

Chapter 3

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

Abstract

Objectives – 1. To determine the suitability of a pharmacological protocol for inducing a range of cardiac outputs in standing horses.
2. To determine whether cardiac output data from simultaneous echocardiographic and thermodilution determinations across a range of values in standing horses could be compared with similar data from anesthetized animals.

Animals – Two horses selected for calm, tractable dispositions. Measurements were made twice on one of the subjects.

Methods – Determinations of cardiac output by M-mode echocardiography were compared with simultaneous determinations by thermodilution. 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). Changes from baseline cardiac output in response to each drug were evaluated.

Data from this experiment was compared to that obtained through an identical protocol in anesthetized horses.

Results – Drug-induced changes in thermodilution cardiac output (l/min/450 kg) averaged 13% for dopamine, 11% for dobutamine, and –27% for detomidine plus butorphanol. Movement of the horses during standing data collection resulted in a mean time of 1.2 minutes required to obtain a satisfactory echocardiographic image in unsedated subjects. Mean time was decreased to 0.6 minutes in sedated subjects. T-tests revealed a significant difference ($p < .05$) between the standing and anesthetized relationship between echocardiographic and thermodilution cardiac output determinations.

Conclusions – Determination of cardiac output in standing horses was prohibitively difficult due to patient movement for both echocardiographic and thermodilution methods. Results in standing horses were significantly different from those obtained in anesthetized animals and thus were unsuitable for comparison.

Introduction

Cardiac output (CO) is one of the key indices of cardiac function. The importance of reliable information about CO for research into cardiovascular function can hardly be overstated. In addition, reliable information about CO could improve anesthetic monitoring and aid the clinical assessment of cardiac abnormalities. Standard methods for determination of CO (thermodilution, dye dilution, Fick method) are time-consuming and require specialized equipment; as such they are only practical within a research setting. In addition, the thermodilution (TD) method is invasive, requiring placement of catheters into the right atrium and pulmonary artery. Such procedures are not without risk, as several authors have reported[1-3]. A method for determining CO quickly, easily, and non-invasively is needed in order to be able to apply knowledge of CO in both the clinical setting and in research which requires the investigator's attention to other, concurrent measurements or procedures.

M-mode echocardiography may offer a quick, non-invasive means of determining CO. However, it can not be performed on exercising animals due to the need for immobility. M-mode CO determinations that have been reported in exercise studies[4-7] are based on measurements made as soon as possible after cessation of exercise, when CO is declining rapidly. It has been impractical to

compare post-exercise echocardiographic results with results obtained by validated methods, because of (1) the difficulty of performing more tedious measurements on horses under the influence of a stimulated sympathetic nervous system, and (2) because established methods of CO determination such as TD are based on the mean of 3-5 sequential measurements which need to be taken in a steady-state condition.

The use of exercise as the stimulus for altering cardiac output has further disadvantages. The exercise stimulus can be applied in a controlled manner by means of a high-speed treadmill, but such equipment is expensive to install and to operate. Alternatively, exercise can be applied in an outside area, but then factors of weather and footing have to be considered, and consistency is more difficult to achieve. Furthermore, unsound individuals can not be studied by means of exercise tests. Data also suggests that post-exercise echocardiography “may not accurately represent exercising cardiac function in normal horses”[8] due to the rapid changes that begin immediately after the cessation of exercise[6].

In spite of the above, comparison of M-mode echocardiographic determinations of CO with a validated method needs to be made at non-resting levels of CO, in order to evaluate assumptions about the reliability of M-mode measurements that have not been tested. This study aimed to determine whether a pharmacological protocol might be used to permit comparison between the methods of M-mode echocardiography and TD across a range of CO values in

conscious horses without requiring the use of exercise. A secondary aim was to determine whether the data gathered in this experiment could be compared with data from an identical procedure applied to anesthetized animals.

Materials and Methods

Horses

This study was approved by the Virginia Tech Animal Care Committee. Two adult horses were used: a 23 year old 425 kg Thoroughbred mare and a 20 year old 442 kg Thoroughbred gelding. Criteria for selection included: (1) normal findings on physical examination of the cardiovascular system, including EKG and echocardiographic exam, (2) absence of significant dysfunction of other organ systems which might affect cardiovascular parameters (such as infectious pulmonary disease or renal dysfunction), and (3) temperament conducive to standing for several hours during procedures. Horses were maintained on pasture plus a once-daily sweet feed ration. Additional hay was provided in winter months.

