

Chapter 5

Determination of Cardiac Output Across a Range of Values in Anesthetized Horses by M-Mode Echocardiography and Thermodilution

Abstract

Objectives – To determine the relationship between CO determinations made by M-mode echocardiography (CO_{echo}) and thermodilution (CO_{TD}) in anesthetized horses, and to discover whether such a relationship could be used to reliably predict CO_{TD} from CO_{echo} .

Animals – Five horses with no evidence of cardiovascular or other systemic disease.

Methods – Determinations of cardiac output by M-mode echocardiography were compared with simultaneous determinations by thermodilution in anesthetized horses. Cardiac output was modified by the administration of dopamine (4 ug/kg/min), dobutamine (4 ug/kg/min), and detomidine (10 ug/kg) plus butorphanol (20 ug/kg). Regression analysis of thermodilution CO

on echocardiographic CO was performed in order to determine a predictive equation.

Results – A significant ($p = 0.001$, $n=16$, $R^2=0.54$) predictive equation was determined by which $CO_{TD} = (0.63 \pm 0.157) * CO_{echo} + (16.6 \pm 3.22)$.

Conclusions – Although thermodilution cardiac output and echocardiographic cardiac output were significantly related and an equation was determined by which CO_{echo} could be used to predict CO_{TD} , the relatively large standard errors associated with the measurements generated a broad 95% prediction interval. This broad range of predicted values inhibits the usefulness of echocardiographic cardiac output determinations for research purposes.

Introduction

The need for non-invasive methods which can determine cardiac output (CO) quickly and easily has been previously described[1]. M-mode echocardiographic calculation of stroke volume can be performed in a clinical setting with relative ease and economy of time, from standard menu options available on diagnostic ultrasound units with cardiac capability. However, values obtained by these calculations in horses have not been

compared with direct volume measurements or with other indirect methods[2]¹. It is reasonable to expect that they will not be highly accurate, as the formulas used are based on geometric assumptions about left ventricular shape which do not hold true for the equine heart[3, 4]. However, preliminary investigations² have shown them to be reasonably repeatable within a given horse, and as such, they may be useful for detection of relative changes in cardiac output.

The objective of this experiment was to determine the relationship between CO determinations made by M-mode echocardiography (CO_{echo}) and thermodilution (CO_{TD}) in anesthetized horses, and to discover whether such a relationship could be used to reliably predict CO_{TD} from CO_{echo} .

Materials and Methods

This study was approved by the Virginia Tech Animal Care Committee. Five adult horses were used: a 12 year old 445 kg Thoroughbred (TB) gelding, a 23 year old 418 kg TB mare, a 17 year old 500 kg TB mare, a 10 year old 609 kg TB gelding, and a 9 year old 563 kg Paint gelding. Criteria for selection included: (1) normal findings on physical examination of the cardiovascular system, including EKG and echocardiographic exam, and (2) absence of significant dysfunction of other organ systems which might affect

¹ Young, L.E. Personal Communication. Animal Health Trust, Newmarket, Suffolk, U.K., 1997.

² Moore, D.P., Unpublished research.

cardiovascular parameters (such as infectious pulmonary disease or renal dysfunction). Three horses were maintained on pasture. One was kept in a paddock with free access to hay, water, and salt, due to difficulties with maintaining body weight. This horse was also fed a sweet feed ration once daily. One horse was donated for terminal procedures; history was not available on that subject.

Horses were moved into a box stall the night before experimental procedures; feed was withheld overnight.

Data collection

Physical Examination : Each subject received a physical examination and complete cardiovascular exam including electrocardiography (Burdick E350, Burdick Inc., Milton, WI) and echocardiography (VFI Impact, Ausonics Corp., N.S.W., Australia). Six electrocardiographic leads were recorded and analyzed for rhythm, PR and QT interval durations, and configuration and duration of P waves and QRS complexes. Complete blood counts and standard serum biochemical profiles were also analyzed.

Subject Instrumentation : Two 8.5 French catheter introducers (Arrow International Inc., Reading, PA) were placed in the jugular vein on one side as distally as possible, after local anesthesia. General anesthesia was induced with a combination of xylazine (1.1 mg/kg), guaifenesin, and ketamine (2.2 mg/kg). Horses were intubated, placed in left lateral recumbency, and maintained under anesthesia with halothane in oxygen. A sterile 7 French 110 cm

thermodilution catheter (Baltherm, Electro-Catheter Corp., Rahway, NJ) was inserted through the most distal introducer, with placement into the pulmonary artery confirmed by analysis of pressure waveforms[5-7] (Protocol Propak Datascope, Datascope Corp., Paramus, NJ). A 1.67 mm internal diameter polyethylene catheter (PE 240, Becton Dickinson, Sparks, MD) was threaded through the proximal introducer until placement in the right atrium was confirmed via pressure tracings as above. After horses were instrumented, they were allowed 10 minutes to acclimate to the instrumentation before baseline measurements were recorded.

