

# **Validation of a new method of determining cardiac output in neonatal foals**

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## (ABSTRACT)

Hypotension is a common finding in hospitalized, critically ill neonatal foals. Hypotension may be a function of low cardiac output or increased cardiac output and decreased systemic vascular resistance. In the first instance, treatment would include fluids and/or inotropes and in the second, fluids and/or vasopressors. Therefore, cardiac output measurements are expected to help guide the treatment of hypotension associated with critical illness and/or anesthesia in neonatal foals. However, a practical and safe method of measuring cardiac output has not been described for the foal.

Lithium dilution, a new method of cardiac output determination not requiring cardiac catheterization, has recently been reported in adult horses. We compared this method to thermodilution in isoflurane anesthetized, 30 to 42 hour old foals and found good agreement (mean bias 0.0474L/min; limits of agreement -3.03 to 3.12) between the two methods in a range of cardiac outputs from 5.4 to 20.4 liters/min. The lithium dilution technique is a practical and reliable method of measuring cardiac output in anesthetized neonatal foals, and warrants investigation in critically ill conscious foals.

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# **Chapter 1: Cardiac output technologies with special reference to the horse.**

## **Introduction**

The cardiovascular system has a great capacity to adapt to the requirements for oxygen delivery under different physiological circumstances. In athletic animals, such as the horse, this ability is very well developed and the cardiac output may be increased to over ten times its resting value during intense exercise. This ability to adapt may also be useful in disease, when tissue oxygen demand can be increased. However, many disease states can result in hemodynamic derangements, that may result in inadequate tissue perfusion. Measuring cardiac output is central to understanding the state of the cardiovascular system.

There are four main situations in which knowledge of cardiac output is clinically useful in the horse. The first is in critically-ill horses and foals, in whom there are frequently derangements of the hemodynamic system and measurement of cardiac output may help guide therapy. The second is in anesthetized animals, because anesthetic agents may have profound cardiovascular effects especially in already compromised horses, such as those undergoing exploratory celiotomy for colic. Knowledge of cardiac output in the individual anesthetized animal can aid optimal titration of anesthetic agents and cardiovascular support. The third is in primary cardiac disease, in which quantifying cardiac output, particularly at exercise, can help determine the likely degree of athletic impairment. The last situation is to further understand the physiology of exercise and the pathophysiology of disease in both clinical and experimental animals.

In the last ten years many new methods of measuring cardiac output have been commercially developed for the human market. This has been chiefly in response to concerns about the safety of pulmonary artery catheterization, which is required for conventional thermodilution, currently the most commonly used method in human critical care. The development of new methods for measuring cardiac output is exciting for equine medicine, especially in regards to better monitoring of clinical patients, in whom the suitability of thermodilution is questionable. Some of these new technologies have now been validated in the

horse, and used to monitor clinical patients. The currently available techniques for measuring cardiac output and their application or potential utility in horses is reviewed.

## **Definitions**

Cardiac output is defined as the amount of blood (in liters) pumped by the heart per minute. The normal value for a resting adult horse (400-500kg) is 32-40 liters/min<sup>1-6</sup>. However, normal cardiac output is a function of body size. For this reason, cardiac output divided by a measure of body size is more appropriate when making comparisons between individuals. This is termed the cardiac index. In horses and small animals, the index usually used for body size is bodyweight in kilograms and the units for cardiac index are ml/kg/min<sup>4,7</sup>. The normal cardiac index of an adult horse is 72-88ml/kg/min<sup>8</sup>. In humans, cardiac output is conventionally indexed by the calculated body surface area (in m<sup>2</sup>)<sup>9</sup>. Indexing by body surface area is also occasionally used in small animals<sup>10</sup>, but precluded to date in horses by the lack of a formula for body surface area.

## **The Fick Principle**

Cardiac output can be calculated by using the Fick principle, named after Adolph Fick who described a theoretical method for measuring cardiac output in 1870, but did not investigate it experimentally<sup>11</sup>. The method was validated in the horse in 1898<sup>12</sup>.

The Fick principle is based on the uptake of oxygen by blood as it flows through the lungs. It is assumed that all of the oxygen that is removed from inspired air is taken up by the blood which passes through the lungs. It is also assumed that the only sources of the oxygen in arterial blood are inspired air and the oxygen in venous blood returning to the lungs. In normal animals, both of these assumptions are very close approximations to the truth. The amount of oxygen removed from inspired air per unit time (VO<sub>2</sub>) can be measured, allowing calculation of the cardiac output. The rate of oxygen uptake by the blood is a function of the rate of blood flow through the lungs and the difference in oxygen content between arterial and mixed venous blood (blood in the pulmonary artery, just about to enter the lungs). Because the entire output of the right heart passes through the lungs, blood flow through the lungs is equivalent to cardiac output.

Therefore, by measuring oxygen uptake by the lungs and arterial and mixed venous oxygen content, cardiac output can be calculated. The equation is as follows:

$$\text{Cardiac Output (CO)} = \frac{\text{Oxygen uptake by the lungs (VO}_2\text{)}}{\text{Arterial Oxygen Content (CaO}_2\text{)} - \text{Mixed Venous Oxygen Content (CvO}_2\text{)}}$$

The arterial sample can be taken from any artery. In adult horses it is relatively easy to catheterize or collect a sample from the transverse facial artery. In foals, the dorsal metatarsal artery is usually preferred. The strict definition of mixed venous blood is blood from the pulmonary artery. This requires passing a catheter or length of sterile tubing via the jugular vein, through the right side of the heart and into the pulmonary artery. The positioning of the catheter should be confirmed by waveform analysis or radiography<sup>13</sup>. In the resting horse, right atrial blood is usually a good approximation of mixed venous blood, but jugular or peripheral venous blood is probably not adequate for this technique<sup>14</sup>.

Oxygen content of the blood is a function of the partial pressure of oxygen, the concentration of hemoglobin and the percent saturation of the hemoglobin. The partial pressure of oxygen (PO<sub>2</sub>) is measured with a blood gas machine. Hemoglobin concentration ([Hb]) is either directly measured, or calculated from the packed cell volume (hemoglobin (g/dl) = 0.294 x packed cell volume (%)). Hemoglobin saturation (SO<sub>2</sub>) is either measured directly or calculated from the measured oxygen tension (PO<sub>2</sub>) using the algorithm derived from equine blood oxygen binding studies<sup>15</sup>. Saturation percentages calculated by commercial blood gas machines should be avoided, since they are based on the human hemoglobin saturation curve. Oxygen content is given by the following equation:

$$\text{Oxygen Content (ml/dl)} = 1.34 \times [\text{Hb}] \times \text{SO}_2 + 0.0031 \text{ PO}_2$$

Oxygen uptake is difficult to measure accurately, and limits the clinical usefulness of the Fick technique. There are two main methods for measuring oxygen uptake. In the first, a closed system is used with either a tight fitting facemask or endotracheal or nasotracheal intubation. The oxygen uptake is calculated from the minute volume, measured with a spirometer, and the difference in fractional oxygen content between inspired and expired air. The closed system is usually only suitable for anaesthetized, sedated or comatose animals. It is particularly useful in mechanically ventilated foals with continuous proximal tracheal gas sampling. However, in adult

horses, it is difficult to obtain sufficiently accurate minute volumes for the technique to be valid. The closed system is difficult to use on conscious animals and unsuitable for exercising animals.

The second method for measuring oxygen uptake, the open flow mask system, avoids the need for a tight fitting facemask and is better tolerated by conscious animals. The open mask technique relies on a pump evacuating the mask at a constant rate, faster than the maximum expiratory rate of the animal. Thus a mixture of room air and expired air is drawn through the mask and into the analysis system. The oxygen concentration of room air is known (20.8%). The dilution of the room air with expired gas reduces the oxygen concentration. The oxygen uptake of the animal is calculated from the change in oxygen concentration from when the mask is open to the air to when the animal is breathing into the mask against time<sup>16</sup>. A refinement of this technique is the one-step nitrogen dilution calibration, which avoids having to accurately calibrate the flow indicator and oxygen analyzer<sup>17</sup>.

The Fick method is very accurate when performed meticulously under ideal conditions. However, it requires a facemask or endotracheal intubation and thus is not suitable for all clinical situations. The need for a pulmonary artery catheter is a further disadvantage. The problems with pulmonary artery catheters will be outlined in the discussion of the thermodilution technique. The major disadvantages of the technique, however, are the requirement for steady state hemodynamics and its inaccuracy at high cardiac outputs without equivalently high tissue oxygen uptake (due to a small  $CaO_2-CvO_2$  gradient), which may limit its accuracy in unstable critically-ill patients, specifically those with hyperdynamic shock.

Carbon dioxide production, instead of oxygen consumption can be used in the Fick equation. In this case, the rate of carbon dioxide elimination by the lungs and the arterial and mixed venous carbon dioxide contents are substituted for the equivalent oxygen variables. The advantage of this technique is that right heart catheterization can be avoided by having the animal rebreathe (permitted to inhale expired air from a bag and no fresh air), until the carbon dioxide tension in the rebreathing circuit plateaus. This carbon dioxide tension ( $pCO_2$ ) is theoretically that of the mixed venous blood and can be used in the equation. This 'indirect Fick technique'<sup>18</sup> has been modified by using the change in carbon dioxide tension with partial rebreathing to estimate the mixed venous carbon dioxide tension<sup>19</sup>. The partial rebreathing technique has been validated in mechanically ventilated animals<sup>20</sup> and may prove applicable for equine anesthesia, but is not yet suitable for non-intubated animals.

## Indicator dilution methods

Indicator dilution methods are based on the work of Stewart and Hamilton<sup>21,22</sup> in the early 20<sup>th</sup> century. An indicator is injected upstream of the heart (in a vein) and measured downstream, either in the pulmonary artery or a peripheral artery. The indicator is diluted by the blood passing through the heart. The area under the time-concentration curve of the indicator downstream from the heart is related to the cardiac output. A typical indicator dilution curve is shown in Figure 1.1. The greater the cardiac output, the greater the effective dilution of the indicator, and therefore the smaller the area under the time-concentration curve.

The equation is as follows:

$$\text{Cardiac Output (Liters/min)} = \frac{\text{Amount of indicator injected (mg)}}{(\text{concentration (mg/L)} \times \text{time (min)})}$$

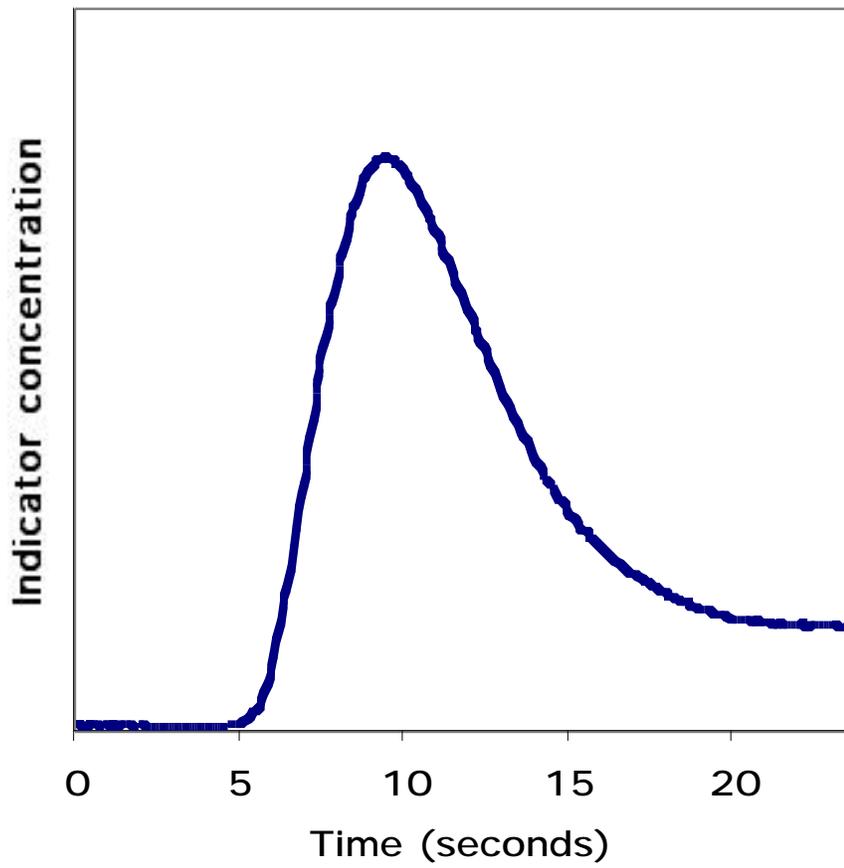
In order for the above equation to be valid, the indicator must be introduced instantaneously into the blood. In practice, this means that the indicator is injected by rapid bolus injection and that insufficiently fast injection is a potential cause of error. Indicator dilution methods also assume complete mixing of the indicator with the blood and no loss of indicator between introduction and detection. Many indicators have been used for cardiac output determination in human medicine and experimental animals. Indocyanine green, thermodilution and lithium have been used in horses and are discussed below.

### Indocyanine green

Indocyanine green is a dye that is easily injectable, nontoxic, rapidly mixed, nondiffusible, rapidly metabolized (by the liver) and measurable<sup>23</sup>. The dye is injected into a central vein, and detected in blood drawn from an arterial line through a photodensitometer. The dye absorbs light at a peak of 779nm. Unfortunately, the light absorption is not a sharp peak which means the densitometer has to be calibrated with samples of the individual patient's blood containing known concentrations of indocyanine green, which is time consuming and a source of potential inaccuracy. In addition, a large volume of blood must be withdrawn, the dye is very expensive,

**Figure 1.1: An indicator dilution curve**

Lithium dilution curve in a 40 hour old foal



and if used repeatedly makes the animal green. Although previously used in horses<sup>24</sup>, this method has fallen out of favor. It is still sometimes used in experimental horses to validate other techniques of measuring cardiac output<sup>25</sup>.

A modification of this method has been developed to avoid the need for withdrawal of arterial blood. In this new technique, the indocyanine green concentration is measured by placing photodiodes across a capillary bed, usually mucous membrane in animals, in a similar way to pulse oximetry. In some human patients, the results do not agree well with thermodilution<sup>26,27</sup>. Further developments will be necessary before this device will be worth assessing in horses, particularly in light of the relative inaccuracy of pulse oximetry reported for the foal<sup>28</sup>.

### **Thermodilution**

Thermodilution is the most commonly used method of determining cardiac output in human critically-ill patients. As the name implies, the indicator used is a bolus of fluid at a different temperature to the blood. The change in blood temperature is detected by a thermistor downstream of the heart. This technique was developed by Fegler in 1954 in dogs<sup>29</sup>, introduced for use in humans by Branthwaite and Bradley in 1968<sup>30</sup> and popularized by Swan and Ganz thereafter<sup>31</sup>. Thermodilution has been used extensively in equine research, both in adults<sup>2-6,32</sup> and foals<sup>33,34</sup>, but the author could find no reports of its use in clinical patients.

