Chapter 6

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

Abstract

Objectives – To determine the suitability of using M-mode echocardiographic determinations of cardiac output (Co_{echo}) as a substitute for thermodilution determinations (CO_{TD}) over a range of cardiac outputs in anesthetized horses.

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). Variance components for each method

were determined. Method comparison analysis was carried out using the procedure of Bland and Altman.

Results – Measurement-to-measurement variability accounted for 28% of the total variation in thermodilution values and 64% of the total variation in echocardiographic values. There was a significant ($p<0.001$) difference between simultaneous thermodilution and echocardiographic CO determinations, with a mean bias of -10 +/- 6.3 l/min. 95% of echocardiographic determinations could be expected to vary from their corresponding thermodilution determinations by –22.3 to + 2.3 l/min.

Conclusions – M-mode echocardiographic determination of cardiac output in anesthetized horses is more variable than thermodilution. The primary factor responsible for the variability is relatively low repeatability of the individual M-mode measurements. CO determinations should be based on the mean of 3-5 steady-state measurements, and variations from published normal values should be interpreted cautiously.

Introduction

M-mode echocardiographic determination of CO is relatively, quick, easy, and non-invasive. As such, it offers significant advantages over standard invasive methods. If it could be shown to be an acceptable substitute for standard methods such as thermodilution, invaluable information about cardiac function could be made accessible in both clinical and research settings. Previous work[1] has shown that TD CO and M-mode echocardiographic CO are significantly related, and that CO_{TD} can be predicted from CO_{echo}. However, the 95% prediction interval is broad, suggesting that the usefulness of M-mode echocardiography for determining CO may be limited. This study aimed to more closely compare the methods of M-mode echocardiography and TD for CO determination, in order to assess whether M-mode echocardiography might be used as a substitute for TD in anesthetized horses. Specifically, we aimed to discover the sources of variability for each method, the bias between methods, and the standard deviation and distribution pattern of the bias.

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 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^{o}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[5, 6]. 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[7]. End-diastolic measurements were made at the onset of the downward motion of the interventricular septum[8-13] 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[7]. 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[14]. 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). 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, to test for effects of subject, treatment within subjects, and measurement to measurement within a treatment within a subject. Bias between the two methods was estimated, and method comparison

analysis was carried out using the procedure of Bland and Altman[15].

Results

There was a significant ($p<0.001$) difference between simultaneous thermodilution and echocardiographic CO determinations, with a mean bias of –10 +/- 6.3 l/min/450 kg (Fig. 6.1). Bias was not proportional to the magnitude of the CO (Fig. 6.2). Ninety-five percent of echocardiographic determinations could be expected to vary from their corresponding TD determinations by –22.3 to +2.3 l/min/450 kg (Fig. 6.2). Measurement-to-measurement variability (within a treament within a subject) accounted for 28% of the total variation in thermodilution values and 65% of the total variation in echocardiographic values (Figs. 6.3, 6.4). Treament effects within subjects accounted for 64% of the total variation in TD measurements and 18% for echocardiographic measurements.

Across-horse coefficients of variation (CVs) for echocardiographic determinations in the baseline condition were 12.5% for CO/450 kg, 2.9% for LVIDd and 3.9% for LVIDs (Table 6.1). Within-horse CVs 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.

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[8-13]. 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[16]. When data was reviewed, this difference in measurement technique was found to have resulted in no difference (i.e. the onset of downward 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[14] 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[17-19]. Onset of action is reported to be within 5 minutes for dopamine and within 2 minutes for dobutamine[18]; our protocol allowed 10 minutes for hemodynamic variables to stabilize[18, 19] 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 proto-col. The detomidine-butorphanol treatment had to be administered last due to the long-lasting effects of detomidine (half-life 72 minutes)[20] and butorphanol (up to 4 hours)[18]. Hemodynamic effects of detomidine are apparent within 15 seconds of IV administration[21], and decreased CO is evident within 5 minutes in conscious horses[22]. Findings from various protocols in the litera-ture suggest that the most stable period for CO after administration of detomidine may be between 5 and 20 minutes[22, 23]. Once again our protocol allowed approximately 10 minutes for hemodynamic variables to stabilize before measurements were begun.