Thermodilution Technique : 57 ml of cooled (-0.1 - 1.6°C) sterile 5% dextrose solution was injected into the right atrium within 1-2 seconds through the polyethylene catheter, via an angiographic pressure injector (Cook, Inc., Bloomington, IN) at 100 psi. Injections were synchronized with the end of expiration. Individual flow measurements were calculated from time x temperature curves analyzed by a cardiac output computer (Cardiomax, Columbus Instruments, Columbus, OH) and recorded on a personal computer. Curves not displaying the characteristic gamma-variate shape were rejected and the measurement repeated. Cardiac output was determined from the mean of 3-6 sequential TD measurements made approximately two minutes apart.

Echocardiographic Technique : A 2.5 MHz phased array sector probe (VFI Impact, Ausonics Corp, N.S.W., Australia) was used in a right-sided parasternal position to obtain a 2-D image of the LV

short axis cross section at the level of the chordae tendinae[8, 9]. The M-mode cursor was placed across the maximum diameter of the LV, and M-mode measurements of the left ventricular internal diameter in systole and diastole (LVIDs and LVIDd) were made using the "leading edge method" recommended by the American Society for Echocardiography[10]. End-diastolic measurements were made at the onset of the downward motion of the interventricular septum[11-16] in three horses. In two horses, end-diastolic measurements were made at the onset of the QRS complex. End-systolic measurements were made at the septum's point of maximum excursion[10]. These measurements were entered into the menu-driven program for calculation of stroke volume (SV) via the cube formula. Five sequential measurements were made as simultaneously as possible with the TD measurements.

Measurements were made by the author in 4 out of 5 horses. In one horse, a more experienced ultrasonographer made the echocardiographic measurements. This was done under direct supervision of the author in compliance with the above guidelines, so as to ensure consistency in all other aspects of the experiment.

Modification of Cardiac Output: Following the five sequential baseline measurements, CO was manipulated by the administration of drugs, following the protocol of Blissitt et al[17]. A summary of this procedure follows: (1) Following baseline measurements, dopamine, 4 ug/kg/min in 5% dextrose solution, was administered for 10 min; CO was then measured as described above, while

infusion continued. Dopamine infusion was stopped for 10 min prior to the next treatment. (2) Dobutamine, 4 ug/kg/min in 5% dextrose solution, was administered for 10 min; CO was then measured as described above, while infusion continued. Dobutamine infusion was stopped for 10 min prior to the next treatment. (3) A bolus dose of detomidine, 10 ug/kg, and butorphanol, 20 ug/kg, was administered. CO was again measured as described above, approximately 10 min after the administration of these drugs.

Data Analysis

Descriptive statistics for the raw data and the CO determinations were calculated using a spreadsheet program (Microsoft Excel 2001). Mixed model analysis of variance was performed using the MIXED procedure of the SAS System (SAS System-8e, SAS Institute, Inc., Cary, NC), in order to determine the contribution of subject, treatment, and replicate measurement to the observed data variability. Regression analysis of thermodilution CO (CO_{TD}) on echocardiographic CO (CO_{echo}) was performed using the REG procedure of SAS. The ninety-five percent prediction interval and ninety-five percent confidence interval for the regression equation were determined and plotted.

Results

Within-horse coefficients of variation averaged 25.2% for the 4 horses in which measurements were performed by the author and 50.6% for the horse measured by a more experienced ultrasonographer.

The effect of the subject in the mixed model analysis of variance was not significant ($p=0.36$ for CO_{TD} , $p=0.18$ for CO_{echo}). CO_{TD} and CO_{echo} were significantly related ($p=0.001$, $n=16$, $R^2=0.54$) by the following equation: $CO_{TD} = (0.63 \pm 0.157) * CO_{echo} + (16.6 \pm 3.22)$. All of the experimental CO determinations fell within the 95% prediction interval (Fig. 5.1).

Discussion

In the first three horses studied, end-diastolic echocardiographic measurements were made at the onset of the downward motion of the interventricular septum (IVS). This method of measurement has been reported to be satisfactory by numerous investigators[11-16]. In the last two horses, end-diastolic measurements were made at the onset of the QRS signal, as recommended by the American Society for Echocardiography[18]. When data was reviewed, this difference in measurement technique was found to have resulted in no difference (i.e. the onset of down-

ward motion of the IVS and the onset of the QRS signal were simultaneous) in all but 6 data points. The six points in which the onset of QRS was not simultaneous with the onset of downward motion of the IVS were dropped from the analysis.