Although there are many variations on thermodilution, the most commonly used method involves catheterization of the right side of the heart. A specially designed, thermistor-tipped catheter is passed into a central vein (almost always the external jugular in horses), through the right atrium and ventricle and into the pulmonary artery. By connecting the distal port of the catheter to a pressure transducer, it is possible to use the pressure waveform to monitor the catheter advancement and confirm its placement in the pulmonary artery<sup>13</sup>. In some species, including humans, inflation of the balloon when the catheter is in the ventricle can help pass it into the right ventricular outflow tract. Inflation of the balloon does not appear to aid correct placement of the catheter in the horse. Correct placement of the catheter can be both challenging and time consuming.

A cold indicator solution is injected into the right atrium or vena cava. The proximal port of catheters designed for use in humans is usually in the correct place in foals, but in adult horses a

separate catheter is required. The site of the proximal port should be confirmed by waveform analysis.

The indicator solution used is usually 5% dextrose or saline. This is either cooled on ice to approximately 4°C, or (only in foals) kept at room temperature. The thermistor at the distal end of the catheter detects temperature changes in the blood passing through the pulmonary artery. As the bolus of cold solution passes the thermistor, a curve of temperature change is generated and cardiac output can be calculated from the area under the curve.

The equation (the Stewart-Hamilton equation) is as follows:

$$\text{Cardiac Output} = \frac{\text{Vol} \times (\text{T}_b - \text{T}_i)}{\text{Tdt}} \times \frac{\text{C}_i \times \text{S}_i}{\text{C}_b \times \text{S}_b} \times \text{K}$$

Where Vol = volume of injectate (ml), subscript b refers to the blood, subscript i refers to the injectate, T = temperature (in °C), Tdt = area under the time-temperature curve, C = specific heat (in cal/g x °C), S = specific gravity and K = calculation constant.

The advantages of thermodilution are three-fold: Once the catheter is inserted, it is cheap to perform measurements; there is no accumulation of indicator (cold), and the small fluid load associated with each measurement is rarely a problem in the horse, allowing multiple repeated measurements. Having a catheter in the pulmonary artery also allows measurement of pulmonary artery and pulmonary arterial occlusion pressures and mixed venous oxygen saturation.

The disadvantages of thermodilution are many, and often preclude its use in clinical cases. Accuracy can be a problem in horses, particularly adults. Methods to reduce error include using an automated injector (rather than hand injecting) for a smooth fast bolus injection, minimal handling of the injectate syringe to avoid temperature changes, weighing syringes to ensure accurate filling and taking each measurement four times, with the average of the closest three determinations taken as the 'true' value. Changes in blood temperature during measurement, which may occur during exercise, also cause inaccuracy. Thermodilution, like other indicator dilution methods, is inaccurate in the presence of intra-cardiac shunts.

Catheterization of the right heart is not a benign procedure. Schlipf *et al*<sup>35</sup> reported multiple cardiac endothelial lesions in all nine adult horses catheterized with a pulmonary artery catheter during a five to six hour period. One horse also had a solitary thrombus on the pulmonary valve. Complications of pulmonary artery catheters are relatively common in human medicine: Vegetative pulmonic valve lesions were found in 4 out of 19 previously catheterized patients at

post-mortem; cardiac dysrhythmias at insertion were recorded in 90/116 catheterizations; and 2 out of 92 catheterized patients had septicemia traced to the catheter<sup>36</sup>. Other problems reported include knotting of the catheter, pulmonary infarction and pulmonary artery rupture. Recent observational studies of pulmonary artery catheterization in human critically ill patients show either no net benefit or an increase in mortality associated with their use<sup>37-39</sup>.

One variation of the thermodilution technique is to use heat instead of cold as the indicator. A heating coil at the proximal end of the catheter is used to produce a series of pulses of heat, which are detected by the distal thermocouple<sup>40</sup>. The advantages of this technique over conventional thermodilution is that no fluid needs to be injected, and the system can produce very frequent estimates of thermodilution. However, in its current format the technique is not accurate at cardiac outputs greater than 10L/min in humans<sup>41</sup>. Furthermore, the pulmonary artery catheter designed for human use is likely to be unsuitable for adult horses, because the heating coil will not be in the correct place. The stiffer catheter may also pose a risk to the equine heart.

A modification of thermodilution which avoids the need for right heart catheterization is 'transpulmonary thermodilution', in which the cold indicator is injected on the right side of the heart and detected by a thermistor inserted into the aorta via a femoral artery. In the limited studies performed in humans to date, the agreement of this method with conventional thermodilution is generally good<sup>42</sup>. Transpulmonary thermodilution is used in one commercial system to provide calibration for continuous cardiac output measurements by the pulse contour analysis method.

### **Lithium Dilution**

Lithium dilution was developed to avoid the need for right heart catheterization for the measurement of cardiac output<sup>43</sup>. In this method, a small bolus of isotonic lithium chloride solution is injected into a vein (central or peripheral). Blood is withdrawn at a constant rate through a lithium specific electrode mounted in line with a peripheral arterial catheter. Cardiac output is calculated from the area under the lithium concentration-time curve. Adjustment for the animals packed cell volume is necessary because lithium is distributed only in the plasma, and cardiac output pertains to the amount of blood, not plasma, pumped out by the heart.

There is good agreement between lithium dilution and thermodilution in anesthetized adult horses (mean bias  $-0.86 \pm 2.8$  L/min)<sup>44</sup> and in foals (mean bias  $0.05 \pm 1.5$  L/min)<sup>33</sup>. We have used the results from lithium dilution cardiac output determinations to guide therapy in several neonatal foals in our clinic<sup>45</sup> and are currently completing work to adapt the technique to exercising horses on the treadmill. In a study of toxicity of lithium chloride in six adult horses, a large dose (60mmol; sufficient for 20-27 measurements in resting horses) was injected over one hour. No effects on mentation, behavior, electrocardiogram, hematological or biochemical parameters were noted. Two of six horses had increased urination 12 hours following injection<sup>46</sup>. In a study on horses exercising on the treadmill, we gave a cumulative dose of 70mmol lithium chloride in fifteen minutes, and noted no adverse clinical effects (Corley, Durando and Birks, unpublished observations). The elimination half-life of lithium chloride in the horse is 47.1 hours<sup>46</sup>.

The main advantage of lithium dilution is that it is relatively non-invasive as it only requires arterial and venous catheters and not cardiac catheterization. It also appears to be very accurate. In a study in pigs, electromagnetic flowmetry, a research technique in which a sensor is implanted at the base of the aorta enabling direct measurement of flow out of the left ventricle was compared to lithium dilution and thermodilution. Cardiac output by lithium dilution using a central vein for bolus injection was found to correlate better with electromagnetic flowmetry ( $r=0.96$ ), than did conventional thermodilution ( $r=0.85$ ). Using a peripheral (ear) vein for injection of the lithium produced a correlation with electromagnetic flowmetry similar to thermodilution ( $r=0.86$ ). A further advantage is the small volume of injectate required (15ml for an adult horse at rest), permitting hand injection of the bolus. The lithium method is also technically less complex than thermodilution or Fick and involves comparatively small capital costs.

The disadvantages of lithium dilution include blood loss, potential limit to the number of daily determinations due to lithium accumulation and inaccuracy in the presence of intra-cardiac shunts. The blood loss associated with withdrawal of arterial blood for lithium dilution is minimal, but should be considered if a large number of determinations are performed on the same subject. The peristaltic pump pulling arterial blood through the lithium sensor withdraws blood at 4ml/min but needs to be operated for less than 2 minutes to obtain a measurement. In a 50kg foal, ten measurements would involve a blood loss of less than 2% of total blood volume.

The accuracy of lithium dilution may decrease with a large number of repeated measurements due to lithium accumulation. Doubling the serum lithium concentration from 0.2mmol/L to 0.4mmol/L has been reported to moderately decrease the agreement between lithium dilution and thermodilution in dogs<sup>47</sup>. The dose (0.17±0.03mmol/kg) required in dogs to reach a plasma lithium concentration of 0.4mmol/L would represent 22-34 repeated measurements in horses and foals. Intra-cardiac shunts can be detected by examination of the dilution curve<sup>48</sup>, and curves generated from these patients are rejected by the analysis software.

The lithium dilution method is used in one commercial system to provide calibration for continuous cardiac output measurements by the pulse contour analysis method.

## **Doppler Echocardiography**

Doppler echocardiography uses the Doppler principle to measure blood flow across the mitral, pulmonary or aortic valve<sup>49,50</sup>. It is assumed that all the blood travelling through the valve is at equal velocity (laminar flow). An ultrasound wave is directed at blood flowing through the valve during systole. The velocity of blood passing through the area of interrogation is recorded by the ultrasound machine, based on the change in frequency of the reflected soundwave (the Doppler principle). The area under the velocity curve (the velocity-time integral) gives the amount of blood flowing through the area of interrogation during one cardiac cycle. This is multiplied by the cross-sectional area of the valve (calculated from ultrasonographic measurements of the valve annulus) and the heart rate to give cardiac output.

The equation is as follows:

$$\text{Cardiac Output (Liters/min)} = \text{VTI} \times \text{valve cross-sectional area} \times \text{HR}$$

Where VTI = velocity time integral, described by the area under the systolic flow profile; HR = heart rate (beats per minute)

It is possible to place the probe on the thoracic wall (trans-thoracic echocardiography) or to place it into the esophagus, over the base of the heart (trans-esophageal echocardiography). Both have been investigated in horses and the trans-esophageal method agrees better with thermodilution than the trans-thoracic technique. The mean bias was reported as 1.82±2.67 L/min<sup>44</sup> and 0.7±4.2 L/min<sup>51</sup> for trans-esophageal Doppler in anesthetized subjects and as 4.01±12.26 L/min for trans-thoracic Doppler in conscious horses<sup>52</sup>. Cardiac output performed by

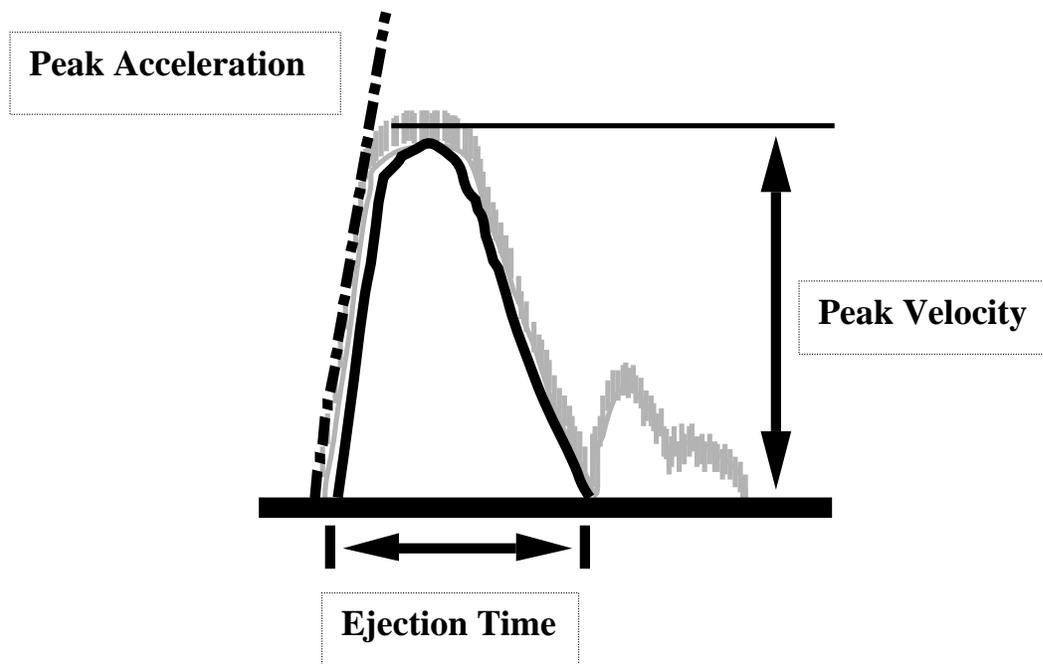
the trans-thoracic technique found a similar correlation coefficient between Doppler and thermodilution cardiac outputs in anesthetized horses (0.88)<sup>25</sup> as was found in conscious horses (0.87)<sup>52</sup>. Mean bias and limits of agreement were not reported in the study using anesthetized horses<sup>25</sup>. The correlation between trans-esophageal Doppler and thermodilution cardiac output in anesthetized horses was 0.94<sup>44</sup>. The difference in performance of the two Doppler echocardiography may be accounted for by the ability to position the probe almost directly over the aortic outflow tract in the trans-esophageal technique, because Doppler measurements are most accurate when the blood flow is close to directly towards or away from the probe. The trans-thoracic technique, in the opinion of the author, is currently not sufficiently precise for clinical or experimental use, even for serially monitoring trends in individual animals.

Two types of Doppler wave can be used, pulsed wave and continuous wave. High pulse repetition frequency Doppler interrogation of the ascending aorta resulted in a closer agreement with thermodilution in anesthetized horses than did continuous wave Doppler (mean bias 0.7±4.2 L/min and 4.0±4.4 L/min, respectively)<sup>51</sup>.

In addition to cardiac output, other hemodynamic information is available from examination of the flow-time curve generated by Doppler. High systemic vascular resistance, hypovolemia and poor myocardial contractility can be predicted from specific changes in the flow-time curve (Figure 1.2)<sup>53</sup>. However, this information is qualitative, not quantitative, and may be more useful for detecting changes in an individual patient than comparing patients.

The main advantages of Doppler determination of cardiac output are that it is a non-invasive technique, it is not affected by intra-cardiac shunts (with the exception of persistent ductus arteriosus) and no disposable items are required. The main disadvantage of Doppler is that the technique is currently only suitable for anesthetized and heavily sedated animals. The technique is unlikely to be able to be adapted to be universally useful in exercising or conscious horses, as a proportion of animals will not tolerate passage of the probe. Other disadvantages are that the current equine probes are too large for foals and small ponies and can be hard to pass<sup>44</sup>, considerable technical expertise is required for accurate measurements<sup>54</sup> and the capital costs are high. Although no venous or arterial access is required for Doppler echocardiography, direct measurements of arterial and central venous pressure are required for useful hemodynamic parameters derived from cardiac output, such as systemic vascular resistance.

**Figure 1.2: Interpretation of the Doppler cardiac output flow-time curve**



High systemic resistance is predicted by a decreased peak velocity and a short ejection time.

Hypovolemia is predicted by a normal peak velocity and a short ejection time.

Poor contractility is predicted by a decreased peak velocity and a decreased peak acceleration.

