Influence of the Respiratory Cycle on Caudal Vena Cava Diameter Measured by Sonography in Healthy Foals: A Pilot Study

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Hypovolemia, which is a major cause of morbidity and mortality in sick foals, can occur rapidly as a result of several underlying disease processes.\(^1,2\) Fluid administration is crucial in the treatment plan of many hospitalized foals. However, because of the immaturity of the kidneys, fluid overload can be more of a problem than hypovolemia in foals receiving fluid therapy.\(^2,3\) The methods that are currently used to assess fluid status in foals recently have come under review, as well as the theories related to fluid administration.\(^3\) Currently, there is no clinical indicator or monitoring modality that can accurately determine the presence of hypovolemia, hypervolemia or return to euvolemia in foals.\(^3\)

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In human medicine, a similar problem exists in determining intravascular volume status in critical patients.\(^4–15\) Recent studies have identified numerous deficiencies with the current methods used to estimate fluid status, including heart rate, blood pressure, physical examination findings, and laboratory findings.\(^3,12,14,15\) A rapid and noninvasive method recently investigated to assess fluid status in humans involves the use of sonography to measure the change in diameter of the caudal vena cava (CVC) with inspiration and expiration.\(^4–14,16,17\)

The CVC changes diameter during the respiratory cycle.\(^4–21\) With inspiration, the CVC diameter in the cranial abdomen decreases and with expiration it increases. Although a number of variables can affect the...
degree of change in CVC diameter during respiration, there is a strong correlation in people between the degree of change in diameter of the CVC and the fluid status of the patient. Hypovolemic patients have a larger change in CVC diameter during the respiratory cycle, whereas hypervolemic patients have very little or no change in the CVC diameter.

In humans, instead of analyzing CVC diameter alone, the CVC collapsibility index (CVC-CI) is used to estimate intravascular volume status. The difference between the maximal CVC (CVCmax) and minimal CVC (CVCmin), divided by CVCmax, and multiplied by 100%, provides the collapsibility index. The CVC-CI in people is negatively correlated with central venous pressure (CVP) and patient volume status.4–11,13,16,17,21 The normal CVC-CI is between 20% and 50% in adult humans.4,5,8 The American Society of Echocardiography and the European Association of Cardiovascular Imaging recommends that CVC and CVC-CI be used together to determine right atrial (RA) pressure.13,16

Studies investigating the CVC and the CVC-CI in equine neonates are lacking. The objective of our study was to assess whether the CVC could be identified where it crosses the diaphragm in healthy foals. The hypotheses were that the CVC could be sonographically identified in healthy foals <1 month of age, and that a statistical difference exists between CVCmax and CVCmin diameters, allowing the CVC-CI to be calculated.

Material and Methods

Ours was a prospective, observational study. Informed client consent, as well as Animal Care and Use Committee approval from the University of Calgary, was obtained.

Animals were privately owned foals, <1 month of age, and assessed as healthy based on a general physical examination. The general physical examination included temperature, pulse and respiration (TPR), mucous membrane color and capillary refill time, <2 second skin tent, absence of ocular and nasal discharge, examination of joints and umbilicus, and appropriate mental status. Weight was determined with a JorVet Walk-on platform scale (J825QM).6 Height at the withers was recorded with a combination of levels and a measuring tape. Recruitment occurred through veterinary clinics and by word of mouth. Foals were excluded from the study if they did not fit the age criteria, if temperament precluded sonographic examination, if the procedure caused undue stress, or if there were inadequate facilities to perform the study. Data were collected between April 14 and June 27, 2016.

The sonographic machine used was a Mindray M7, with a 3.5–5 MHz convex probe.6 The depth setting used was 12–20 cm, with the focus position typically set at the level of the CVC or as deep as the limitations of the ultrasound machine would allow. Alcohol was used to provide conduction of the signal. Scanning at least 5 dogs before applying the skill to foals was noticed localizing the CVC at the level of the diaphragm on dogs, and realized the technique of locating and measuring the CVC. Both observers practiced locating the CVC at the level of the diaphragm on dogs, scanning at least 5 dogs before applying the skill to foals.