This study utilized the pharmacological protocol of Blissitt et al[17] in order to modify CO. Dopamine and dobutamine were administered first, since their short half lives (approximately 2 minutes for each) should ensure that no carry-over effect influenced subsequent treatments. Drug activity is reported to cease within 10 minutes after dopamine or dobutamine is discontinued[19-21]. Onset of action is reported to be within 5 minutes for dopamine and within 2 minutes for dobutamine[20]; our protocol allowed 10 minutes for hemodynamic variables to stabilize[20, 21] before measurements were begun. Although either dopamine or dobutamine could have been administered first, the consistent order of dopamine first, dobutamine second was maintained in order to treat all subjects in the same manner and to conform to the previously validated protocol. The detomidine-butorphanol treatment had to be administered last due to the long-lasting effects of detomidine (half-life 72 minutes)[22] and butorphanol (up to 4 hours)[20]. Hemodynamic effects of detomidine are apparent within 15 seconds of IV administration[23], and decreased CO is evident within 5 minutes in conscious horses[24]. Findings from various protocols in the literature suggest that the most stable period for CO after administration of detomidine may be between 5

and 20 minutes[24, 25]. Once again our protocol allowed approximately 10 minutes for hemodynamic variables to stabilize before measurements were begun.

Rigorous application of statistical rules may call into question the use of TD for calibration of echocardiographic CO determinations, because calibration is properly applied in situations where a new method of measurement is compared to a known quantity. In this experiment we have used TD as an indicator of the true CO, but its variability is well documented [26-30], and the true value of the CO remains unknown. However, indirect measurements are required for most investigations into CO, since direct measurement is extremely invasive and potentially life-threatening. Thus, as a practical matter, imperfect measurement methods must substitute for a true gold standard, bearing in mind the limitations of such application of statistical theory. The chief limitation is that, while our calibration equation would hold for the data of this experiment, subsequent experiments might generate a different equation. Nevertheless, our findings are valuable since there is not a direct correspondence between TD and echocardiographic CO determinations³, and the relationship between values generated by the two methods has not, to this author's knowledge, previously been defined in horses.

Data analysis revealed that CO determinations by the two techniques are significantly related. However, the 95% prediction

³ Such as $CO_{TD} = 1.3 \times CO_{echo}$, for example.

interval is broad. For a given CO_{echo} value of, for example, 20 l/min/450 kg, the predicted CO_{TD} value would fall between 18 and 41 l/min/450 kg (Fig. 5.1). Across the range of COs examined in this experiment, a 20% increase in CO_{echo} from 20 to 24 l/min/450 kg, for example, would correspond to a change in predicted CO_{TD} from 18-41 l/min/450 kg to 19-44 l/min/450 kg (Fig. 5.2). Such a broad range of predicted values is usually a result of much within-subject variation, and will determine the sensitivity of the technique for detecting serial changes in CO[2]. With the prediction interval estimated for this experiment, CO_{echo} would have to change by more than 100% in order to be 95% confident that the determined value represents true hemodynamic change.

Readers may be accustomed to thinking of the prediction interval as a confidence interval (C.I.), since it is the range within which we expect 95% of the observations to fall. However, in regression analysis the 95% C.I. represents the range within which we can say (with 95% confidence) that the true regression line lies. Or, for any given value of X the 95% C.I. represents the range which we can say (with 95% confidence) includes the true mean of Y[31]. This is given by the formula $Y_{\text{fit}} \pm (t_{.975} \times se_{Y_{\text{fit}}})^4$, while the 95% prediction interval is calculated using the standard deviation of individual values of $Y - Y_{\text{fit}}$, termed S_{pred} . The prediction interval is thus $Y_{\text{fit}} \pm (t_{.975} \times S_{\text{pred}})$ [31]. The difference between $se_{Y_{\text{fit}}}$ and S_{pred} can be seen in Fig. 5.3. The larger values of S_{pred} result in the

⁴ Y_{fit} = the value of Y fitted to the regression line at any given value of x.

prediction interval being wider than the C.I., as illustrated by Figures 5.1 and 5.4. This is because the prediction interval reflects individual variation around the regression line, while the C.I. reflects only the mean value of Y for a given X. The C.I. can thus be narrowed by increasing the number of observations, while the prediction interval is less affected by increasing n[31].