## **Bioimpedance**

Transthoracic electrical bioimpedance was developed as a totally non-invasive method of measuring cardiac output. Blood has a relatively high electrical conductivity compared to solid tissues and air. Arterial blood flow is pulsatile. The pulsatile flow in the great arteries results in changes in thoracic impedance, with the magnitude of change corresponding to the amount of blood flowing and therefore cardiac output<sup>55</sup>. A small electrical current is applied to the thorax, and electrodes placed on the thorax and neck detect the tissue conductivity. To the author's knowledge, bioimpedance has not been used to measure cardiac output in horses. However, a bioimpedance device to measure total body water and extracellular fluid volume has recently been validated in normal horses<sup>56</sup> although its accuracy in dehydrated animals is questionable<sup>57</sup>.

The biggest concern with bioimpedance is precision of the measurements. Whilst some studies in human patients have demonstrated sufficient accuracy for clinical use<sup>58</sup>, others have not<sup>59</sup>, particularly in the setting of pulmonary edema and pleural effusion<sup>60</sup>. It is possible that these devices may be made more accurate in the future. However, it seems unlikely that bioimpedance devices with algorithms designed for human patients will ever be sufficiently accurate for use in the horse.

## **Pulse Contour Analysis**

Pulse contour analysis calculates the cardiac output from the arterial pressure waveforms. The area under the arterial pressure tracing during systole represents blood flow in the catheterized vessel, and is therefore related to cardiac output<sup>61,62</sup>. The start of systole is marked by the initial rapid increase in pressure from the baseline, and the end of systole is marked by the dicrotic notch (the point at which the aortic valve closes). Blood flow after the dicrotic notch is due to elastic recoil of the arteries. The elasticity of arteries varies with age and sex<sup>63,64</sup> and therefore this technique needs to be calibrated for each individual. Current methods of calibration include arterial thermodilution and lithium dilution. Following calibration, pulse contour analysis can provide continuous, beat to beat, accurate cardiac outputs for up to 24 hours before further

calibration is required<sup>65,66</sup>. However, marked changes in systemic vascular resistance may result in inaccuracy and the requirement for recalibration<sup>67</sup>.

To the author's knowledge, pulse contour analysis has not been used to measure cardiac output in horses. The technique has been used in exercising humans<sup>68</sup>, and has the potential to be used in critical care, anesthesia and study of exercise physiology of horses and foals.

## **Conclusion**

The development of new technologies to measure cardiac output represent exciting opportunities for equine clinicians and researchers. Improved information on the hemodynamic system can only help our understanding of physiology and pathophysiology of the horse. Many of the techniques described in this review may eventually be suitable for use in the horse. The Fick method, dye dilution, thermodilution, lithium dilution and Doppler echocardiography have all been used successfully in research settings. Of these, with the currently available technology, lithium dilution appears best suited to the equine clinic.

## **Chapter 2: Hemodynamic monitoring in critically ill neonatal foals.**

### **Introduction**

Disturbances of the cardiovascular system are very common in critically ill neonatal foals, and are especially prevalent in septicemia (Table 2.1) and hypoxic ischemic encephalopathy (HIE)<sup>69</sup>, which together are responsible for 44% of deaths in foals less than a week old<sup>70</sup>. Recognition and appropriate treatment of these disturbances is an important part of therapy. Although other therapies may be more specific for the underlying condition (for example antimicrobials in septicemia), stabilization of the cardiovascular system is essential to allow time for these treatments to work. Perturbations of the cardiovascular system may also cause other organs, such as the kidney, to fail<sup>71</sup>. Furthermore, persistent poor gastrointestinal perfusion may allow transmural migration of bacteria<sup>72,73</sup>, resulting in or compounding existing sepsis.

### **Monitoring hemodynamic parameters – indications, techniques and interpretation**

The hemodynamic variables monitored in an individual foal will depend largely on its clinical status. In ambulatory foals it might be appropriate solely to monitor heart rate and the frequency of urination, whereas in recumbent obtunded foals, blood pressure and exact urine output should also be measured. In current clinical practice central venous pressure and certainly cardiac output, pulmonary arterial pressures and cardiac output derived variables are reserved for foals that do not respond as predicted to therapy, or who demonstrate major cardiovascular disturbances. Other measures of tissue perfusion, such as laser Doppler and gastric tonometry, are not yet practical in clinical cases or are yet to be validated in the horse.

Typically, changes in behavior or alertness lag behind onset of cardiovascular shock. Thus, foals may be able to maintain themselves in sternal recumbency and continue to appear alert despite major increases in heart rate and falls in blood pressure and urine output. Indicators for

**Table 2.1: Data from the 70 foals presenting to the Equine Medical Center in 2000-1, for which an admission blood culture and mean arterial pressure were recorded**

Parameter	Number of foals	Mean MAP $\pm$ SD at admission (mmHg)	<i>p</i> value 2 tailed t-test
Positive blood culture at admission	24	59.3 $\pm$ 14.8	p=0.003
Negative blood culture at admission	46	70.2 $\pm$ 11.8	
Died or euthanized during hospitalization	23	57.3 $\pm$ 16.8	p=0.001
Survived to hospital discharge	47	70.9 $\pm$ 9.4	

MAP = mean arterial pressure

more aggressive hemodynamic monitoring include poor urine output, more than transient tachycardia, development of peripheral or pulmonary edema, seizure activity, obtundation, acute renal failure, respiratory compromise and institution of mechanical ventilation.

## **Heart rate**

The normal heart rate of a resting neonatal foal is 70 to 100bpm. The heart rate may be higher (up to 130bpm) during periods of activity or excitement<sup>74</sup>. High heart rates are common in hypovolemic shock, septic shock and severe anemia. However, any of these conditions may exist with an apparently normal heart rate, due to failure of physiologic compensation. Very low heart rates (less than 60bpm) are usually seen in hypothermic foals (Table 2.2). Low or high heart rates may be accompanied by cardiac arrhythmias. Because of the increased myocardial oxygen demand associated with tachycardia, it should always be investigated by means of an electrocardiogram and interpreted in context of urine output and arterial blood pressure.

## **Blood pressure**

The normal mean arterial blood pressure of the thoroughbred foal is 69-111mmHg<sup>75</sup>. Blood pressure can be measured either directly, via cannulation of an artery or indirectly with oscillometry or Doppler techniques. The artery of choice for direct monitoring is the dorsal metatarsal artery, but the facial artery, radial artery and caudal auricular artery may also be catheterized<sup>76</sup>. The over-the-wire technique<sup>77</sup> can make catheterization easier, especially in hypotensive or edematous foals. The arterial catheter can be connected to a electronic pressure transducer or, less optimally, a manometer. In either case, careful positioning of the device at the level of the sternal manubrium and zeroing are essential to producing meaningful results. The arterial catheter should be well secured by means of sutures or instant bonding glue and bandaging, and special care needs to be taken when repositioning the foal and during struggling activity. The arterial catheter requires either continuous flushing via a pressure infusor system or intermittent flushing with saline or heparinized saline solution. It should be remembered that the arterial catheter is a potential site for thrombosis and a portal for infection.

**Table 2.2: Rectal temperature on admission of foals presenting to the Equine Medical Center in 1998-2000**

Parameter	Number of foals	Mean Rectal Temp ± SD at admission (°F)	<i>p</i> value 2 tailed t-test
Heart rate less than 60bpm at admission	6	96.5±3.2	p=0.025
Heart rate 60bpm or greater at admission	125	100.7±2.1	
Died or euthanized during hospitalization	31	99.9±2.7	p=0.12 (NS)
Survived to hospital discharge	106	100.7±2.1	

NS = Not Significant

Indirect blood pressure monitoring has the advantage of being non-invasive and simple to perform. However, the reliability of the technique has been questioned, based on work in adult horses<sup>78,79</sup>. We recently investigated oscillometric measurements of arterial blood pressure from the coccygeal artery of healthy neonatal foals and found good agreement with direct pressure measurements for mean and diastolic, but not systolic, pressures<sup>80</sup>. It is important to use an appropriate bladder width for the patient's tail girth. We used a bladder width to tail girth ratio of 1:1.9 to 1:2.8, which is greater than the previously recommended ratio for foals of 1:4 to 1:5<sup>76</sup>.

The decision to use indirect or direct blood pressure measurements will depend on equipment available and the status of the patient. Direct blood pressure monitoring offers the advantage of accuracy and continuous data, whereas indirect blood pressure is non-invasive and avoids the need to maintain an arterial catheter. It is advisable to repeat indirect measurements at least twice before making any therapeutic decisions based on them.

Hypotension is common and important in neonatal foals presenting to referral hospitals (Table 2.1). Decreased arterial pressures can result from either decreased cardiac outputs or arterial vasodilation (decreased systemic vascular resistance). The distinction is important, because different therapies may be required for each scenario. Unfortunately, it is not easy to distinguish between these pathophysiological states on clinical grounds. This is illustrated by a study of human critically ill patients, in which the attending physicians were unable to predict if cardiac output and systemic vascular resistance were low, normal or high in over 50% of cases. Furthermore, when this data became available to the clinicians, major changes of therapy were instituted in 45% of patients<sup>81</sup>.

It is preferred to titrate therapy to mean, rather than systolic, blood pressure because mean pressure better reflects organ perfusion pressure<sup>82</sup>. The optimum mean arterial pressure has not been determined for foals, and probably varies between individuals and pathophysiological states. However, based on work in other species, blood pressures below 60mmHg are likely to be deleterious, because this is the point where autoregulatory control of blood flow to the heart, brain and kidneys ceases, resulting in pressure-dependent organ perfusion<sup>82-84</sup>. Limited evidence from human critical care suggests there may be no additional advantage of titrating therapies to achieve a blood pressure of 75 or 85mmHg over 65mmHg<sup>85</sup>.

The cardiovascular system should be reviewed and treatments considered if the mean arterial pressure falls below 69mmHg. This is the lower limit of the normal range<sup>75</sup> and gives a

'buffer zone' for treatments to start working above 60mmHg. However, the blood pressure should not be viewed in isolation. It is important to remember that blood pressure is not equivalent to blood flow or tissue perfusion. Urine output can be a very useful guide to end-organ perfusion and in many foals may be a more useful indicator of cardiovascular status than blood pressure alone.

## **Urine output**

The normal urine output of a four day old foal is 148ml/kg/day, which is approximately 6ml/kg/hr<sup>86</sup>. However, for a critically ill foal treated with intravenous fluids, this figure may have little relevance. In these foals, the fluid balance rather than the absolute urine output should be considered. The fluid balance is the difference between the hourly volume of all infusates and urine production. In a fluid replete animal without diarrhea this difference should be small, reflecting insensible fluid loss, fecal fluid and water lost during normal homeostasis<sup>87</sup>.

Urine output is measured by attaching a closed collection system to an indwelling urinary catheter. 12Fr foley catheters, 33cm long for fillies and 64cm for colts, make good urinary catheters and avoid the need to suture the catheter to the foal for retention. For fillies a stylet (for example a #3 polyethylene catheter) placed in the center of the catheter can make it easier to pass. Urinary catheters should always be placed with appropriate sterile techniques. A surgical drainage bag or standard fluid set and empty fluid bag can be used for urine collection. The surgical drainage bag has the advantage of valves to prevent back-flow and ease of emptying. The risk of urinary catheterization, which is ascending infection, needs to be weighed against the benefits of accurate determination of urine output and protection of the foal from lying in urine. In the case of recumbent foals, this second benefit can significantly help in nursing management of the foal and the avoidance of urine scalding.

The response in urine output to changes in the cardiovascular system is not linear because of the existence of many different feedback mechanisms. Thus urine output can only provide a gross indication of cardiovascular status. The effect of increasing mean arterial pressure on renal blood flow and glomerular filtration rate is damped across the normal physiological range of blood pressure, resulting in little change in urine output. However, in the failing circulation renal

blood flow is decreased both directly and via neuroendocrine feedback mechanisms, resulting in decreased urine output<sup>88</sup>. A falling urine output may precede other signs of circulatory shock.

It is important to note that many variables other than circulatory status can decrease urine output in the neonatal foal. Acute renal failure may result in oliguria, anuria or, uncommonly in foals, polyuria. Measuring the urine specific gravity may help distinguish hemodynamic (pre-renal) renal insufficiency from renal failure. The specific gravity is expected to be close to isotonic (1.010) in renal failure, and higher than this with pure circulatory disturbances. However, the normal urine specific gravity of nursing foals may be very dilute at 1.001 to 1.009<sup>89</sup>. Hyperglycemia above the renal threshold will result in an osmotic diuresis. The exact renal threshold for the foal has not been determined and probably varies to some degree between individuals. However, it is probably higher than for adult horses and, based on simultaneous measurements of blood glucose and glucose in urine in our clinic, may be higher than 240mg/dl in some individuals.

Some foals produce small amounts of urine despite apparently adequate hemodynamics (Table 2.3). In human neonates a syndrome of inappropriate antidiuretic hormone secretion is well recognized<sup>90</sup> and it is possible a similar syndrome can occur in neonatal foals. Urinary catheters sometimes become blocked and defects in bladder wall integrity may be overlooked at admission. Therefore any investigation of low urine output should include a ultrasonographic examination of the peritoneal space and confirmation of an empty bladder.

The cardiovascular system should be reviewed if the urine output is less than 2/3 of the volume of fluid delivered (including all infusates and enteral feeding). Large decreases in urine output demand immediate attention. Urine output can be especially useful to evaluate a change in therapy. For example, a treatment which increases mean arterial pressure but decreases urine output has almost certainly not improved tissue perfusion.

## **Lactate**

The normal jugular venous lactate concentration of one to six month old foals is 0.9 to 1.65 mmol/L<sup>91</sup>. We measured arterial and venous lactate in five normal, conscious 30-42 hour old foals restrained on a mat. The lactate concentration in blood from the dorsal metatarsal artery was  $2.17 \pm 0.49$  mmol/L and jugular venous lactate was  $2.18 \pm 0.35$  mmol/L. These foals showed

**Table 2.3: Details of urine output and hemodynamics in a 51kg, septic foal**

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53 hour old septic foal, being treated with 1mcg/kg/min furosemide

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**Urine output data**

Total infusate (Fluids, Drugs, TPN)	452ml/hr	8.86ml/kg/hr
Mean Urine Production (over 4 hours)	63.75ml/hr	1.25ml/kg/hr
Mean difference (Ins – Outs)	388.25ml/hr	7.61ml/kg/hr
Urine Specific Gravity		1.022

**Hemodynamic data**

SAP	MAP	DAP	RAP	
104mmHg	65mmHg	47mmHg	5mmHg	
HR	CO	CI	SV	SVR
84bpm	12.05L/min	236ml/kg/min	144ml	412 dynes.s.cm-5

**Interpretation:** Foal is mildly hypotensive, but cardiac output and stroke volume are mildly increased. Systemic vascular resistance is moderately decreased. Despite normal to low right atrial pressure, high stroke volume suggests possible hypervolemia. Oliguria probably of renal cause, although low SVR might be contributing.

