Chapter 4

Use of Dopamine, Dobutamine, and Detomidine Plus Butorphanol to Alter Cardiac Output in a Study Comparing the Measurement Methods of M-Mode Echocardiography and Thermodilution in Anesthetized Horses

Abstract

Objectives – 1. To determine the suitability of a pharmacological protocol for inducing a range of cardiac outputs in anesthetized horses. 2. To determine whether such a protocol could be used in a study comparing the methods of M-mode echocardiography and thermodilution for determination of cardiac output.

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 (CO) 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). Data was analyzed to determine whether drug treatments induced a significant effect and whether there was any interaction between drug treatment and measurement method.

**Results** – Drug treatments induced a significant effect across subjects (p = 0.001 for thermodilution). Drug-induced changes in thermodilution CO (l/min/450 kg) from baseline ranged from –10 to 32% for dopamine, 38 to 128% for dobutamine, and –12 to 9% for detomidine plus butorphanol. For detomidine plus butorphanol, changes from pre-detomidine values ranged from –40 to –52%. There was no significant interaction between drug treatment and measurement method (p=0.86).

**Conclusions** - Dopamine, dobutamine, and detomidine plus butorphanol, at the dosages used in this study, can be used to induce a range of cardiac outputs across which the measurement methods of M-mode echocardiography and thermodilution can be compared in anesthetized horses. Dobutamine treatment was the most reliable for increasing CO, and resulted in the largest changes in CO. Detomidine plus butorphanol did not significantly decrease CO relative to baseline, but did produce significant decreases from the immediately preceding condition. Therefore it can be useful for inducing additional changes in cardiac output, but does not increase the overall range of cardiac output values available for study.
Introduction

The importance of reliable information about cardiac output (CO) and the need for a method of determining CO quickly, easily, and non-invasively have been previously described [1]. M-mode echocardiography can be used to measure stroke volume (SV), which gives CO when multiplied by heart rate. M-mode echocardiography meets the objectives of being relatively quick, easy, and non-invasive. However, M-mode CO determinations need to be compared with direct volume measurements or with other indirect methods that have been previously validated. Previous attempts to make such comparisons in standing horses [1] proved prohibitively difficult due to patient movement. Method comparison could be carried out in anesthetized horses, but the methods need to be compared over a range of CO values. The aim of this study was to determine whether a pharmacological protocol could be used to induce a range of cardiac outputs in anesthetized horses, and whether such a protocol could be used in a study comparing the methods of M-mode echocardiography and thermodilution (TD) for determination of CO.
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 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), guiafenesin, 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[2-4] (Protocol Propak Datascpe, 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:_ Five sequential measurements of left ventricular internal diameter (LVID) in systole and diastole were made as simultaneously as possible with the TD measurements. The LVID values were entered into the menu-driven program for calculation of stroke volume (SV) via the cube formula.

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 [5]. 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**

The MIXED procedure of the SAS System (SAS System-8e, SAS Institute, Inc., Cary, NC) was used to perform mixed model analyses of variance for TD and for echocardiography. Significance of the effect of drug treatment across subjects was assessed by a test of fixed effects on the TD data. Separate mixed effects models using the subsample means (CO determinations rather than individual measurements) were used to explore possible interactions between drug treatment and measurement method.

**Results**

Drug treatments induced a significant effect across subjects (p=0.001 for thermodilution). Within individual subjects, changes from baseline ranged from –10 to 32% (mean 7.6%) for dopamine, 38 to 128% (mean 73.6%) for dobutamine, and –12 to 9% (mean –1.9%) for detomidine plus butorphanol (Figure 4.1, Table 4.1). For detomidine plus butorphanol, changes from pre-detomidine values ranged from –40 to –52% (mean –45.3%). There was no significant
interaction between drug treatment and measurement method (p=0.86).

**Discussion**

**Modification of Cardiac Output**

This study utilized the pharmacological protocol of Blissitt et al[5] 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[6-8]. Onset of action is reported to be within 5 minutes for dopamine and within 2 minutes for dobutamine[7]; our protocol allowed 10 minutes for hemodynamic variables to stabilize[7, 8] 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)[9] and butorphanol (up to 4 hours)[7]. Hemodynamic effects of detomidine are apparent within 15 seconds of IV administration[10], and decreased CO is evident
within 5 minutes in conscious horses[11]. 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[11, 12]. Once again our protocol allowed approximately 10 minutes for hemodynamic variables to stabilize before measurements were begun.

**Baseline Cardiac Output**

Baseline CO values were notably lower than normal values reported for conscious horses[13], as expected, in all 5 subjects (Table 4.1). Grosenbaugh et al[14] reported that CO was decreased by 16.9% after 15 minutes of halothane anesthesia following the same induction protocol used in this experiment. Depression of CO progressed to 37.1% after 30 minutes and 43.9% after 45 minutes. Other investigators have reported similar progressive decreases in CO with halothane anesthesia[15-18]. After approximately one hour of anesthesia CO may stabilize[19] or begin to increase [15, 20-23]. The use of controlled ventilation contributes to decreased CO[17, 21, 24] and may blunt the return towards pre-anesthetic levels[19, 23].