The wide CO prediction interval has not been addressed in previous reports on the repeatability of M-mode echocardiographic measurements, which have largely focused on across-horse coefficients of variation[32, 33]. What sources of within-subject variation might be contributing to the wide prediction interval? One possible source which must be considered is operator error. Subtle differences in imaging planes can occur without changing the appearance of the echocardiographic image, and such differences can alter measurements. In an effort to assess how much operator error may have contributed to the variability detected in this study, coefficients of variation for the author's measurements were compared to those for a more experienced ultrasonographer. The fact that the average CV of the individual measurements obtained by the author was less than that obtained by the more experienced ultrasonographer suggests that operator error was not a major factor.

Another possible source of within-subject variation is true physiologic change. It is well known that CO fluctuates with respiration. However, all of our measurements were made during

the end-expiratory pause, so this should not have increased the variation in our results. Conscious horses are known to have more variable homeostatic control of stroke volume than humans[2]. In fact, Hiraga et al[5] found considerable beat-to-beat variation in SV during steady state conditions in horses instrumented with sonomicrometer crystals on the heart. Previous studies on the repeatability of M-mode echocardiographic measurements have used the mean of 3-5 consecutive cardiac cycles (a “run”) for each determination. This averages out the effect of the respiratory cycle on SV, and is likely to also compensate for subtle variations in homeostatic control of SV. Our results may have been improved if we had used the mean of 3-5 consecutive cardiac cycles for each echocardiographic measurement. This possibility warrants further investigation. However, as measured in this experiment, M-mode echocardiography gives results which are too variable to have confidence in its use for precise determinations of CO.

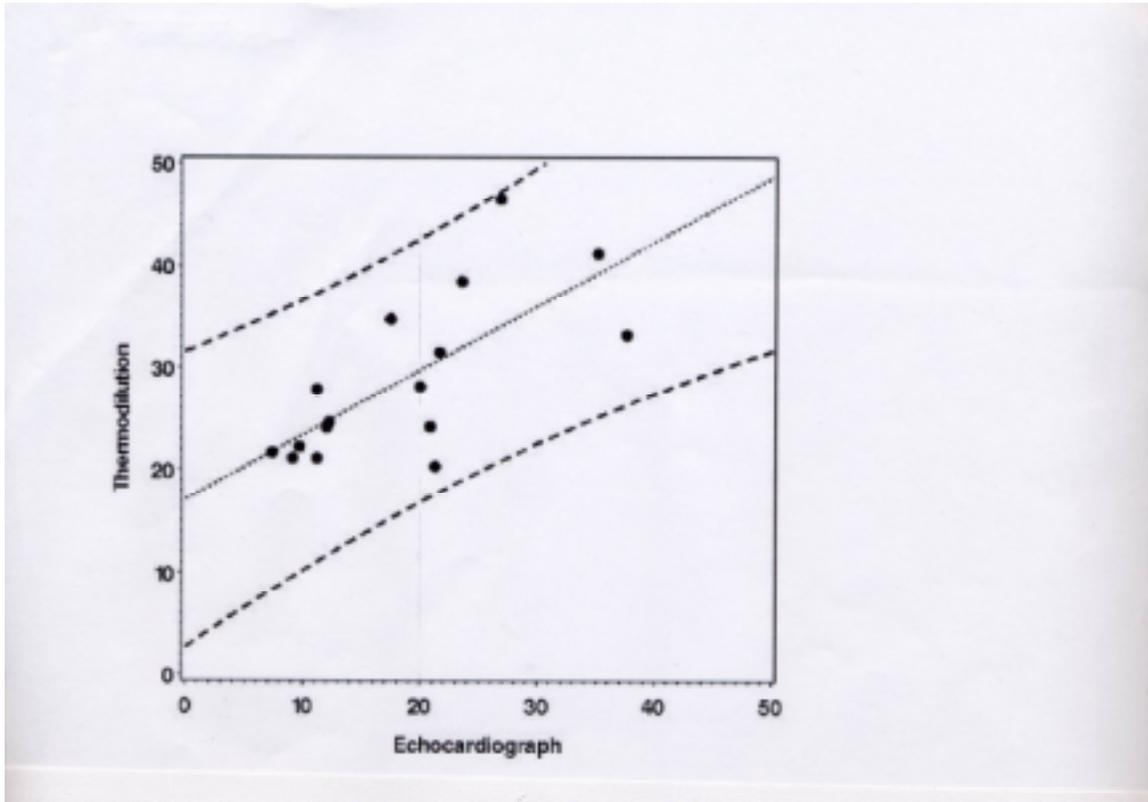


Fig. 5.1 Cardiac outputs (l/min/450 kg) as determined by simultaneous thermodilution and M-mode echocardiography, plotted with the predictive regression equation $CO_{TD} = (0.63 \pm 0.157) * CO_{echo} + (16.6 \pm 3.22)$ and the 95% prediction interval.