**Decision:** Increase furosemide infusion to 2mcg/kg/min. (it would have been reasonable to start a low dose of a vasopressor concurrently. This was not done)

**Urine output data after change of treatment (over subsequent 4 hours)**

Total infusate (Fluids, Drugs, TPN)	403ml/hr	7.90ml/kg/hr
Mean Urine Production (over 4 hours)	343.75ml/hr	6.74ml/kg/hr
Mean difference (Ins – Outs)	59.25ml/hr	1.16ml/kg/hr
Urine Specific Gravity		1.010

**Hemodynamic data after change of treatment**

SAP	MAP	DAP	RAP	HR
103mmHg	74mmHg	52mmHg	5mmHg	88bpm

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SAP= Systolic arterial pressure; MAP = Mean arterial pressure; DAP = Diastolic arterial pressure; RAP = Right atrial pressure; HR = Heart rate; CO = Cardiac output; CI = Cardiac Index; SV = Stroke Volume; SVR = Systemic vascular resistance.

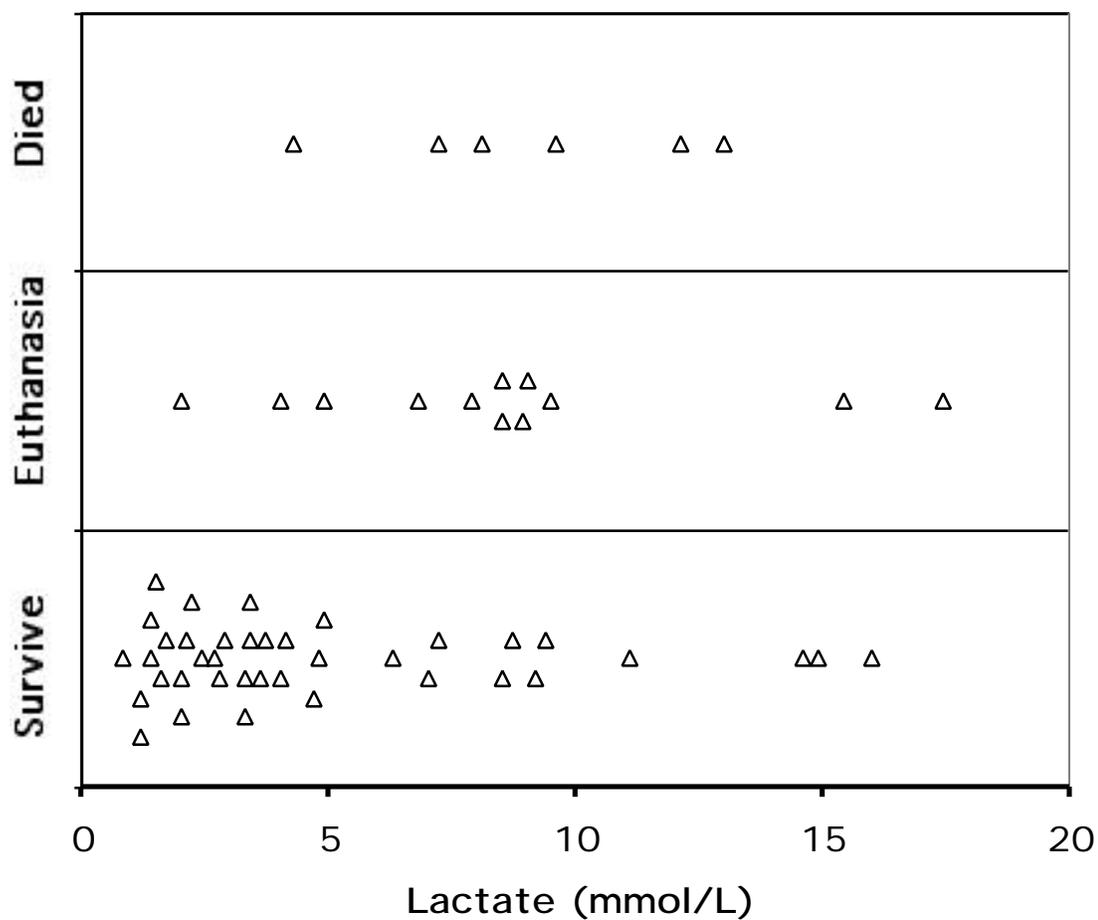
some struggling activity. It is possible that, if blood lactate could be measured in resting neonatal foals without disturbing them, values comparable to one to six month old foals would be found.

In critically ill foals, lactate should be measured, rather than calculated from the anion gap or simplified strong ion difference<sup>92</sup>, because non-ketone unidentified anions may contribute to the anion gap in endotoxemia and sepsis<sup>93,94</sup>. Many different lactate analyzers are commercially available, some of which have been validated in the horse<sup>95-97</sup>.

Increased blood lactate concentrations in critically ill patients may be due to inadequate tissue perfusion, hypoxemia, increased tissue oxygen demands, decreased blood hemoglobin concentration or a combination of these factors<sup>98</sup>. In sepsis, increased lactate concentrations do not always reflect poor tissue perfusion. Pyruvate dehydrogenase is inactivated in sepsis by over production of pyruvate dehydrogenase kinase, thus decreasing the rate of conversion of pyruvate to acetyl CoA for use in the tricarboxylic acid (TCA) cycle. The excess pyruvate is converted to lactate by lactate dehydrogenase, irrespective of tissue oxygen supplies<sup>99</sup>. Increased blood concentrations may also be a reflection of acute renal failure, severe motor seizures or catecholamine, nitroprusside or bicarbonate administration<sup>98</sup>.

Blood lactate concentrations can be a very useful guide to the adequacy of tissue oxygen delivery and thus help guide hemodynamic therapy. Where hyperlactemia is due to hemodynamic disturbances, decreasing blood lactate concentrations suggest that tissue perfusion is being improved. Conversely, if blood lactate concentrations increase in response to therapies aimed at improving hemodynamics, these therapies should be urgently reviewed. Unfortunately, decreases in plasma lactate concentration can lag behind improved cardiovascular status<sup>100</sup> and therefore therapy cannot be titrated to blood lactate concentrations. In human septic shock patients, high blood lactate concentrations are a predictor of mortality<sup>98,101</sup>. An arterial lactate concentration was measured at admission in 56 foals presenting to the Equine Medical Center in 2000 and 2001. Although there was a statistical association of higher lactate concentrations with ultimate non-survival ( $p=0.0004$ ; Mann-Whitney U test), there was considerable overlap between ultimate survivors and non-survivors (Figure 2.1). Thus admission lactate concentration cannot be used in isolation to predict survival in our population of critically-ill foals.

**Figure 2.1: Admission lactate and survival in 56 foals presenting to the Equine Medical Center in 2000-1**



## **Pulse oximetry**

In five normal 30-42 hour old conscious foals restrained on a mat, we found an arterial hemoglobin saturation of  $96.9 \pm 1.63\%$  by direct reflectance photometry of the blood. Pulse oximetry offers a non-invasive method of monitoring arterial hemoglobin oxygenation saturation. It is based on detection of light emitted by two light-emitting diodes of differing wavelengths that are preferentially absorbed by oxyhemoglobin and deoxyhemoglobin, respectively. This allows the percentage saturation of blood passing by the sensor to be calculated. Most pulse oximeters will also calculate a pulse rate, based on the pulsatile flow within the arteriolar bed. Pulse oximetry probes intended for human fingers can be placed on foal tongues, ears or lips; reflective probes can be used on the forehead<sup>28</sup> and rectal probes may also be used. In foals that are not completely comatose, all of these types of probes are difficult to maintain.

The pulse oximeter gives useful information regarding oxygen delivery to the tissues and the functioning of the cardiopulmonary unit. Decreases in saturation below 93% should warrant immediate investigation of the cardiorespiratory system. Pulse oximetry may be particularly useful in mechanically ventilated foals. Although clinically useful to follow trends and warn of hemoglobin desaturation, the absolute accuracy of pulse oximetry in the foal is only moderate and varies with the site<sup>28</sup>.

## **Central Venous Pressure**

The normal central venous pressure of a neonatal foal is 2 to 9mmHg<sup>34</sup>. Central venous pressure (CVP) is measured by placing a catheter in the jugular vein of sufficient length that its tip is in the right atrium or intrathoracic vena cava. The catheter is connected to a pressure transducer, positioned and zeroed at the level of the sternal manubrium<sup>34,102</sup>. If a 20cm or longer catheter is placed in the jugular of a neonatal foal, its tip is almost always intra-thoracic. This can be confirmed by variation of the pressure waveform with breathing or radiography. Intra-thoracic venous pressure closely approximates right atrial pressure. Thus the same catheter routinely used for administration of fluids can be used for monitoring CVP. Use of double or triple-lumen catheters allows simultaneous administration of fluids and measurement of CVP.

The CVP varies with breathing and therefore relying on the electronically averaged mean as the value for CVP may be misleading, especially during hyperpnea or mechanical ventilation<sup>103</sup>. For accurate measurement of the CVP, a simultaneous electrocardiogram recording is required<sup>103</sup>. The central venous pressure should be measured as the mean of the *a* wave at end-expiration. The *a* wave at end-expiration can be identified in the last waveform prior to the rapid fall in pressure indicating inspiration in spontaneously breathing foals, and in the last waveform prior to the rapid rise in pressure in mechanically ventilated foals. The *a* wave falls in the P-R interval<sup>103</sup>.

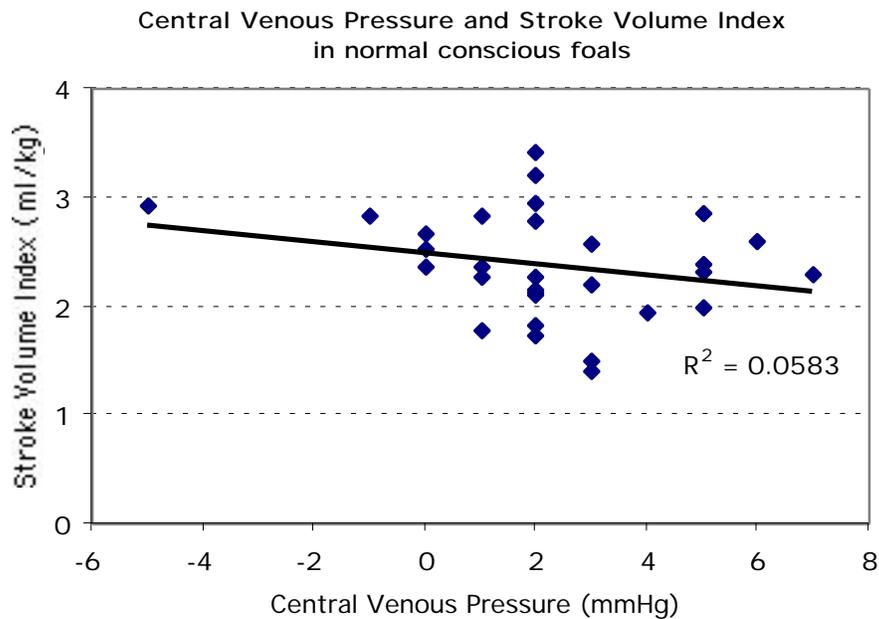
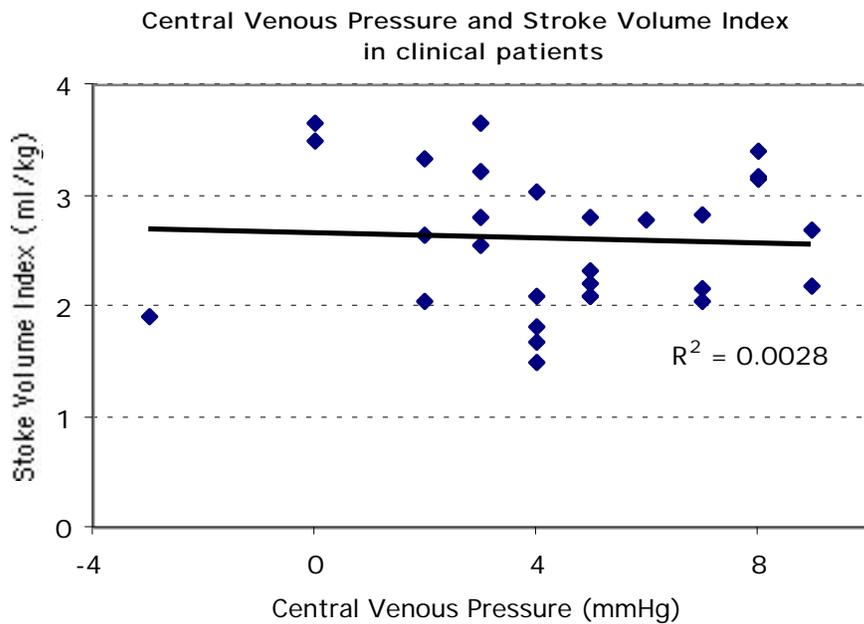
The aim of volume replacement in critically ill patients is usually to maximize cardiac output, by increasing end-diastolic volume to close to the flat part of the Frank-Starling curve. This is usually achieved at a CVP of 6 to 12mmHg in human patients<sup>104</sup>. A low central venous pressure may be an indicator of insufficient circulating volume and the need for fluid therapy in humans<sup>103</sup>. However, in both normal and critically-ill neonatal foals the correlation between CVP and cardiac stroke volume is poor (Figure 2.2). This mirrors work in human pediatric patients which demonstrates a poor correlation between CVP and volume status<sup>105</sup>. Therefore, the response to a fluid challenge may be a more reliable way of assessing volume status in the foal than the numerical value of the central venous pressure. A bolus of 10ml/kg crystalloids or 2-3ml/kg colloids is delivered and the cardiovascular system is reassessed. In humans, a CVP increase in response to this challenge of less than 1mmHg is associated with hypovolemia, whereas an increase of greater than 3mmHg indicates probable fluid overload<sup>106</sup>. Comparable numbers have not been validated in foals. Assessment of response to a fluid challenge should include heart rate, mean arterial pressure and urine output.

## **Cardiac Output**

The normal cardiac output of neonatal foals aged 4 hours to 5 days old has been measured as 200±25ml/kg/min or 7.5 to 12.5L/min for a 50kg foal<sup>34,107</sup>. Between 6 and 14 days of age, cardiac output is reported to be 225±30ml/kg/min<sup>34</sup>.