The Bland-Altman method was used to compare inter-rater variability and an R package “MethComp” was used for analysis.22 A linear mixed effects model was used to detect any difference between CVCmax and CVCmin by the “nlme” package.23

Two sonographic examinations were performed per observer, giving 2 or 4 complete data sets per foal. The duplicate examination occurred after removal of the probe from the foal and saving of the cineloops (approximately 1 minute). Foals were examined by 1 or both observers as availability of the 2 observers performing scans and cooperation of the foals allowed. Whenever possible, examinations were performed by both observers. Foals remained standing and restrained, whereas the person performing the sonographic examination was switched when both observers performed the examination (approximately 2 minutes). The CVC measurements were taken retrospectively on recorded M-Mode cineloops at the largest diameter during expiration and smallest diameter on inspiration. The CVCmax and CVCmin were recorded within the same respiratory cycle. The CVC-CI was calculated by the following equation: ([CVCmax − CVCmin]/CVCmax) × 100%.

Observer 1 had 12 years of experience with clinical sonography. Observer 2 was a novice sonographer who had completed three 3-hr sonographic laboratory sessions. Both observers were trained for 4 hours by an experienced sonographer familiar with the technique of locating and measuring the CVC. Both observers practiced localizing the CVC at the level of the diaphragm on dogs, scanning at least 5 dogs before applying the skill to foals.

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Fig 1. Schematic of the right side of a foal, with approximate location of ribs and sonographic probe shown for the subxiphoid window.
For both models, the assumptions of normality and equal variances required for the model were checked and met. A \( P \) value \( \leq 0.05 \) was considered statistically significant. Intraclass correlation coefficient (ICC) also was used to express Intra- and inter-rater variability by SPSS© software.\(^2\) For inter-rater variability, the mean of the 2 measurements for each observer was used. All other statistical analyses (D’Agostino & Pearson omnibus normality test and column statistics) were performed by Prism software.\(^7\)

**Results**

Sixty foals were enrolled in the study. The CVC was identified in 58 of 60 foals. One foal was excluded because of excessive gas in the colon, the second was excluded because of synchronous diaphragmatic flutter (singultus), which precluded accurate measurements of the CVC in M-Mode. Breeds included 35 Quarter Horses, 12 Warmbloods, 10 Standardbred, 2 Draft crosses, and 1 Haflinger cross. Age varied from 1 day to 30 days, with a mean of 15 \( \pm \) 7.9 days. Foal data are presented in Table 1. Seventeen foals had sonographic examinations performed only by the first observer, 16 by the second observer, and 25 foals were examined by both observers.

The CVC\(_{\text{min}}\) and CVC-CI data passed the D’Agostino & Pearson omnibus normality test, but the CVC\(_{\text{max}}\) did not. Among all measurements, CVC\(_{\text{max}}\) median was 1.99 cm and interquartile range (IQR) was 1.71–2.3 cm, CVC\(_{\text{min}}\) mean was 1.49 \( \pm \) 0.38 cm (median, 1.51 cm; IQR, 1.22–1.72 cm), and the CVC-CI mean was 26 \( \pm \) 10% (median, 26%; IQR, 19–32%). Table 2 shows the results from the linear mixed effects model. The intercept was statistically significant which indicates that there was a statistically significant difference between CVC\(_{\text{max}}\) and CVC\(_{\text{min}}\), after adjusting for rater effect \( (P < 0.001) \). The mean difference between CVC\(_{\text{max}}\)

### Table 1. Foal mean parameters.

| Foal Parameters | Mean  | Standard Deviation |
|-----------------|-------|--------------------|
| Weight (kg)     | 75.7  | \( \pm \) 17.5     |
| Height (cm)     | 102.2 | \( \pm \) 6.4      |
| Temperature (°C)| 38.6  | \( \pm \) 0.4      |
| Pulse (bpm)     | 113.1 | \( \pm \) 22.9     |
| Respiration (brpm) | 46.9  | \( \pm \) 21.9     |

Including the weight in kilograms (kg), the height at the withers in centimeters (cm), the rectal temperature in degrees Celsius (°C), the pulse in beats per minute (bpm) and the respiratory rate in breaths per minute (brpm).