Data collection

Three sets of data were collected from standing subjects. Subject 1 was used twice for data collection because difficulties with

dopamine administration during the first period resulted in a lack of drug effect. During the second data collection period this horse was uncooperative and thus only baseline and sedated (detomidine plus butorphanol) measurements were made.

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. 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, 9, 10] (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 4-5 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[11, 12]. 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[13]. End-diastolic measurements were made at the onset of the downward motion of the interventricular septum[14-19], and end-systolic measurements were made at the

septum's point of maximum excursion[13]. These measurements were entered into the menu-driven program for calculation of stroke volume (SV) via the cube formula. Four to five sequential measurements were made as simultaneously as possible with the TD measurements.

Modification of Cardiac Output : Following the 4-5 sequential baseline measurements, CO was manipulated by the administration of drugs, following the protocol of Blissitt et al[20]. 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 : Responses to the pharmacological protocol were evaluated graphically and by calculation of the percent change in TD CO from baseline.

Regression analysis was performed through a spreadsheet program¹ in order to examine the relationship between echocardiographic and TD CO determinations. A student's t-test was performed to evaluate the hypothesis (a) that inclusion of data obtained on two different days from Subject 1 made no significant difference in the relationship between echocardiographic and TD CO determinations.

Cardiac output data from this experiment was then compared to that obtained through an identical protocol in anesthetized horses[21]. A t-test was performed to evaluate the hypothesis (b) that the use of anesthesia made no significant difference in the relationship between echocardiographic and TD CO determinations. Since Subject 1 was also used in the anesthetized group, further t-tests evaluated the hypothesis (c) that the exclusion of anesthetized data from this subject had no effect on the relationship between those echocardiographic and TD CO determinations.

Results

During standing data collection in this experiment, the time taken to obtain an echocardiographic image suitable for CO measurement ranged from 0-7 minutes (0-4 minutes with the exception of one measurement in an uncooperative horse) (mean

¹ Microsoft Excel 2001

1.2 minutes for baseline, dopamine, and dobutamine measurements, 0.6 minutes for detomidine measurements).

With the exception of three outliers, sequential TD measurements in standing horses were made 2-7 minutes apart (mean 3.9 minutes). The three outliers of 14, 15, and 19 minutes were due to equipment failure (1 case) or the horse resisting restraint (2 cases). Other TD measurements were delayed beyond the ideal of two minutes because of the need to make echocardiographic measurements simultaneously. Although the need to synchronize measurements caused delays in the time between TD measurements, TD and echocardiographic measurements were able to be made within a mean of 0.4 minutes of each other in one subject, and 0.8 minutes in another. The third subject was not cooperative, and required an average of 2.2 minutes between TD and echocardiographic measurements.

There was a mean increase in cardiac output of 13% for dopamine and 11% for dobutamine, and a decrease of 27% for detomidine plus butorphanol (based on TD determinations) (Fig. 3.1) (Table 3. 1).

T-tests revealed the following: (a) that there was no significant difference ($p > 0.9$) in the relationship between echocardiographic and TD CO determinations when Subject 1 was used twice vs only once; (b) that the relationship between echocardiographic and TD CO determinations in the standing horses (slope -0.1 , $p=0.68$) was significantly different ($p < .05$) from the

anesthetized comparison group (slope 0.8, $p=.001$); (c) that the relationship between echocardiographic and TD CO determinations in the anesthetized comparison group was not altered by excluding data from Subject 1 ($p >0.5$).

Discussion

This study utilized the pharmacological protocol of Blissitt et al[20] 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[22-24]. Onset of action is reported to be within 5 minutes for dopamine and within 2 minutes for dobutamine[23]; our protocol allowed 10 minutes for hemodynamic variables to stabilize[23, 24] 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)[25] and butorphanol (up to 4 hours)[23]. Hemodynamic effects of detomidine are apparent within 15 seconds of IV administration[26], and decreased CO is

evident within 5 minutes in conscious horses[27]. 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[27, 28]. Once again our protocol allowed approximately 10 minutes for hemodynamic variables to stabilize before measurements were begun.