Across-horse variability in this study was somewhat lower than previously reported values, presumably because previous reports have all been in conscious horses[6, 24-29]. Table 6.1 shows the comparison between previously published results and those of this experiment.

It has already been established[1] that TD and echocardio-graphic CO determinations are significantly related. However, this does not necessarily indicate that echocardiographic determinations will serve as an acceptable substitute for TD. Agreement and repeatability also need to be assessed. As an example of the danger of relying solely on a strong statistical relationship between two

measurement methods, Stetz et al[30] point out that many studies have reported high regression coefficients for simultaneous Fick and TD measurements, “yet examination of individual data points may frequently show discrepancies of 50% or more between the two methods.”

In this study, echocardiography was biased such that it under-estimated TD CO by an average of 10 l/min/450 kg (Fig. 6.1). Such bias need not preclude the usefulness of echocardiography if it is consistent across the full range of measured values. Examination of Figure 6.2 shows that the bias is not proportional to the magnitude of the CO. However, the standard deviation of the bias is large (+/- 63%). Thus, given an echocardiographic CO determination of, for example, 30 l/min/450 kg, we could only say with 95% certainty that the corresponding TD determination would be between 28 and 52 l/min/450 kg. Further investigation disclosed the source of this lack of repeatability. Examination of the covariance parameter estimates showed that, while drug treatments were responsible for a signifi-cant portion of the variability in CO measurements (as desired), a more important factor was measurement-to-measurement varia-bility. This variability was among the subsamples that were used for each CO determination, i.e. among the values which we would hoped would be nearly the same. Such variability has been previously documented for TD and is the reason for the generally accepted recommendation to use the mean of 3-5 measurements for each CO determination[30-32]. When that is

done, the SEM% (SEM/mean CO) should be able to be contained within 2-5%[30]. Within these limitations, TD CO determination has proven to be clinically useful, allowing differences in CO of 6-15% to be determined with 95% confidence[30]. However, the larger the SEM%, the greater the difference must be between two CO determinations in order to be confident that they are truly different. This raises a concern about echocardiographic CO determination, in which a full 64% of the total variability in the model was attributed to measurement-to-measurement variability.

Previous reports of within-horse variability of M-mode echocardiography measurements have reflected day-to-day variation rather than variation among the individual measurements used to determine the reported value[24-26]. Young et al[25] calculated that, of the total variation in LVIDd and LVIDs measured over 6 days, 81% was due to between-horse differences and 19% was due to day-to-day variation within horses. Sampson et al[24] estimated the CV for repeated measuring periods on an individual horse to be 1.9-2.5% for LVIDd and 3.2-7.6% for LVIDs. In contrast, Patteson et al[26] reported a significant difference in LVIDs between day 1 and day 2. They hypothesized that this was due to differences in echocardio-graphic technique, most likely involving subtle differences in imaging planes. It is easy for the ultrasound beam to be angled in a dorsal to ventral direction without altering the appearance of the cross-sectional echocardiographic image; this

results in an imaging plane too far below the mitral valve and erroneous measurements.[1]

The primary factor contributing to greater variation among our subsamples than previous authors have found between the means of different days is likely the time between measurements used to determine the mean. Our subsamples were taken approximately 2 minutes apart, as they were timed to coincide with TD measure-ments. The studies mentioned above used the mean of 3-5 consecu-tive 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. Had we used the mean of 3-5 consecutive cardiac cycles for each echo-cardiographic measurement, our results may have been improved. However, one author[33] has recently reported across-horse CVs from a run of 3 consecutive cardiac cycles on single days; results were moderately more variable than those reported here.

In addition to true physiologic variation, operator error may also contribute to subsample-to-subsample variability. Those errors can be technical (failure to achieve the correct imaging plane), or interpretive (incorrect identification of endocardial borders). The fact that the average CV of the individual measurements obtained by the author was less than that obtained by a more experienced

[1] Corley, K.C.C., personal communication, 1/00.

ultrasono-grapher suggests that operator error was not a major factor in the variability seen in this experiment.

The variability of M-mode echocardiographic CO measurements within individual horses is an area of investigation that needs to be more widely reported on, as many reports have relied on M-mode echocardiographic measurements without addressing whether the method offers adequate repeatability.