Many methods of measuring cardiac output have been published for humans and experimental animals. Three of these methods, the Fick method, thermodilution and lithium dilution have been described in neonatal foals<sup>33,34,107-109</sup>. The Fick method calculates the cardiac

**Figure 2.2: The correlation between stroke volume and central venous pressure in neonatal foals**



output from the rate of oxygen consumption and the arterial to mixed venous difference in oxygen content. This method requires careful analysis of expired gas volume and inspired and expired oxygen concentrations, is difficult to perform and thus is not practical in clinical practice. This is underscored by an experimental study in neonatal foals, in which the cardiac output measured by Fick varied greatly between time points in the same individual, between individuals and from the results of two thermodilution studies<sup>34,107,109</sup>.

The two other methods described in neonatal foals are indicator dilution methods, in which an indicator is injected as a bolus upstream of the ventricle(s) and a detection device measures the time-concentration curve of the indicator downstream of the ventricle. The cardiac output is calculated from the Stewart Hamilton equation and is related to the area under the curve<sup>110</sup>.

Thermodilution is the indicator dilution technique most commonly used in human critical care. For this technique, a thermistor-tipped catheter is introduced via the jugular vein, through the right heart and into the pulmonary artery. Catheter position can be confirmed by waveform analysis, radiography or echocardiography. A bolus of 5ml iced saline<sup>34,107</sup> or 8ml room temperature 5% dextrose solution<sup>33</sup> is injected into the right atrium, through the proximal port of the thermodilution catheter. The change in blood temperature is detected by the thermistor in the pulmonary artery and the cardiac output is calculated from the curve generated. Measurements are usually done in quadruplicate, with the mean of the closest three readings taken as the value. The advantages of thermodilution are lack of indicator accumulation and the availability of other relevant variables (pulmonary pressures and mixed venous oxygen saturation) from the same catheter. The main disadvantages are the risk of catheter-associated endocardial or valvular lesions<sup>35</sup>, technical difficulty in placing and maintaining the catheter and inaccuracy of the technique in the presence of intra-cardiac shunts.

Lithium dilution is a new technique, recently described in humans and adult horses<sup>44,111</sup>. Measurements require venous and arterial catheters, but not cardiac catheterization. A bolus of lithium chloride (0.3 to 0.45mmol) is injected into the jugular vein, and the blood is withdrawn from a peripheral artery through a lithium-specific electrode. The cardiac output is calculated from the time-lithium concentration curve generated<sup>44</sup>. We recently evaluated the lithium dilution method in neonatal foals, and found good agreement with thermodilution<sup>33</sup>. Relatively large doses of lithium chloride have been shown to have no clinical effects in adult horses<sup>46</sup>. The advantages of the lithium technique are ease of measurement and the avoidance of cardiac

catheterization. The disadvantages are lithium accumulation may decrease accuracy after a large number of measurements<sup>47</sup> and inaccuracy in the presence of intra-cardiac shunts. We have used this technique in critically ill foals and believe that it is the only currently validated technique suitable for clinical use in equine neonates.

In hypotensive septic shock, the cardiac output may be increased or decreased. Data from human medicine suggests that it is not possible to predict the cardiac output from the heart rate, blood pressure and urine output<sup>81,112</sup>. Knowing cardiac output is central to selecting appropriate treatments for hypotension that is unresponsive to fluid therapy. In foals with low cardiac output, positive inotropes such as dobutamine are the treatment of choice. In foals with normal or high cardiac output, vasopressors such as norepinephrine are indicated. In either case, the response to the selected therapy should be evaluated by repeating all hemodynamic measurements, including cardiac output. However, prompt measurements of cardiac output allow earlier selection of appropriate treatments, decreasing the duration of organ hypoperfusion. We have found cardiac output measurements particularly useful when the expected response to therapy has not occurred (Tables 2.3 and 2.4). It should be noted that requirement for vasoactive drugs does not necessarily portend a poor prognosis. The hospital discharge rate for foals treated with these drugs at the Marion duPont Scott Equine Medical Center was 73% in 1998 and 67% in 1999<sup>113</sup>, compared to total discharge rates of 88% and 71%, respectively.

The measurement of cardiac output also allows the calculation of a number of other hemodynamic variables (Table 2.5), which can be useful in assessing the hemodynamic system or the response to treatment.

## **Derived hemodynamic parameters**

Several hemodynamic variables can be calculated from cardiac output, heart rate, blood pressure and blood gases. These include stroke volume, systemic vascular resistance, oxygen extraction ratio, global oxygen delivery and global oxygen uptake (Table 2.5).

**Stroke volume** should be interpreted in light of the fluid status and central venous pressure of the animal. A low stroke volume, despite a high central venous pressure or in spite of an adequate fluid challenge is consistent with cardiac failure. A greater than normal stroke volume suggests that hypovolemia is unlikely.

**Table 2.4: Details of urine output and hemodynamics in a 51kg, septic foal**

72 hour old septic foal, treated with 1.4mcg/kg/min furosemide  
 Current vasoactive treatments: 3mcg/kg/min dobutamine, 1.5mcg/kg/min norepinephrine

**Urine output data**

Total infusate (Fluids, Drugs, TPN)	622ml/hr	12.2ml/kg/hr
Mean Urine Production (over 2 hours)	475ml/hr	9.3ml/kg/hr
Mean difference (Ins – Outs)	+147ml/hr	2.9ml/kg/hr

**Hemodynamic data**

SAP 63mmHg	MAP 50mmHg	DAP 39mmHg	RAP 5mmHg	
HR 96bpm	CO 10.7L/min	CI 209ml/kg/min	SV 112ml	SVR 336 dynes.s.cm-5

**Interpretation:** Foal is hypotensive. Cardiac output and stroke volume are in the normal range. Systemic vascular resistance is decreased. The norepinephrine is already at a high infusion rate.

**Decision:** Examine the effect of increasing cardiac output with dobutamine (to 6mcg/kg/min – no change in norepinephrine treatment)

**Urine output data after change of treatment (60 minutes after initial data)**

Total infusate (Fluids, Drugs, TPN)	705ml/hr	13.8ml/kg/hr
Mean Urine Production (over 1 hour)	300ml/hr	5.9ml/kg/hr
Mean difference (Ins – Outs)	+405ml/hr	7.9ml/kg/hr

**Hemodynamic data after change of treatment (60 minutes after initial data)**

SAP 56mmHg	MAP 38mmHg	DAP 29mmHg	RAP 5mmHg	
HR 100bpm	CO 11.76L/min	CI 231ml/kg/min	SV 118ml	SVR 231 dynes.s.cm-5

**Interpretation:** Treatment change is unsuccessful. The cardiac output has increased but the mean blood pressure and systemic vascular resistance have markedly decreased. End organ tissue perfusion is likely to be worse since urine output has decreased relative to infusate.

**Decision:** Restore the dobutamine to 3mcg/kg/min and increase the rate of norepinephrine infusion. The effects of this change could not be examined, as the foal died within 1 hour.

SAP= Systolic arterial pressure; MAP = Mean arterial pressure; DAP = Diastolic arterial pressure; RAP = Right atrial pressure; HR = Heart rate; CO = Cardiac output; CI = Cardiac Index; SV = Stroke Volume; SVR = Systemic vascular resistance.

**Table 2.5: Calculations for derived hemodynamic variables.**

Parameter	Calculation	Units	Normal values for 1 day old foals
Cardiac Index (CI)	$\frac{\text{Cardiac output (L/min)} \times 1000}{\text{Bodyweight (kg)}}$	ml/kg/min	197.3 ± 12.0
Stroke volume (SV)	$\frac{\text{Cardiac Output (L/min)} \times 1000}{\text{Heart rate}}$	ml	107 ± 6.4
Systemic vascular resistance (SVR)	$\frac{(\text{MAP} - \text{CVP}) \times 80}{\text{Cardiac output}}$	dynes.s.cm <sup>-5</sup>	708 ± 74
Arterial oxygen content (CaO <sub>2</sub> )	1.34 x [Hb] x SaO <sub>2</sub> + 0.0031 PaO <sub>2</sub>	ml/dl	15.8 ± 1.3*
Venous oxygen content (CvO <sub>2</sub> )	1.34 x [Hb] x SvO <sub>2</sub> + 0.0031 PvO <sub>2</sub>	ml/dl	13.0 ± 1.3*
Global oxygen delivery (DO <sub>2</sub> )	$\frac{\text{CaO}_2 \times \text{Cardiac Index}}{100}$	ml O <sub>2</sub> /kg/min	31
Global oxygen uptake (VO <sub>2</sub> )	$\frac{(\text{CaO}_2 - \text{CvO}_2) \times \text{Cardiac Index}}{100}$	ml O <sub>2</sub> /kg/min	5.6
Oxygen extraction ratio (O <sub>2</sub> ER)	$\frac{(\text{CaO}_2 - \text{CvO}_2) \times 100}{\text{CaO}_2}$	%	18.0 ± 0.02*
Pulmonary vascular resistance (PVR)	$\frac{(\text{PAP} - \text{PAOP}) \times 80}{\text{Cardiac output}}$	dynes.s.cm <sup>-5</sup>	194 ± 37

MAP = mean arterial pressure; CVP = Central venous pressure; [Hb] = hemoglobin concentration (g/dl); SaO<sub>2</sub> = arterial hemoglobin saturation; PaO<sub>2</sub> = arterial oxygen tension (mmHg); SvO<sub>2</sub> = venous oxygen saturation; PvO<sub>2</sub> = venous oxygen tension (mmHg); PAP = mean pulmonary arterial pressure (mmHg); PAOP = Pulmonary arterial occlusion pressure (mmHg).

Normals from Thomas *et al* (1987), except as specified below.

\*data from 5 conscious, healthy 30-42 hour old mixed breed foals in lateral recumbency.

Calculated from other data presented. Intended as a guide only.

**Systemic vascular resistance** is an indicator of vasodilation or constriction. It is a useful parameter to determine the root cause of hypotension and the response to drugs. However, since this is a derived parameter, treatments should be titrated to mean arterial pressure, not systemic vascular resistance<sup>82</sup>.

**Global oxygen delivery** is a measure of the amount of oxygen delivered to the tissues per minute. This parameter is a measure of the function of the cardiorespiratory system. Its importance is to remind the clinician that cardiac output is only part of the equation, and that hemoglobin concentration and arterial oxygen tension should also be considered. This variable only describes the rate at which oxygen is entering the systemic circulation. The proportion of cardiac output received, and therefore the oxygen delivery, varies markedly between individual organs.

**Global oxygen uptake** is a measure of overall tissue oxygen utilization. This parameter gives an indication of whether organs are able to utilize the delivered oxygen. In normal animals, the oxygen uptake reflects metabolic oxygen requirements and increasing oxygen delivery will not increase oxygen uptake. There are two situations in which increasing oxygen delivery will not increase a reduced oxygen uptake. The first is where there is significant shunting past some organs. If some organs are adequately perfused, but local vascular constriction or dilation is preventing perfusion of other organs, increasing cardiac output may simply increase flow through the already perfused organs. The second situation is sepsis. Biochemical changes to the cells may reduce oxygen uptake in sepsis despite adequate oxygen delivery<sup>99</sup>. As for global oxygen delivery, individual organs may vary markedly from the global parameter.

**Oxygen extraction ratio** describes the percent of oxygen delivered that is utilized by the tissues. Its main advantage over the global oxygen delivery and uptake parameters is that it does not require cardiac output measurement. The disadvantage is that it cannot distinguish between the contribution of these two factors to the ratio. A decreasing oxygen extraction ratio results from decreased oxygen uptake without a change in oxygen delivery or increased oxygen delivery without a change in oxygen uptake. Conversely a high oxygen extraction ratio may represent decreased relative oxygen delivery or increased relative oxygen uptake.

## **Pulmonary arterial pressures**

Pulmonary arterial pressures are measured by introducing a catheter into a major vein (usually the external jugular in foals), and advancing it through the right atrium and ventricle into the pulmonary artery. Catheter position is confirmed by waveform analysis, radiography or echocardiography. If a thermistor-tipped catheter is used (see above), the same catheter may be used for pulmonary pressure measurements and thermodilution cardiac output calculations.

Advancing the catheter into the pulmonary vasculature until it is in complete contact with the vessel wall, forms a continuous column of blood between the tip of the catheter and the pulmonary vein. The resultant pressure recordings (the pulmonary artery wedge pressure (PAWP)) reflect the pulmonary venous pressure, which is the filling pressure for the left atrium. The same effect may be obtained by inflating a balloon at the end of the catheter to occlude the pulmonary artery branch. In this case, it is known as the pulmonary artery occlusion pressure (PAOP). Wedge and occlusion pressures are affected by breathing and mechanical ventilation in a similar way to CVP. They should also be measured at end expiration. The *a* wave occurs near the end of the *qrs* complex<sup>13</sup>. The pulmonary vascular resistance can be calculated from pulmonary arterial pressure, pulmonary arterial wedge pressure and cardiac output (Table 2.5), and gives similar information to the systemic vascular resistance, but referring to the pulmonary circulation.

Persistent fetal circulation has been reported in neonatal foals<sup>114</sup>, and may be associated with pulmonary hypertension<sup>115</sup>. Hypoxemia<sup>115</sup> and low dose endotoxin administration<sup>107</sup> may also result in pulmonary hypertension. In human infants, prenatal maternal administration of nonsteroidal antiinflammatory drugs is a particular risk factor for post-natal pulmonary hypertension<sup>116</sup>. Although administration of this class of drug to mares in late pregnancy with colic or laminitis is relatively common, the effects on the newborn foal are still unknown. Inhaled nitric oxide is a potent vasodilator in foals with experimentally induced pulmonary hypertension, and it is possible that this treatment would have clinical benefit<sup>117</sup>.

Pulmonary arterial occlusion pressure is an indicator of left atrial filling pressure and thus volume status. In cases of single chamber cardiac dysfunction, PAOP is superior to CVP for assessing fluid needs. However, this advantage may be theoretical in neonatal foals, as single chamber cardiac dysfunction is rare.

## **Patient monitoring**

The most important part of monitoring the cardiovascular system is repetition. Profound changes can occur very rapidly in the critically-ill foal, and the response to treatment may change with changes in underlying pathophysiological derangements. The response to treatment should always be measured and not assumed.

Close monitoring of all recumbent foals is warranted, as septic shock and other cardiovascular disturbances may develop following admission. This is illustrated by data from seven foals which presented to the Equine Medical Center in 1999 and required norepinephrine to reverse hypotension. In these foals, the mean time from admission until first use of inotropes (dobutamine or dopamine) was 10 hours 46 minutes and the range was 1 hour 50 minutes to 26 hours. The first use of inotropes marks the onset of severe, fluid-refractory hypotension. The mean time until norepinephrine administration was 29 hours 46 minutes<sup>113</sup>.

Most new developments in hemodynamic monitoring in human medicine have one of two objectives. The first is to reduce the invasiveness of monitoring, and includes such technology as bioimpedance monitoring. The second is to examine tissue perfusion and oxygenation rather than the equivalent whole body parameters, and includes such technology as gastric tonometry and jugular venous bulb saturation monitoring. The reliability and utility of these measurements is still debated in human medicine, and it may be some time before they can be clinically applied to foals.