### Table 2. Linear mixed effects model of the difference between the maximum and minimum caudal vena cava measurements obtained in healthy foals.

| Parameter                  | Estimates | Std. Error | \( P \)-value |
|----------------------------|-----------|------------|---------------|
| Fixed effects              |           |            |               |
| (Intercept)                | 0.515     | 0.032      | <0.001        |
| Factor (observer 2)        | 0.025     | 0.023      | 0.269         |
| Factor (observer 1)        | 1         | –          | –             |
| Random effects             |           |            |               |
| Animal                     | 0.211     | –          | –             |
| Rater nested within animal | 0.028     | –          | –             |

The parameter estimates of the fixed effects from a linear mixed effect model, using animals, and rater nested within animals as random effects.
and CVC_{min} was 0.515 cm, with a standard error of the mean (SEM) of 0.031 cm.

Bland-Altman plots for inter-rater agreement are shown in Figure 3. Inter-rater agreement of the CVC-CI differed by an average of 0.9% (95% limits of agreement, −12.5 to +10.7%). The ICC for intrarater variability of CVC_{max} was 0.540 (95% confidence interval [CI], 0.286–0.724) and 0.545 (95% CI, 0.288–0.728), of CVC_{min} was 0.550 (95% CI, 0.299–0.730) and 0.594 (95% CI, 0.354–0.761), and of CVC-CI was 0.894 (95% CI, 0.812–0.942) and 0.853 (95% CI, 0.741–0.919) for observers 1 and 2, respectively. The ICC for inter-rater variability of CVC_{max} was 0.712 (95% CI, 0.448–0.862), CVC_{min} was 0.686 (95% CI, 0.406–0.848), and CVC-CI was 0.884 (95% CI, 0.755–0.947).

Discussion

We demonstrated that it is possible to identify and measure the diameter of the CVC at the subxiphoid site in standing healthy foals <1 month of age. The CVC_{max} and CVC_{min} showed a significant difference in size during the respiratory cycle (mean difference, 0.52 cm) making it possible to calculate the CVC-CI. Human medical literature suggests the CVC-CI is a good indicator of intravascular volume status because it is less affected by hypovolemic compensatory mechanisms than are other clinical parameters (e.g., blood pressure, capillary refill time) used to indirectly assess volume status. Experienced practitioners have identified the challenge of assessing intravascular volume status in foals. Our study determined that it is possible to calculate the CVC-CI in healthy foals <1 month of age, which is the first step in determining if this technique may be useful in assessing intravascular volume status in foals. Further studies would be required to establish the clinical validity of the CVC-CI in sick foals, including whether there is a correlation with right atrial pressures and other methodologies used to assess intravascular volume status.

The statistical difference of CVC_{max} and CVC_{min} in the current study is similar to what has been reported in human medicine; the CVC diameter is larger during expiration than inspiration. This occurs for several reasons including a change in pressures within the thorax during the respiratory cycle, the compliance of the CVC, and the motion of the diaphragm. Respiratory changes result in a change in positive and negative pressures within the thorax. These pressure changes influence the vascular volume within the thorax and abdomen. Negative pressure draws blood into the thoracic CVC from the abdominal CVC, causing the CVC to decrease in size within the abdomen whereas the positive pressure of expiration pushes blood from the thoracic CVC into the abdominal CVC. Currently, most studies of CVC-CI have been performed in humans and it is unknown how species variation impacts pressure changes within the thorax and abdomen and CVC diameter during the respiratory cycle. Veins are compliant and not subject to the same compensatory vasoconstriction as arteries are, allowing intravascular volume

Fig 3. (A,B,C) Bland-Altman plots for the caudal vena cava (CVC) maximum, CVC minimum diameter, and the caudal vena cave collapsibility index (CVC-CI) inter-rater variability (n = 25). The lines connecting the dots indicate the first and second examination performed by each observer for an individual foal. The bold horizontal line is the mean difference between observers 1 and 2. The finer horizontal lines represent the 95% limit of agreements for mean difference.
The Bland-Altman inter-rater agreements did not show a statistical difference, indicating good repeatability for the measurements assessed. The CVC-CI 95% limits of agreement for inter-rater variability showed variation of up to 23%, whereas for intrarater variability, the variation was considerably less (15%). These findings are similar to those of a study reported previously that also failed to find a statistical difference in CVC-CI for neonates and adults.14