Some authors have attempted to compensate for variability in a measurement method by using the mean of the closest 3 out of 5 measurements for each CO determination[34]. However, in a study using sonomicrometer crystals implanted on the heart to measure cardiac dimensions, Hiraga et al[2] found considerable beat-to-beat variation in stroke volume during steady state conditions. It may be that the echocardiographic method, which calculates CO from the volume of a single beat, is picking up beat-to-beat variability which is averaged out in steady-state techniques such as TD. If M-mode echocardiography could be compared to another single-beat method such as Hiraga's, perhaps its performance would appear more favorable. However, in comparison with the established steady state method of TD, M-mode echocardiography as measured in this experiment gives results which are too variable to have confidence in its use for precise determinations of CO.

Table 6.1 Coefficients of variation (CV) for Cardiac Output and Left Ventricular Internal Diameter in Diastole (LVIDd) and Systole (LVIDs) as measured by M-mode echocardiography, for the present study, compared with previously published results in conscious horses.

M-mode Echocardiographic Variable	Present Study	Range of Previously Published Results
CV (%), Cardiac Output	12.5	13.5[33] - 17.4[24]
CV (%), LVIDd	2.9	4.4[28] - 9[25]
CV(%), LVIDs	3.9	5.7[29] - 11[6]

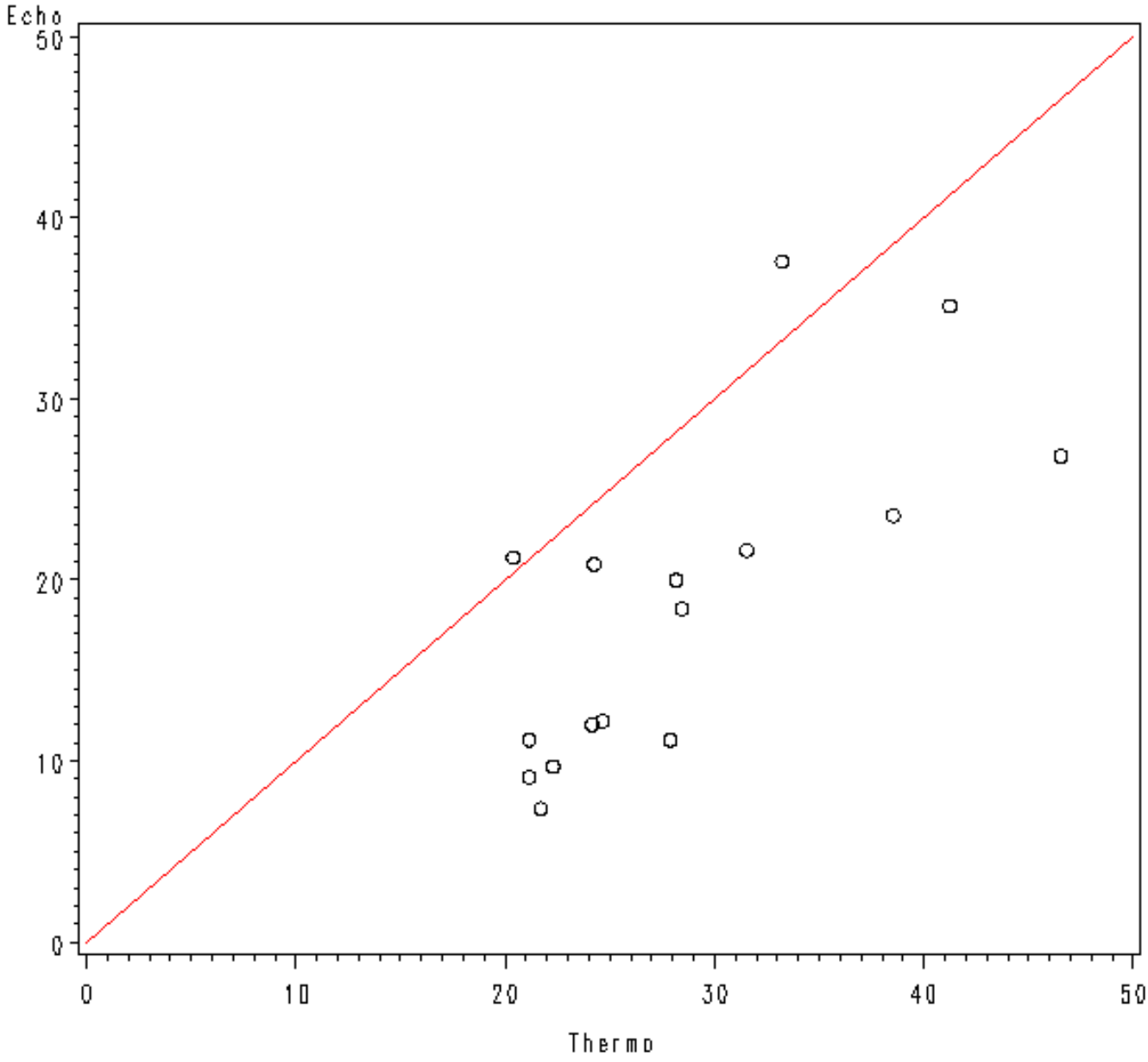

Fig. 6.1 Cardiac output (l/min/450 kg) as determined by thermodilution and by M-mode echocardiography, with line of equality.