Since the pharmacological protocol used in this experiment sought to produce a range of cardiac outputs, the fact that CO was decreased from normal resting values at the beginning of the experiment did not interfere with the objective of the study.
Response to Dopamine

Responses to dopamine infusion in individual subjects varied widely (Figure 4.1, Table 4.1). Subject 4, which experienced very minimal increase in CO in response to dopamine, showed a relative lack of hemodynamic stability during anesthesia for unknown reasons. Mean blood pressure decreased from 50 mm Hg at the start of dopamine infusion to 32 mm Hg at the end. This horse also exhibited runs of ventricular tachycardia after several of the iced injections. It seems possible that whatever unique physiologic factors were contributing to this horse’s instability may have also blunted the potential response to dopamine’s inotropic effects.

Subject 2 experienced no notable increase over baseline CO in response to dopamine, and subject 5 experienced a paradoxical decrease in CO (Figure 4.1, Table 4.1). No apparent reason could be determined for these unexpected responses.

The other two horses responded with increases of 12% (Subject 1) and 32% (Subject 3) (Figure 4.1, Table 4.1). Stetz et al [25] have recommended that there should be a difference of 6-15% between determinations of CO in order to be confident of clinical significance. This is based on a SEM% (percent standard error of the mean; SEM/mean CO) of 2-5% which they found in a review of nine studies of TD reproducibility. Based on these recommendations, we can be confident that we achieved a clinically significant response to
dopamine infusion in 1 out of 5 horses, with a possibly significant response in a second horse.

Other studies of halothane-anesthetised horses in lateral recumbency have obtained CO increases of approximately 50-58% from dopamine infusions of 5 ug/kg/min[26]. A similar dose resulted in an approximate 17% increase in CO in halothane-anesthetised ponies in dorsal recumbency [27]. These results may have been affected by previous administration of lower doses of dopamine in each experiment, but it still seems surprising that we did not obtain a greater increase in CO from our dose of 4 ug/kg/min. Other authors have noted variable responses to dopamine in anesthetized horses, however. Both Robertson et al[28] and Swanson et al[29] reported that at 5 ug/kg/min, dopamine’s effect on HR in halothane anesthetized horses was extremely variable, with some increased, some decreased, and some unchanged. In human cardiovascular anesthesia, dopamine is valued principally for its dopaminergic effects, while other agents are preferred for inotropic effects.

Response to Dobutamine

Dobutamine induced clinically significant increases in CO in 4/4 horses (Figure 4.1). (Data collection had to be discontinued prematurely in one subject due to development of atrial fibrillation.) Reports of CO responses to dobutamine infusions of 4-5 ug/kg/min in halothane-anesthetized horses have been variable.
Our responses were similar to those obtained by Swanson and Muir [30]. Others have reported changes in CO ranging from none (until after 40 min. of continuous infusion)[31] to increases over baseline of 151% [26] and 203%[27]. Swanson and Muir obtained increases of 47% and 60% from only 1 ug/kg/min dobutamine during anesthesia with 5 and 10 cm H₂O positive end-expiratory pressure, respectively[32].

**Response to Detomidine plus Butorphanol**

Detomidine plus butorphanol markedly decreased CO in 3/3 horses. (Data collection could not be completed in one subject due to development of second-degree A-V block and bradycardia, which changed over time to sinus block.) Although detomidine values were not very different from baseline determinations, presumably due to pre-existing halothane-induced myocardial depression, changes from pre-detomidine values were marked (Figure 4.1). The use of detomidine plus butorphanol in this experiment thus provided one additional change which could be measured, but it did not increase the range of cardiac outputs over that which would have been produced by halothane anesthesia plus the dobutamine treatment alone.

Effects of constant-dose detomidine infusion in halothane-anesthetized horses have been reported by several investigators [33, 34] Effects of a bolus dose of 80 ug/kg in halothane-anesthetized horses have also been reported [9, 35]. Unfortunately there is not
enough published information about plasma detomidine levels in response to varying bolus doses to directly compare these authors' results to our own. Muir et al [12] reported changes in numerous hemodynamic variables 20 and 40 minutes after a bolus dose of 10 ug/kg in halothane anesthetized horses. Heart rate was decreased by 30 and 25%, respectively; CO decreased by 40 and 18%.

Detomidine in conscious horses at 10 ug/kg has been shown to decrease CO by 35.6% from baseline at 5 min. and by 34.1% at 15 min[11]. By 30 min. the decrease 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[36]. 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 [37], and decreases of 20.8% in another[38]. In a study by Rutkowski et al, administration of butorphanol after xylazine produced no further alterations in hemodynamic variables beyond those produced by xylazine alone[38]. Muir[12] found that in halothane anesthetized horses, administration of 40 ug/kg produced no changes in hemodynamic variables. Based on these reports, the changes in CO which we observed in response to detomidine plus butorphanol seem to fall within the expected range.
Overall Effectiveness of the Pharmacological Protocol

The pharmacological protocol as a whole was effective in inducing a range of cardiac outputs for study. Dopamine could be deleted from the protocol without any decrease in the range of cardiac outputs produced, as dobutamine was more effective and more consistent in our hands. Use of detomidine plus butorphanol provided an additional change in CO which could be measured, and so may be beneficial in future studies. However, it did not increase the overall range of CO values, and so could be deleted in studies concerned primarily with obtaining the largest possible range of CO.

In order for the pharmacological protocol to be an appropriate tool for inducing a range of CO in a method-comparison study, it also had to be established that the drug treatments did not affect the two measurement methods differently. The lack of significance in the test for interaction shows that this is the case.