## **Conclusion**

In order to successfully understand and treat hemodynamic disturbances, all available parameters should be examined rather than single measurements in isolation. In many cases heart rate, indirect blood pressure and urine production will give enough information to make rational treatment decisions. However, in more complex abnormalities or when the response to treatment is unexpected or unsatisfactory, more complete invasive hemodynamic monitoring may be warranted.

## **Chapter 3: Treating hemodynamic disturbances in critically ill neonatal foals.**

### **Introduction**

Assessment and treatment of hemodynamic disturbances are closely linked. The response to the previous treatment is the most reliable guide to further treatment, and is especially important if direct cardiovascular monitoring is limited. For this reason, all treatments should be closely monitored and should be adapted if the intended response is not achieved. Fortunately, the rapid response of the cardiovascular system to change and the short half-life of many of the drugs used in critical care allow rapid appraisal of each therapeutic intervention, permitting a step-wise approach to treatment to be adopted. One caveat to this approach is that the ultimate goal is adequate tissue oxygen delivery, not the correction of any measured hemodynamic variable. Therefore, assessments should include clinical and laboratory markers of tissue perfusion such as level of consciousness and blood lactate concentration, which make take hours rather than minutes for appreciable changes. In oliguric and anuric foals with little or no intrinsic renal dysfunction, restoration of urine output is often the first sign of improved tissue perfusion.

### **General Principles**

The goal of hemodynamic therapy is the restoration of tissue perfusion and oxygen delivery. Unfortunately, it is not possible to guarantee adequate tissue perfusion if blood pressure, urine output, cardiac output or oxygen delivery are restored to normal values. This may be for one of two reasons. Firstly, uneven tissue distribution of blood flow in disease may prevent adequate perfusion of some organs. Secondly, values found in normal healthy foals may be inappropriate targets for hemodynamic therapy because tissue oxygen demands are usually increased in disease<sup>118</sup>. Survivors of human septic shock have supranormal oxygen delivery, which is significantly higher than eventual non-survivors<sup>119</sup>. This observation led to a series of small clinical trials investigating whether increasing oxygen delivery to the values found in survivors improved mortality or morbidity. These small trials had conflicting results, with a few trials

showing decreased mortality with supranormal oxygen delivery<sup>119-121</sup>, some trials showing no difference<sup>122,123</sup>, and one trial suggesting increased mortality or morbidity<sup>124</sup>. A very large trial was then conducted, which found no difference in mortality between groups in which a normal or increased cardiac output was the goal of therapy<sup>125</sup>. The most likely reason for the failure of increasing oxygen delivery to improve outcome is that patients destined not to survive are unable to increase oxygen uptake in response to the increased delivery<sup>126</sup>, due to pathophysiological changes to intracellular and mitochondrial metabolism<sup>99</sup>.

This body of research in human septic patients ultimately does not provide much guidance for therapy of the individual foal. It seems clear that therapy should be tailored to the individual, and that strategies to change one or more measured hemodynamic parameters to set numerical values are unlikely to be optimum for all foals. Based on currently available evidence, mainly from the human adult literature<sup>82,118</sup> and clinical experience, the following guidelines are offered:

**Heart rate:** Therapeutic interventions that result in a reduction in heart rate towards or within the normal range (70-100bpm) are likely to be beneficial. However, specific therapies to reduce the heart rate (for example beta-adrenergic blockade or alpha-2 agonists) are highly likely to be detrimental and should be avoided without specific indication. We have observed tachycardia (heart rate of 120-130bpm) in survivors for up to 10 days after reversal of shock, and during time of otherwise marked clinical improvement. The reason for this is unclear.

**Blood pressure:** Mean arterial pressure should always be maintained over 60mmHg, and diastolic blood pressure should probably be maintained over 45mmHg. If vasopressors are required for therapy, they should be titrated to maintain blood pressure within the low end of the normal range (69-111mmHg<sup>75</sup>), because their effects on different organs may be uneven. Systemic hypertension appears to be rare in foals. In human adults, a diastolic blood pressure of greater than 110-120mmHg is considered a hypertensive crisis requiring immediate therapy<sup>127</sup>. We have not encountered blood pressures this high in neonatal foals, and therefore have no recommendations for when to initiate therapy.

**Urine output:** Hemodynamic interventions that result in an increase in urine output are likely to be beneficial. Specific therapies to increase urine output (for example loop diuretics) should only be considered if hemodynamic causes of decreased urine output can reasonably be ruled out. Furosemide decreases cardiac output and increases systemic vascular resistance in normal adult horses<sup>128</sup>, but decreases pulmonary arterial pressure and carotid artery pressure in exercising

adult horses<sup>129</sup>. The effects of this drug on the hemodynamics of critically ill foals are unknown, and therefore the cardiovascular system should be examined carefully prior to and following its use.

**Lactate:** Reducing lactate to its normal range (<2.5mmol/L in a recumbent foal) should be a major goal of treatment of the cardiovascular system. In critically-ill humans, failure to decrease the blood lactate concentration after twenty-four hours of treatment is associated with poor outcomes<sup>98</sup>. Lactate kinetics have not been investigated in critically ill foals.

**Central Venous Pressure:** The optimal central venous pressure in the foal is unknown. Central venous pressure should probably not be a major target of therapy because it is only weakly associated with stroke volume in foals (see Chapter 2).

**Cardiac Output and Stroke Volume:** Moderately increased cardiac output (up to 1.5 times the value for a normal foal) based on increased stroke volume rather than heart rate is probably beneficial. However, massive loading with crystalloid fluids to achieve this goal is inadvisable as it may predispose to generalized edema<sup>118</sup>.

**Systemic Vascular Resistance:** Therapy should not be titrated to mean arterial pressure, not systemic vascular resistance<sup>82</sup>. However, calculation of systemic vascular resistance can be very useful to guide choice between therapeutic options. Supranormal systemic vascular resistances should be avoided, because they are likely to be associated with reduced end-organ perfusion and the optimal systemic vascular resistance in individual critically-ill patients may be below the normal range<sup>118</sup>.

**Global Oxygen Delivery and Global Oxygen Uptake:** The general principle of titrating to oxygen transport is that oxygen delivery should be increased until there is no further increase in oxygen uptake<sup>118</sup>. This assumes that oxygen uptake is delivery dependent in disease, and will no longer increase with delivery once the metabolic requirements of the tissues are met. Although this appears to be an elegant way to titrate therapy, it is difficult in practice with intermittent monitoring, because of evolving pathophysiological derangements in the foal. Furthermore, some increases in oxygen uptake may be due to the therapeutic intervention. For example increasing cardiac work with inotropes can increase measured oxygen uptake.

**Pulmonary Pressures:** We have no clinical experience with serially monitoring pulmonary pressures in critically-ill neonatal foals and cannot give specific recommendations for therapy. In human adults, it is suggested not to exceed a pulmonary artery occlusion pressure of 20mmHg<sup>118</sup>.

## Therapy for hypotension

Early treatment of hypotension is desirable to avoid prolonged tissue hypoperfusion, hypoxic damage and reperfusion injury. Unfortunately, hypotension can occur rapidly without evidence of changes in clinical status (Table 3.1), and it is therefore necessary to serially monitor blood pressure in at risk foals. Foals at risk of developing hypotension include septic foals, foals following perinatal asphyxia and all those recumbent for non-orthopedic reasons.

Blood pressure is a function of cardiac output and vascular resistance. Initial therapy should be aimed at cardiac output until no further improvement is achieved or it is established that cardiac output is already above the normal range. Cardiac output is a function of heart rate and stroke volume.

Heart rate is rarely decreased except in hypothermic animals (see Chapter 2). If the heart rate is below 40bpm, rapid preparations for cardiopulmonary resuscitation should be made. The foal should be intubated, and ventilation assisted with a self-inflating resuscitation bag, connected to 100% oxygen, if available. If the heart rate fails to increase after 30 seconds of positive pressure ventilation, chest compressions should be initiated<sup>130</sup>.

Stroke volume may be decreased for one of four reasons. One is inadequate cardiac filling, which is usually due to inadequate circulating volume. A second possible reason is reduced myocardial function due to sepsis or other generalized disease which occurs in end-stage sepsis in humans<sup>131</sup>, but which we have not yet been able to document in foals. Two other reasons for decreased stroke volume are pericardial effusion, which we have seen in foals with generalized edema, and congenital cardiac anomalies, both of which can be detected with echocardiography. Echocardiography can also be used to subjectively assess chamber filling, which can help guide selection of therapy. However, the relationship of echocardiographic findings to stroke volume or circulating volume has not been investigated in the neonatal foal.

In adult animals with hypovolemia, cardiac output is usually maintained by increasing heart rate to compensate for decreased stroke volume. This is not always the case in compromised neonatal foals. Five of fifteen foals presenting to the Marion duPont Scott Equine Medical Center in 2000-1 with a mean arterial pressure of 60mmHg or less, had a heart rate in the normal range (70-100bpm). One foal had a heart rate of 30bpm. It is likely that the hypotension was due to decreased stroke volume in three of the five foals with a normal heart rate, as they responded to fluid therapy alone. Four of eight foals with tachycardia and hypotension also responded to

**Table 3.1: The onset of shock**

Parameter	Mean value in previous 3 hours (hour -6 to -4)	Mean value in 3 hours prior to first onset of hypotension (hour -1 to -3)	Mean values at the first onset of hypotension (MAP<69mmHg) (hour 0)	Range of change from hours -6 to -4 to hours -1 to -3
Heart rate (bpm)	89.9	96.5	101.7	0 to +10.66
Respiratory rate (bpm)	32.4	30.7	26.3	-8 to +4
Temperature (F)	99.7	100.6	101.2	-0.2 to +1.87
Urine output (ml)	495	575	629	-283 to +450
MAP (mmHg)	77.5	77.8 <sup>a</sup>	64.7 <sup>a</sup>	-14.7 to +10.7

MAP = mean arterial pressure

<sup>a</sup>p<0.05 (two tailed t-test). No other changes are statistically significant

Data from the 7 foals presenting to the Equine Medical Center in 1999-2001, which developed persistent hypotension at least 8 hours after admission (range 9-55 hours; mean 19.1 hours). The data examines the period in the six hours before the mean arterial pressure first decreased below 69mmHg, at the onset of hypotension.

fluid therapy without the need for further cardiovascular support. One foal with tachycardia was euthanised before the effectiveness of fluid therapy could be determined.

## **Fluid therapy**

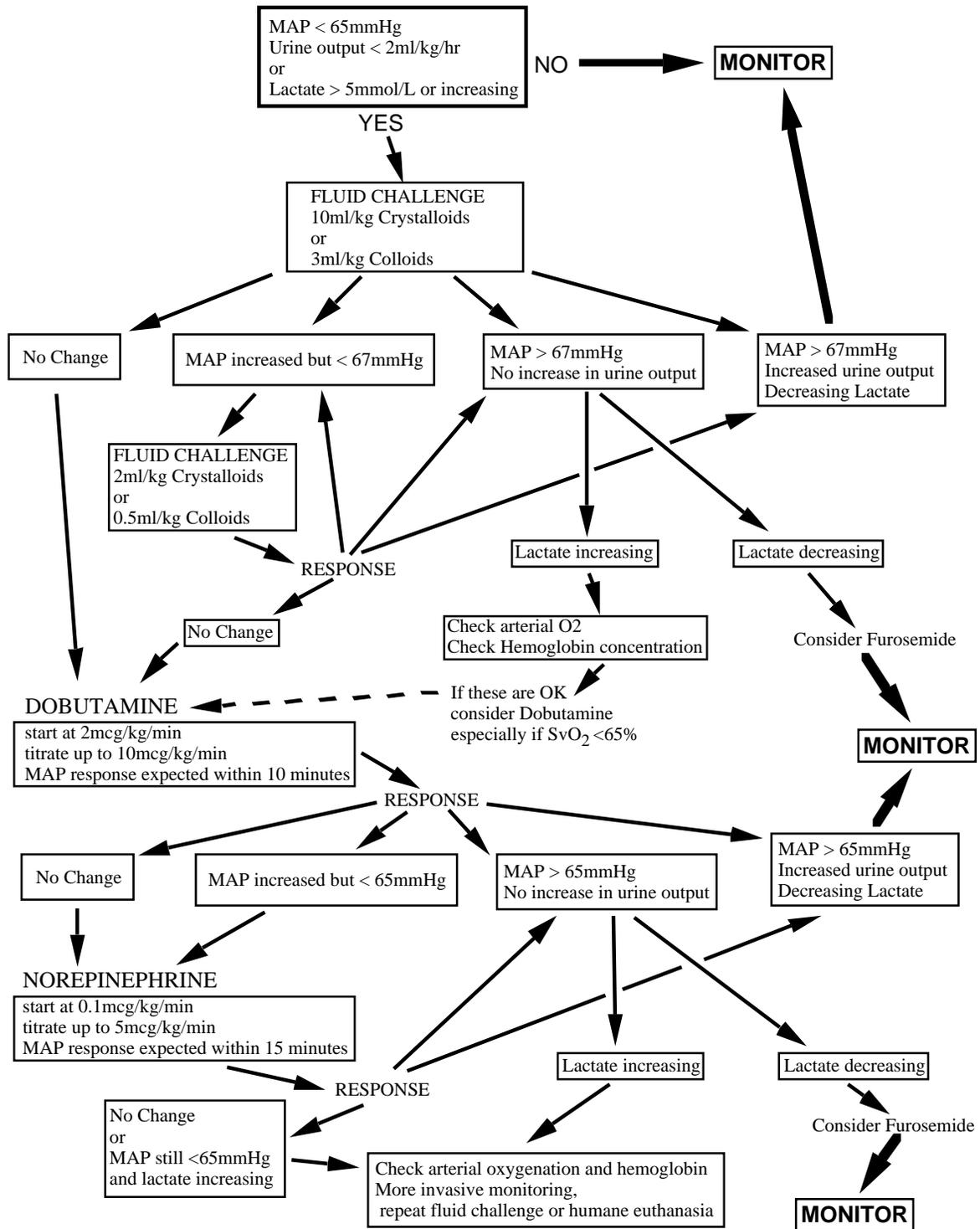
The initial approach to hypotension is to assess the adequacy of circulating volume. This is usually done by means of a fluid challenge (Figure 3.1). We typically give 10ml/kg of crystalloids over 10-15 minutes or 3ml/kg of hetastarch at 10ml/kg/hr and remeasure all cardiovascular parameters. If the blood pressure improves immediately after the fluid challenge, previous hypovolemia can be assumed. Although the time span will be too short to accurately measure the rate of urine production, increased flow in the urine collection system can also often be seen. If the foal responds to the fluid challenge, the need for additional fluids should be assessed. This can be done by further smaller fluid boluses (2ml/kg crystalloids or 0.5ml/kg hetastarch) until no further improvement is noted. However, in hypotensive foals at admission that have not been previously treated with fluids, we usually give 5% of bodyweight as polyionic crystalloid fluids at 40-60ml/kg/hr and then reassess the cardiovascular system. In foals with known renal insufficiency, fluid challenges should be done less aggressively (2-3ml/kg of crystalloids or 0.5ml/kg hetastarch) but still represent an effective way of carefully titrating fluid input to the animals needs.