Further research is needed to establish validated CVC-CI measurements for healthy and unhealthy foals of different ages. Our study had several limitations that should be considered. All M-Mode cineloops were evaluated by 1 nonblinded observer, which may have caused bias in the CVC-CI measurements obtained. Also, we evaluated health status between CVC-CI values in sick foals might produce. Foals in our study were assessed in the standing position. The position of the patient is known to influence CVC diameter in people, with left lateral recumbency creating the smallest diameter, right lateral recumbency the largest, and standing the window. Although this window is most commonly described in human medicine, it is possible that there are other windows that would allow better measurement of CVC diameter in foals. Small sample size may have detected differences that would falsely increase the size of the CVC. Good inter-rater variability measured by ICC for CVC-CI was present in both observers. This finding suggests that the skill to find the CVC in foals is not difficult because of the stress of separation from the mare or handling may have occurred in the time it took observers to measure and record the CVC.19,28 Finally, the angle of M-Mode relative to the CVC may have varied between observers, which would falsely increase the size of the CVC. Good inter-rater agreement on all measurements suggests that the skill to find the CVC in foals is not difficult because of the stress of separation from the mare or handling may have occurred in the time it took observers to measure and record the CVC.19,28
synchronous diaphragmatic flutter, so although we could identify the CVC, we were unable to attain a cine loop with complete respiratory cycles.

Conclusions

The CVC can be measured in healthy standing foals and a significant difference was seen between CVC_max and CVC_min. This finding allowed us to calculate the CVC-CI, which may have clinical relevance in assessment of volume status. The lack of significance of inter-rater variability between 2 observers suggests that the CVC-CI can be easily and consistently calculated during sono graphic measurement by both novice and more experienced sonographers. Finally, it is a noninvasive and rapid procedure that healthy foals tolerate well and has the potential to provide a technique to assess the intravascular volume status of foals by calculation of the CVC-CI. Further research into validation of reference values for normal and abnormal CVC-CI values is required before this concept can be applied in clinical settings.