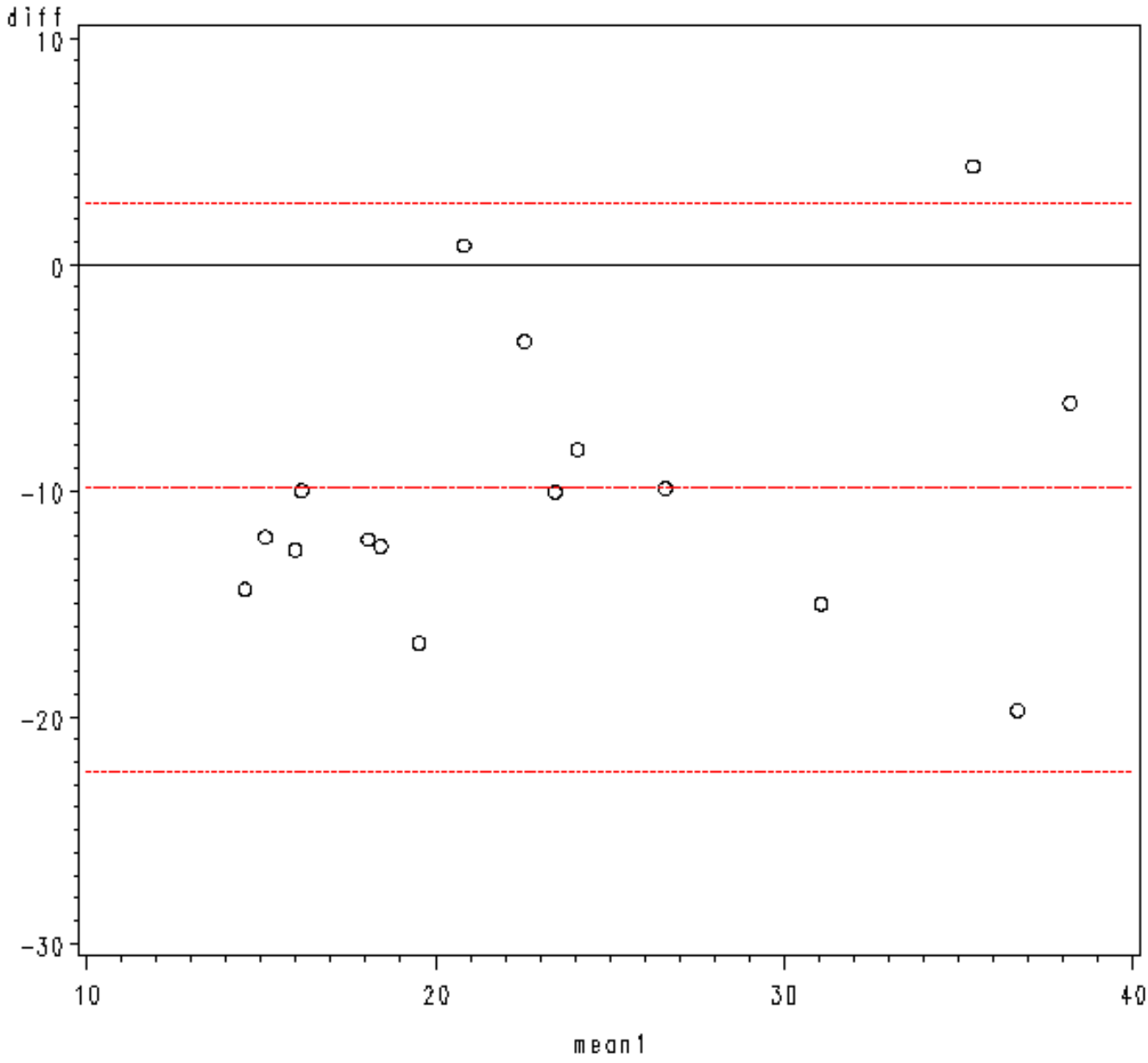

Fig. 6.2 Difference between simultaneous thermodilution and echocardiographic determinations of cardiac output (l/min/450 kg) plotted against the average of the two methods.

Fig. 6.3