In foals where it is possible to monitor cardiac output, and thus calculate stroke volume, this information can be used to guide fluid therapy. It has been our approach to try to maintain the stroke volume above the published normals<sup>34,118</sup> to ensure adequate cardiac output, especially if vasopressors are to be used. In foals with pulmonary edema, a more conservative approach is probably warranted and fluids should be delivered to maintain stroke volume within the normal range.

In foals that do not adequately respond to a fluid challenge, vasopressors or inotropes are indicated.

# Figure 3.1: Possible algorithm for treatment of hypotension in neonatal foals

Intended as a guide for when cardiac output monitoring is not available. Treatment should always be tailored to the individual case.



## **Inotropes**

Inotropes, such as dobutamine, increase cardiac output by increasing myocardial contraction and thus stroke volume. In hyperdynamic shock, where cardiac output is normal or increased, their value is uncertain. Dobutamine decreases systemic vascular resistance and mean arterial pressure in critically-ill human patients, which is thought to be due to beta-2 adrenergic vasodilation<sup>132,133</sup>. We have observed a similar phenomenon in an as yet limited number of critically-ill foals. This effect may make dobutamine a poor initial choice for hyperdynamic shock, as it is predicted to worsen the already decreased systemic vascular resistance. However, the beta-2 adrenergic stimulation may be beneficial to prevent over-constriction of arterioles when vasopressors such as norepinephrine are used. Limited evidence from human critical care suggests that gastrointestinal perfusion is better with the combination of low dose dobutamine (5mcg/kg/min) and norepinephrine than with norepinephrine alone<sup>134</sup>.

Dobutamine is indicated in foals with decreased stroke volume despite adequate fluid resuscitation. It is also probably indicated in foals where cardiac output cannot be measured, prior to initiating vasopressor therapy (Figure 3.1). Dobutamine increases cardiac work and thus oxygen consumption, which may be important when oxygen delivery is marginal. It may also cause tachycardia in under fluid resuscitated animals<sup>82</sup>.

## **Dopamine**

Dopamine is a catecholamine with alpha-adrenergic (pressor), beta-adrenergic (inotropic) and dopaminergic effects. In other species the dopaminergic effects predominate at low doses (1-5mcg/kg/min), the beta effects at moderate doses (5-10mcg/kg/min) and the alpha-effects at high doses (above 10mcg/kg/min)<sup>135</sup>. However, because the plasma concentration of dopamine with a given infusion rate is extremely variable between individuals<sup>136</sup>, the effects of dopamine may be extremely unpredictable. In a randomized, blinded trial of different doses of dopamine in normal conscious neonatal foals, we found the results were highly variable between foals.

Low dose dopamine does not increase creatinine clearance in normal adult horses<sup>137</sup>, and the utility of low dose (or 'renal dose') dopamine in prevention or treatment of renal failure is questionable<sup>135,138</sup>. High dose dopamine is not as effective as norepinephrine for restoring

hemodynamics in human hyperdynamic shock<sup>139</sup>. Based on a single case, this may also be true in foals. Norepinephrine successfully reversed hypotension in a foal which had failed to respond to high dose dopamine (24mcg/kg/min)<sup>113</sup>.

## **Norepinephrine**

Pressor agents, such as norepinephrine, are a logical choice for hyperdynamic shock as they act to increase vascular tone and thus systemic vascular resistance. Norepinephrine has only recently been widely accepted as a treatment for human sepsis. Previously norepinephrine had been reserved for use as a last resort in many hospitals, with predictably poor outcomes, due to concerns about the negative effects on renal perfusion in healthy subjects<sup>82</sup>. Recent evidence has shown increased renal blood flow in endotoxic dogs<sup>140</sup> and increased urine output in septic humans<sup>141</sup> following norepinephrine administration. A recent study compared norepinephrine and dopamine to dopamine alone in human sepsis and found considerably lower hospital mortality (62% vs. 82%) in the norepinephrine group<sup>142</sup>. We investigated norepinephrine in a series of critically ill neonatal foals that failed to respond to dobutamine and/or dopamine. We found an increase in mean arterial pressure in six of seven foals and an increase in urine output in all foals, coincident with the start of the norepinephrine infusion<sup>113</sup>. Inappropriately high doses of norepinephrine may increase cardiac afterload and decrease stroke volume and may reduce end-organ perfusion. Blood pressure, urine output and other cardiovascular parameters should be carefully monitored during norepinephrine infusion. The highest dose of norepinephrine we have used in a foal that ultimately survived is 1.5mcg/kg/min.

## **Treatment failure**

If a change in therapy does not produce an improvement in the cardiovascular system, it is important to critically evaluate the response to that treatment. This may involve increasing the intensity of hemodynamic monitoring.

Foal with severe peripheral edema and presumed capillary leak can represent a significant challenge, as it can be very difficult to maintain intravascular volume and tissue perfusion. In human medicine, fluid therapy is titrated to pulmonary artery occlusion pressure (15-20mmHg)

in these patients. As a last resort, we have had success with small boluses of hypertonic saline (1ml/kg) followed by colloids (plasma or hetastarch). However, although we were able to restore hemodynamics and resolve the peripheral edema, these patients have ultimately not survived due to other organ system failures.

In patients that do not respond to a logical sequence of fluid therapy, inotropes and pressors (Figure 3.1) and in which these treatments have been titrated within reasonable limits, the welfare and economic implications of continuing treatment should be seriously considered.

## **Conclusion**

Support of the cardiovascular system is a central tenet of critical care. An ordered, logical, aggressive approach is most likely to meet with success, both in terms of ultimate survival and in reduction of morbidity and therefore duration of intensive care.

## **Chapter 4: Paper accepted for publication in Equine Veterinary Journal**

This paper describes the methodology and results of the experiments undertaken for this thesis.

Contributions of the individual authors:

The project was conceived, carried out and written up by Kevin Corley. Dr. Lydia Donaldson participated in development of the experimental protocol, anesthetized the foals and provided technical assistance with the execution of the research and participated in writing after the first draft was complete. Dr. Martin Furr participated in development of the experimental protocol, provided technical assistance with the execution of the research and participated in writing after the first draft was complete.

# **Comparison of lithium dilution and thermodilution cardiac output measurements in anesthetized neonatal foals**

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**Keywords:** foal; cardiac output; anesthesia; lithium chloride; lithium dilution; thermodilution

## **Summary**

Knowledge of cardiac output is expected to help guide the treatment of hypotension associated with critical illness and/or anesthesia in neonatal foals. However, a practical and safe method of measuring cardiac output has not been described for the foal. Lithium dilution, a new method of cardiac output determination not requiring cardiac catheterization, has recently been reported in adult horses. We compared this method to thermodilution in isoflurane anesthetized, 30 to 42 hour old foals and found good agreement between the two methods in a range of cardiac outputs from 5.4 to 20.4 liters/min. The lithium dilution technique is a practical and reliable method of measuring cardiac output in anesthetized neonatal foals, and warrants investigation in critically ill conscious foals.

## **Introduction**

A practical, reliable method of measuring cardiac output is important for monitoring of both anesthetized foals and critically ill conscious foals. Anesthesia causes profound changes in the cardiovascular system, to which equine neonates may be physiologically unable to adapt<sup>143</sup>. Hypotension and abnormalities of cardiac output are important components of septicemia and hypoxic-ischemic encephalopathy<sup>69,144</sup>, the leading causes of death of neonatal foals<sup>70</sup>. In both

conscious and anesthetized hypotensive foals, selecting appropriate treatments can be challenging in the absence of complete hemodynamic information. Hypotension may be a function of low cardiac output or of increased cardiac output and decreased systemic vascular resistance. In the first instance, treatment would include fluids and/or inotropes and in the second, fluids and/or vasopressors. Adjustments in treatment are currently based on heart rate, blood pressure measurements, urine output and subjective clinical assessment. Data from studies of humans in shock suggests that clinicians cannot predict cardiac output and systemic vascular resistance from these variables<sup>81,112</sup> and that treatments aimed at improving cardiac index and oxygen delivery improve outcome<sup>81,112,121</sup>. Thermodilution has been used to measure the cardiac output of neonatal foals in a research setting<sup>34,107</sup>. However, to date, the measurement of cardiac output has not been reported in clinical cases, possibly because of the unsuitability of thermodilution for use in the equine neonatal intensive care unit.

A new method of measuring cardiac output has recently been described in adult horses<sup>44</sup>, humans and human neonates<sup>48,111</sup>. In this method, a small bolus of isotonic lithium chloride is administered intravenously and measured by drawing arterial blood past a dedicated sensor. Cardiac output is calculated from the time-concentration curve of lithium in the arterial blood. Cardiac catheterization, which may be associated with pathology in the adult horse<sup>35</sup> and has been reported to increase mortality in human patients<sup>37</sup>, is not necessary. The equipment required for the technique is relatively inexpensive and measurements are technically straightforward. The lithium dilution method may therefore be particularly suited to monitoring cardiac output in critically ill neonatal foals.

The aim of this study was to compare lithium dilution cardiac output determination to thermodilution.

## **Materials and Methods**

### **Animals**

Four male and two female crossbred foals (30 to 42 hours old; bodyweight  $53.5 \pm 8.5$ kg) were used in this study. Each foal was used once. All foals were delivered uneventfully at term. The foals were determined to be healthy by physical examination, complete blood count and

plasma biochemistry. All foals had plasma IgG concentrations greater than 800 mg/dl. The foals were leased and returned to their owners following the experiment. The protocol was approved by the Virginia Tech Animal Care Committee.

### **Instrumentation**

Foals were sedated with diazepam<sup>1</sup> (5mg i.v.). A nasotracheal tube was passed and foals were induced and maintained under anesthesia with isoflurane<sup>2</sup>. All foals were placed in left lateral recumbency on a heating pad set at 37°C. An intravascular sheath<sup>3</sup> was placed in the right jugular vein, and a triple-lumen, 7 French, balloon-tipped thermodilution catheter<sup>4</sup> was passed through the sheath and positioned in the pulmonary artery. Catheter position was confirmed by appropriate pressure waveform<sup>5</sup>. In all cases, the proximal port was in the right atrium. A 20ga catheter<sup>3</sup> was placed in the greater metatarsal artery using the Seldinger technique<sup>77</sup>. Appropriate sterile techniques were used for all procedures. The electrocardiogram and arterial blood pressure were monitored<sup>5</sup> continuously throughout the experiment. Following venous catheterization, infusions of 10ml/kg/hr lactated Ringers' solution and 2.5ml/kg/hr 2.5% dextrose / 0.45% sodium chloride were maintained throughout the experiment.

### **Cardiac output determination**

Thermodilution cardiac output was determined as described<sup>34,110</sup>, using a hand bolus injection of 8ml room temperature 5% dextrose solution<sup>1</sup> in the proximal port of the thermodilution catheter. The cardiac output was calculated for each measurement by means of a dedicated computer (Cardiomax II)<sup>4</sup>. The mean of the three closest measurements for each experimental period was taken as the cardiac output. The positioning of the thermodilution catheter was confirmed immediately before and after each measurement set.

Arterial hemoglobin and sodium concentrations are required for the lithium dilution technique and these parameters were determined prior to measurement (STAT Profile-M7<sup>6</sup>). Lithium dilution cardiac output measurements were determined according to the manufacturers instructions<sup>7</sup>, except as noted below. A 2 or 3ml bolus of 150mM lithium chloride<sup>7</sup> was placed in a specially designed extension set<sup>7</sup> (capacity 3ml), attached to the proximal port of the thermodilution catheter. The bolus was delivered by manually flushing the extension set with

8ml heparinized sodium chloride solution. Because of the very short time that it took for the lithium to arrive in the sensor following injection and to allow the twelve seconds of stable baseline required for accurate cardiac output calculation, the bolus was injected at least ten seconds after initiating the measurement.

Unusually shaped dilution curves were rejected by the dedicated software (8 out of a total of 96 measurements for lithium dilution) and in each case the measurement was immediately repeated. 2mls (0.3mmol) of lithium chloride solution was used for the majority of measurements. In some instances curve rejection was due to an insufficient increase in lithium concentration above baseline, preventing software calculation of cardiac output. In such cases, the measurement was immediately repeated with 3mls (0.45mmol) lithium chloride bolus. In all cases, this resulted in a curve that was appropriate for computer analysis. When very high cardiac outputs were anticipated (infusion of 15mcg/kg/min dobutamine), the initial measurement was performed with 3mls lithium chloride. The mean of the two cardiac outputs calculated by lithium dilution for each experimental period was used.

### **Experimental protocol**

At least 45 minutes elapsed between induction and the first measurement, allowing instrumentation of the foal and anaesthetic stabilization. The cardiac output was changed by sequential treatment with dobutamine (2-15 mcg/kg/min), phenylephrine (2 mcg/kg bolus, followed by a constant infusion of 1-3 mcg/kg/min) and nitroprusside (0.33-1 mcg/kg/min) and by increasing the depth of anaesthesia. Each infusion or anaesthetic plane was continued for at least 20 minutes, and measurements were made after 10 minutes to allow the cardiac output to stabilize. Not all drugs or all doses were used in all foals.

For each infusion or anaesthetic plane, thermodilution cardiac output was measured four times and lithium dilution cardiac output was determined twice. The lithium dilution measurements were performed immediately before and after the third thermodilution calculation and all measurements were performed in as rapid succession as possible. The heart rate was measured immediately prior to the first and third thermodilutions, as an indicator of cardiovascular stability.

## Statistical analysis

The paired cardiac outputs, as determined by the thermodilution and lithium dilution methods, were compared with linear regression analysis (Systat version 5.2.1<sup>8</sup>) and Bland Altman analysis<sup>145,146</sup>. To address concerns about the effect of lithium accumulation, the mean difference in cardiac outputs (thermodilution-lithium) for the first and last experimental periods for each foal were compared using the Wilcoxon Signed Rank Test. A *p* value of less than 0.05 was considered significant.

## Results

42 pairs of cardiac outputs were obtained in the six foals. Three pairs were discarded because the distal end of the thermodilution catheter was no longer in the pulmonary artery as determined by pressure waveform analysis immediately after the measurement set. This left 39 measurement pairs for further analysis. The number of valid pairs of measurements from individual foals ranged from four to ten. Indicator dilution curves with a normal attack, decay and shape were generated in all foals. The mean cumulative dose of lithium delivered was  $0.095 \pm 0.017$  mM/kg bodyweight and the highest dose was 0.119 mM/kg.