Footnotes

1. Hollis AR, Boston RC, Corley KT. Plasma aldosterone, vasopressin and atrial natriuretic peptide in hypovolaemia: A preliminary comparative study of neonatal and mature horses. Equine Vet J 2008;40:64-69.
2. Palmer JE. Fluid therapy in the neonate: Not your mother’s fluid space. Vet Clin North Am Equine Pract 2004;20:63–75.
3. Palmer J. Update on the management of neonatal sepsis in horses. Vet Clin North Am Equine Pract 2014;30:317–336, vii.
4. Stawicki SP, Braslow BM, Panebianco NL, et al. Intensivist use of hand-carried ultrasonography to measure IVC collapsibility in estimating intravascular volume status: Correlations with CVP. J Am Coll Surg 2009;209:55–61.
5. Stawicki SP, Adkins EJ, Eiferman DS, et al. Prospective evaluation of intravascular volume status in critically ill patients: Does inferior vena cava collapsibility correlate with central venous pressure? J Trauma Acute Care Surg 2014;76:956–963; discussion 63–4.
6. Zhang Z, Xu X, Ye S, et al. Ultrasonographic measurement of the respiratory variation in the inferior vena cava diameter is predictive of fluid responsiveness in critically ill patients: Systematic review and meta-analysis. Ultrasound Med Biol 2014;40: 845-853.
7. Ferrada P, Murthi S, Anand RJ, et al. Transthoracic focused rapid echocardiographic examination: Real-time evaluation of fluid status in critically ill trauma patients. J Trauma 2011;70:56–62; discussion -4.
8. Nagdev AD, Merchant RC, Tirado-Gonzalez A, et al. Emergency department bedside ultrasonographic measurement of the caval index for noninvasive determination of low central venous pressure. Ann Emerg Med 2010;55:290–295.
9. Natori H, Tamaki S, Kira S. Ultrasonographic evaluation of ventilatory effect on inferior vena cava configuration. Am Rev Respir Dis 1979;120:421–427.
10. Ciozza W, Kedan I, Kehi DW, et al. The efficacy of sonographic measurement of inferior vena cava diameter as an estimate of central venous pressure. Cardiovasc Ultrasound 2016;14:33.
11. Kieliszczyk J, Baranowski W, Kosiak W. Usefulness of ultrasonography in the evaluation of a neonate’s body fluid status. J Ultrason 2016;16:125–134.
12. Aydin SA, Ozdemir F, Taskin G, et al. Is there a relationship between the diameter of the inferior vena cava and hemodynamic parameters in critically ill patients? Niger J Clin Pract 2015;18:810–813.
13. Karacadag B, Januszkiewicz E, Szmygel L, et al. Inferior vena cava/aorta diameter index in the assessment of the body fluid status - a comparative study of measurements performed by experienced and inexperienced examiners in a group of young adults. J Ultrason 2014;14:273–279.
14. Durajski K, Januszkiewicz E, Szmygel L, et al. Inferior vena cava diameter index in the assessment of the body fluid status - a comparative study of measurements performed by experienced and inexperienced examiners in a group of adult patients. J Ultrason 2016;16:125–134.
15. Wesson HK, Khan S, Ferrada P. Ultrasound as a tool for fluid status assessment in the trauma and critically ill patient. Int J Surg 2016;33:190–195.
16. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–270.
17. Stawicki SP, Papadimos TJ, Bahner DP, et al. Correlations between pulmonary artery pressures and inferior vena cava collapsibility in critically ill surgical patients: An exploratory study. Int J Crit Illn Inj Sci 2016;6:194–199.
18. Nordenström B, Norhagen A. Effect of respiration on venous return to the heart. Am J Roentgenol Radium Ther Nuel Med 1965;95:655–661.
19. Gignon L, Roger C, Bastide S, et al. Influence of diaphragmatic motion on inferior vena cava diameter respiratory variations in healthy volunteers. Anesthesiology 2016;124:1338–1346.
20. De Vecchis R, Balci C. Inferior vena cava and hemodynamic congestion. Res Cardiovasc Med 2015;4:e28913.
21. Moreno FL, Hagan AD, Holmen JR, et al. Evaluation of size and dynamics of the inferior vena cava as an index of right-sided cardiac function. Am J Cardiol 1984;53:579–585.
22. Carstensen B, Gurrin L, Ekstrom C, et al. MethComp: functions for analysis of agreement in method comparison studies.
R package version 1.22.2. 2015 https://CRAN.R-project.org/package=MethComp.

23. Pinheiro J, Bates D, DebRoy S, et al. nlme: linear and non-linear mixed effects models. R package version 3.1-129. 2017 https://CRAN.R-project.org/package=nlme.

24. Landers RN. Computing intraclass correlations (ICC) as estimates of intrarater reliability in SPSS. Winnower 2015;2:81744.

25. Shih AC, Queiroz P, Vigani A, et al. Comparison of cardiac output determined by an ultrasound velocity dilution cardiac output method and by the lithium dilution cardiac output method in juvenile horses with experimentally induced hypovolemia. Am J Vet Res 2014;75:565–571.

26. Thomas WP, Madigan JE, Backus KQ, et al. Systemic and pulmonary haemodynamics in normal neonatal foals. J Reprod Fertil Suppl 1987;35:623–628.

27. Magdesian KG. Monitoring the critically ill equine patient. Vet Clin North Am Equine Pract 2004;20:11–39.

28. Kimura BJ, Dalugdugan R, Gilcrease GW, et al. The effect of breathing manner on inferior vena cava diameter. Eur J Echocardiogr 2011;12:120–123.

29. Bowra J, Uwagboe V, Goudie A, et al. Interrater agreement between expert and novice in measuring inferior vena cava diameter and collapsibility index. Emergency Med Australas 2015;27:295–299.

30. Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instrument in psychology. Psychol Assess 1994;6:284–290.

31. Gui J, Guo J, Nong F, et al. Impact of individual characteristics on sonographic IVC diameter and the IVC diameter/aorta diameter index. Am J Emerg Med 2015;33:1602–1605.

32. O’Brien F, Walker IA. Fluid homeostasis in the neonate. Paediatr Anaesth 2014;24:49–59.

33. Fielding CL, Magdesian G, Edman JE. Determination of body water compartments in neonatal foals by use of indicator dilution techniques and multifrequency bioelectrical impedance analysis. Am J Vet Res 2011;72:1390–1396.