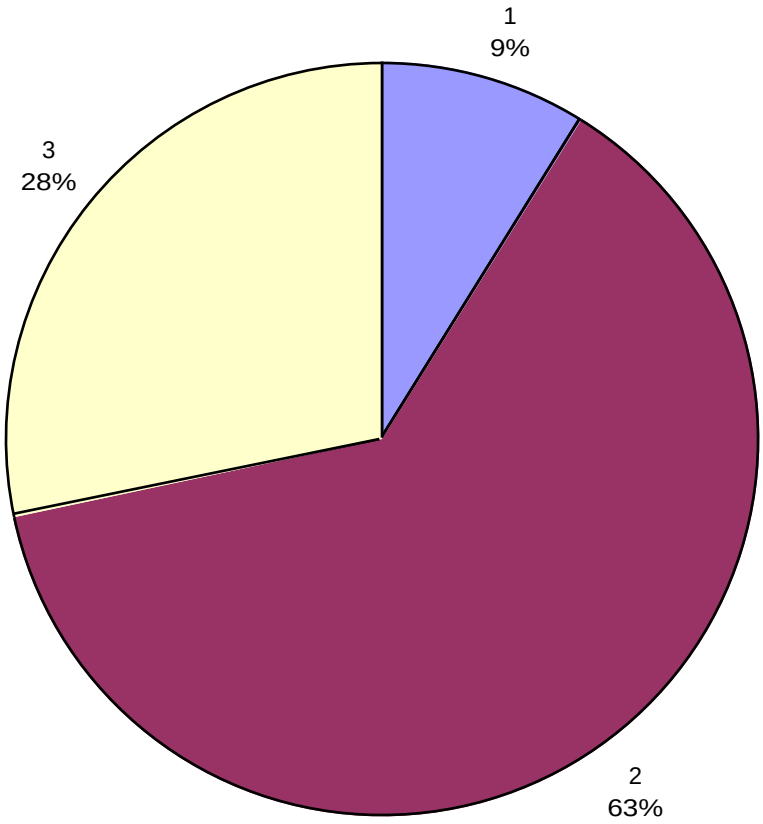

Fig. 6.3 Portions of the total measurement variability for CO measurement by thermodilution which were due to (1) subject, (2) treatment to treatment within a subject, and (3) subsample to subsample variation.