In this study, intravenous infusion of dopamine and dobutamine at a constant rate was difficult in standing subjects due to patient movement. The correct infusion rate (number of drops/sec.) was set via a thumb-control on the I.V. line, but as the horse's head moved up and down this altered the actual rate of infusion. In Subject 1, administration of dopamine at the calculated dose rate should have emptied the drug reservoir in 25 minutes; however, over half of the drug solution remained at that time. The increase in CO noted in that subject in response to dopamine can be attributed to two high measurements of 53.8 and 61.6 l/min/450 kg. The two high measurements may have been due to a sudden increase in heart rate, as heart rate was noted to be quite labile in conscious horses. Records of heart rate were obtained from the echocardiogram, as EKG leads had to be disconnected for safety reasons. It seems possible that a significant change in heart rate occurred in the 1-2 minutes between these high TD measurements and the corresponding echocardiographic measurements.

In Subject 2, CO increased 4% in response to dopamine administration. This is within the range of error for TD CO

determination[29] and thus can not be considered clinically significant. Although we have not found published reports of CO response to dopamine administration in conscious horses, we had expected a greater increase based on published reports in anesthetized horses[30-32]. It seems likely that unevenness in the dose rate due to the horses' raising and lowering their heads affected response to this drug.

Our subjects increased CO by 12% and 10% in response to dobutamine. Hinchcliff et al[33] observed a 6% increase in TD CO in response to 0.5 ug/kg/min dobutamine. In other experiments [21], this author has found dobutamine to be more reliable than dopamine for inducing a positive inotropic effect. This is consistent with the findings of Swanson et al[34], who reported that responses to dopamine were more variable than were responses to equivalent doses of dobutamine.

Detomidine plus butorphanol consistently decreased CO, by 16-35% below baseline. Detomidine in conscious horses at 10 ug/kg has been reported to decrease CO by 35.6% from baseline at 5 min. and by 34.1% at 15 min[27]. By 30 min. the decrease in that report had lessened to 21.0%. Butorphanol in conscious horses at 5, 10, and 20 times the dose used in this experiment produced no alterations in CO, HR, or MAP[35]. While CO responses to a combination of detomidine and butorphanol have not been reported, combinations of the similar alpha-2 agonist xylazine with butorphanol in conscious horses have resulted in decreases in CO of

15.2% after 5 min. in one report[36], and decreases of 20.8% in another[37]. Based on these reports, the changes in CO which we observed in response to detomidine plus butorphanol seem to fall within the expected range.

Cardiac output measurements were much easier to obtain after administration of detomidine plus butorphanol, as illustrated by the decrease in mean time required to obtain a satisfactory echocardiographic image. In order to obtain such an image, the horse must stand still with the right foreleg advanced. Proper placement of the ultrasound probe took anywhere from 9 seconds to over 3 minutes in a series of 15 measurements performed on a cooperative horse by 3 different ultrasonographers^c. The horses in this study resisted attempts to keep them immobile, in spite of having been selected for quiet dispositions and having been habituated to the examination environment and the non-invasive aspects of the experimental protocol. This resulted in longer than ideal delays between sequential measurements, raising concern that CO may have varied from the desired "steady state."

Movement of the horses during data collection also presented a risk to the safety of personnel and equipment. EKG and blood pressure monitoring were abandoned due to the risk of an increased number of cables attached to the horse.

The difficulties described above prevented a full assessment of the suitability of the pharmacological protocol. Detomidine plus

^c Moore, D.P., unpublished research, 1/4/00.

butorphanol was clearly useful for lowering CO, and our experience suggests that dobutamine may be more reliable than dopamine for increasing CO in standing horses. However, the obstacle of patient movement needs to be overcome before the pharmacological protocol can become a useful tool in our hands.

It was expected that mean CO in the standing horses would be different from the comparison, anesthetized group. Data from the two groups could still have been compared if the echocardiographic: TD relationship was the same. However, the difficulties discussed above contributed to a lack of any significant relationship between echocardiographic and TD determinations for the standing horses, and made this data unsuitable for comparison with that from the anesthetized group.