and move them to a lower elevation feedlot for beef. He/she specifically markets his/her low PAP bulls ( $< 41$  mmHg) with a premium of approximately \$2000 to \$5000 per bull.

The decisions and benefits of PAP testing are different in commercial beef herds. In these herds, the objective is to develop genetics to minimize HMD losses on both the male and female side. A Colorado ranch at 1950 m (6400 ft) has PAP tested since 1988 to develop HMD resistance. This herd also summer ranges at elevations of 3000 to 3650 m (10,000–12,500 ft). Initially, this herd was losing more than 5% of the cattle to HMD. Income was also lost from bull sales because of bulls that were sold with a guarantee but later developed HMD. This herd tests bulls and replacement heifers and culls all animals with PAP of greater than 41 mmHg. Over the years of PAP testing, the mean PAP measurement in the herd was reduced from 48 mmHg to 37.8 mmHg. No clinical cases of HMD have

been reported since 1990. In addition, the standard deviation of the PAP measurements was greatly reduced. The owner readily insists that PAP testing is the only reason they are still in business.

From these examples, it is apparent that PAP testing is essential for profitability at high elevation. PAP testing identifies high-risk animals before clinical signs or death from HMD occurs, and allows for selective breeding for resistant cattle. It also serves as a marketing tool for selecting animals that are adapted to live at high altitude and will pass on genetics for resistance to HMD.

### Continued research

PAP measurement remains the best marker and selective management tool for the control of HMD in cattle. However, the response of individual animals and the ability to predict the risk of developing clinical HMD is still tremendously variable. Ongoing research is directed at identifying other physiologic or genetic markers that will help classify cattle at risk of high-altitude pulmonary hypertension and clinical HMD. Potentially, these tests could be used in conjunction with PAP measurements or could replace PAP testing as a management tool for controlling HMD in cattle.

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