The drug infusions and anaesthetic plane variation resulted in a range of cardiac outputs from 5.4 to 20.4 liters/min. The mean bias (mean difference) between thermodilution and lithium dilution measurements of cardiac output was 0.0474 L/min, and the 95% confidence interval for the mean bias was -0.445 to 0.539. The limits of agreement were -3.03 and 3.12 (Figure 4.1). The 95% confidence interval for the upper limit of agreement was 2.27 to 3.97 and the confidence interval for the lower limit of agreement was -2.18 to -3.88. Linear regression analysis demonstrated a correlation coefficient (*r*<sup>2</sup>) of 0.985 (Figure 4.2). There was a significant difference between the first and last experimental period for each foal, with the lithium measurements underestimating thermodilution in the first period (mean difference  $0.84 \pm 0.95$  L/min) and overestimating thermodilution in the last (mean difference  $-0.45 \pm 1.5$ ) (*p*=0.046). There was also a tendency for the lithium dilution technique to overestimate thermodilution at cardiac outputs less than 10 L/min (mean bias  $-0.72 \pm 1.5$  L/min) and to underestimate thermodilution at cardiac outputs of 13 L/min or greater (mean bias

0.66±1.3L/min). The mean difference between the heart rates taken before the first and third thermodilutions was -0.15bpm, the range was 0 to 10bpm and the standard deviation was 4.79.

Foals recovered routinely from anesthesia, and no clinical effects of the lithium administration were discernable.

## Discussion

This experiment showed a good correlation between thermodilution and lithium dilution determinations of cardiac output, a negligible mean bias and small limits of agreement over a wide range of cardiac outputs. Therefore, the lithium dilution is as an acceptable alternative to thermodilution for measuring cardiac output in neonatal foals.

These results are in agreement with the recently published study in adult anesthetized horses, which found a correlation coefficient of 0.94, and a mean bias of -0.86L/min<sup>44</sup>. In that study, the carotid artery was the source of the arterial blood as all experimental subjects had previously undergone a carotid loop transposition<sup>44</sup>. We were interested in the direct clinical application of this method to neonatal foals and thus catheterized the dorsal metatarsal artery in our subjects. This artery is in the preferred site in the awake and recumbent foal<sup>76</sup>.

A possible source of error for indicator dilution methods, such as lithium dilution and thermodilution, is the presence of intra-cardiac shunts. Shunts lead to over-estimation of cardiac output, since the indicator solution is either diverted through the shunt or diluted by blood passing through the shunt, resulting in decreased time-concentration integral of signal arriving at the post-ventricular sensor<sup>147</sup>. This is a particular concern in neonatal foals because flow through the ductus arteriosus has been reported to continue in the first few days of life<sup>148</sup>, and it has been postulated that there may also be bidirectional shunting through the foramen ovale<sup>76</sup>, as demonstrated in lambs<sup>149</sup>.

Although intra-cardiac shunts will affect the calculation of cardiac output, they should be detectable by examination of the indicator dilution curve. For techniques such as conventional thermodilution, where indicator detection is in the pulmonary artery, left to right shunts and right to left shunts both result in early recirculation, and either an extra peak following the main peak or prolongation of the decay phase<sup>147,150</sup>. For techniques with indicator detection in the systemic circulation, such as lithium dilution, left to right shunts result in early recirculation and right to

left shunts additionally cause a slurring of the initial attack of the main curve<sup>48</sup>. In a human neonate with a right to left shunt, the slurring of the attack phase and early recirculation were readily detectable with lithium dilution<sup>48</sup>.

The attack and decay phase of the indicator dilution curves were normal for each foal, and therefore no evidence of shunting was seen, although this does not completely rule out very small shunts. It is possible that the ductus arteriosus had closed in all of these healthy, term foals. This would be in agreement with an angiographic study of four foals, which found ductus arteriosus closure in all foals at twenty-four hours of age<sup>151</sup>. However, the possibility of shunts should be considered if the technique is used on younger, premature or sick foals in which the ductus arteriosus or foramen ovale may still be patent.

A further potential source of error for the lithium dilution technique is accumulation of lithium with repeated determinations of cardiac output. Doubling the serum lithium concentration from 0.2mmol/L to 0.4mmol/L has been reported to decrease the agreement between lithium dilution and thermodilution in dogs<sup>47</sup>. We found that lithium dilution tended to slightly underestimate thermodilution at the beginning of the experiment and slightly overestimate it at the end. This would be the expected if increased background lithium concentration led to a smaller detected increase in lithium signal and thus higher calculated cardiac outputs. At high plasma lithium concentrations, there tends to be positive drift of the baseline lithium concentration detected by the sensor. The software is programmed to warn the user of positive baseline drift when this occurs during a measurement, which did not occur during this study. However, we did not measure serum lithium concentrations in this study, and it was not possible to separate possible effects of lower cardiac output and lithium accumulation, since they both occurred at the end of the experiment. The mean cumulative lithium dose ( $0.095 \pm 0.017$ ) used in this experiment was closer to the dose ( $0.08 \pm 0.03$ mmol/kg) required to achieve a lithium serum concentration of 0.2mmol/L than the dose ( $0.17 \pm 0.03$ mmol/kg) required for a lithium concentration of 0.4mmol/L in the canine study<sup>47</sup>.

Potential hazards to the patient associated with the lithium chloride technique are those of arterial catheterization, and possible toxicological effects of the lithium chloride. The arteries that had been catheterized were examined twelve to twenty-four hours after the experiment and daily for seven to ten days. No adverse effects of arterial catheterization were found. The clinical status and electrocardiogram were monitored throughout anesthesia and no effects of lithium

administration were noted. There were no apparent clinical effects attributable to the lithium chloride following recovery. A slightly larger dose of lithium chloride (mean 0.127mmol/kg) has been given over one hour to conscious adult horses in a toxicity study. No effects on mentation, behavior, electrocardiogram, hematological or biochemical parameters was noted, with the exception of increased urination 12 hours post injection in two of six horses<sup>46</sup>.

The blood loss associated with withdrawal of arterial blood for lithium dilution is minimal, but should be considered if a large number of determinations are performed on the same subject. The peristaltic pump, which withdraws blood at 4ml/min, was operated for no longer than 2 minutes for any measurement. There was no net volume loss in this experiment, since a combined total of 10 to 11ml of lithium chloride and heparinized saline were injected for each measurement. However, the erythrocytes withdrawn were lost to the foal. In a 50kg foal, ten measurements would involve a blood loss of less than 2% of total blood volume.

Current methods of measuring cardiac output include thermodilution, dye dilution, trans-thoracic impedance and trans-esophageal ultrasonography. Thermodilution has been described in experimental foals<sup>34</sup> and remains the standard in human critical care, but there are many complications associated with pulmonary artery catheters. Schliff *et al*<sup>35</sup> examined the hearts of nine adult horses catheterized with a pulmonary artery catheter during a five to six hour period. All had multiple endothelial lesions and one horse had a solitary thrombus on the pulmonary valve. Many other complications of pulmonary artery catheters are recorded in human medicine, including cardiac dysrhythmias in 90/116 catheterizations<sup>36</sup> and a recent observational study of human critically ill patients showed pulmonary artery catheterization might increase mortality<sup>37</sup>. None of the six foals in this study had any clinical signs associated with the pulmonary catheter. The heart of one of these foals, which succumbed to Tyzzer's disease at five weeks of age, was normal at *post mortem* examination. Pulmonary artery catheters can also be difficult to place. Trans-esophageal Doppler echocardiography and trans-thoracic impedance are potentially practical methods for measuring cardiac output in foals<sup>76</sup>, but have not been validated in these animals. Furthermore, both techniques require expensive equipment, considerable technical expertise<sup>54</sup> and do not avoid the need for arterial and central venous catheterization if hemodynamic variables such as systemic vascular resistance are to be calculated.

The lithium dilution technique is a practical and reliable method of measuring cardiac output in anesthetized neonatal foals, and warrants investigation in critically ill conscious foals.

### **Manufacturers' addresses**

<sup>1</sup>Abbott Laboratories, North Chicago, IL

<sup>2</sup>Halocarbon Laboratories, River Edge, NJ

<sup>3</sup>Arrow International Inc., Reading, Pennsylvania, USA

<sup>4</sup>Columbus Instruments, Ohio, USA

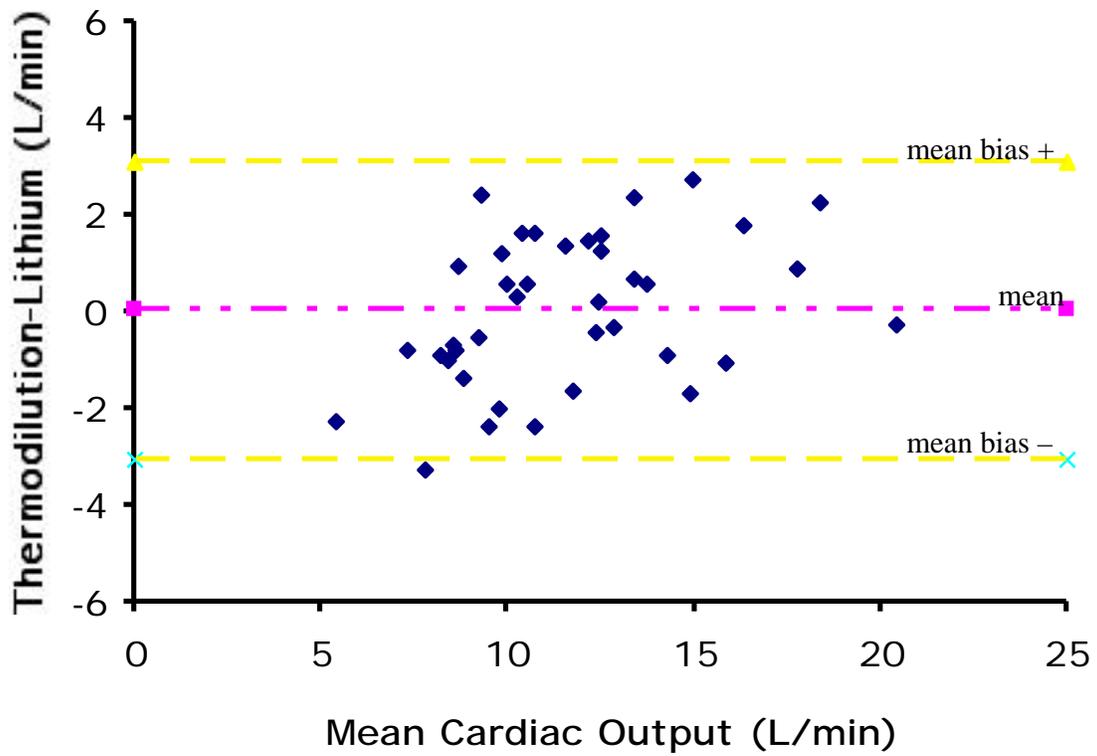
<sup>5</sup>ProPaq Encore 206EL, Protocol Systems Inc., Beaverton, Oregon, USA

<sup>6</sup>NovaBiomedical, Waltham, Massachusetts, USA

<sup>7</sup>LiDCO Ltd., London, UK

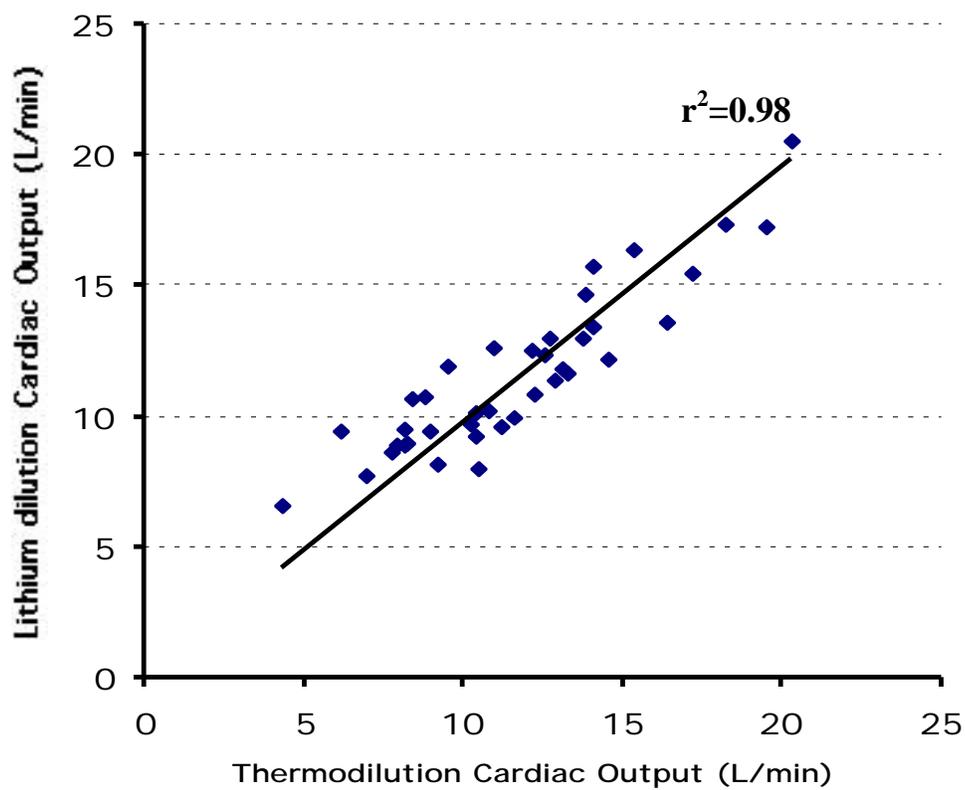
<sup>8</sup>SPSS Science, Chicago, Illinois, USA

**Figure 4.1: Bland-Altman analysis of thermodilution and lithium dilution cardiac output measurements in neonatal foals**



SD = standard deviation

**Figure 4.2: X-Y plot of thermodilution and lithium dilution cardiac output measurements in neonatal foals**



## Chapter 5: Conclusion

The results demonstrated good agreement between lithium dilution and thermodilution measurements of cardiac output in normal, anesthetized neonatal foals. In contrast to the previous study in adult horses, we catheterized an artery readily accessible in clinical patients (the dorsal metatarsal artery) allowing direct clinical application of the results.

Lithium dilution appears to represent an accurate, practical method for monitoring cardiac output in neonatal foals. We have followed this research by investigating the hemodynamic status of critically-ill foals presenting to the clinic<sup>45</sup>. It is hoped that by gaining better insight into the hemodynamic perturbations of these patients, we will be able to better support their cardiovascular system. This may, eventually, lead to better outcomes for some neonatal foals undergoing intensive care.

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## **Vita**

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