Fig. 6.4

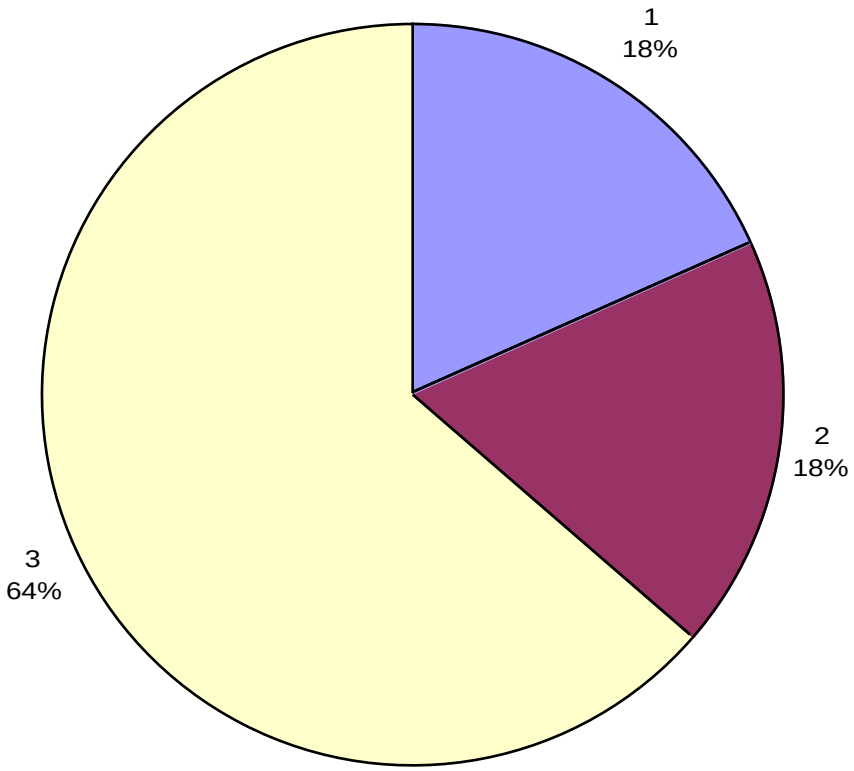

Fig. 6.4 Portions of the total measurement variability for CO measurement by M-mode echocardiography which were due to (1) subject, (2) treatment to treatment within a subject, and (3) subsample to subsample variation.

Bibliography

1. Moore, D.P. *Determination of cardiac output in horses by M-mode echocardiography and thermodilution.*, in *Veterinary Medical Sciences*. Submitted 2003, Virginia Polytechnic Institute and State University: Blacksburg.
2. Hiraga, A., *et al*. Changes in left ventricular dynamics during graded exercise, in *Fifth International Conference on equine Exercise Physiology*. 1998;
3. Pascoe, J.R., *et al*. Cardiac output measurements using sonomicrometer crystals on the left ventricle at rest and exercise, in *Fifth International Conference on Equine Exercise Physiology*. 1998;
4. Sampson, S.N., Tucker, R.L., and Bayly, W.M. Relationship between VO2max, heart score, and echocardiographic measurements obtained at rest and immediately following maximal exercise in Thoroughbred horses, in *Fifth International Conference on Equine Exercise Physiology*. 1998;
5. Long, K.J., J.D. Bonagura, and P.G.G. Darke. Standardised imaging technique for guided M-mode and Doppler echocardiography in the horse. *Equine Vet J* 1992; 24(3): p. 226-235.
6. Slater, J.D., and Herrtage, M.E. Echocardiographic measurements of cardiac dimensions in normal ponies and horses. *Equine Vet J Suppl 19* 1995: p. 28-32.
7. Sahn, D.J., DeMaria, A., Kisslo, J., and Weyman, A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circ* 1978; 58(6): p. 1072-83.
8. Popp, R.L. and D.C. Harrison. Ultrasonic cardiac echography for determining stroke volume and valvular regurgitation. *Circ* 1970; 41(3): p. 493-502.
9. Uehara, Y., M. Koga, and M. Takahashi. Determination of cardiac output by echocardiography. *J Vet Med Sci* 1995; 57(3): p. 401-407.
10. Kronik, G., J. Slany, and H. Mosslacher. Comparative value of eight M-mode echocardiographic formulas for determining left ventricular stroke volume. A correlative study with thermodilution

and left ventricular single-plane cineangiography. *Circ* 1979; 60(6): p. 1308-1316.
11. O'Callaghan, M.W., *et al*. Comparison of echocardiographic and autopsy measurements of cardiac dimensions in the horse. *Equine Vet J* 1985; 17(5): p. 361-368.
12. Burggraf, G.W. and J.O. Barker. Left ventricular volume changes after amyle nitrite and nitroglycerine in man as measured by ultrasound. *Circ* 1974; 49: p. 136-143.
13. Tucker, R.L., *et al*. Selected echocardiographic parameters and right sided pressures of the mule, in *Fourth International Conference on Equine Exercise Physiology*. 1994;
14. Blissitt, K.J., Young, L. E., Jones, R. S., Darke, P. G., and Utting, J. Measurement of cardiac output in standing horses by Doppler echocardiography and thermodilution. *Equine Vet J* 1997; 29(1): p. 18-25.
15. Bland, J.M., and Altman, D.G. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986(Feb. 8): p. 307-310.
16. Sahn, D., *et al*. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circ* 1978; 58(6): p. 1072-83.
17. Schwinn, D.A. Cardiac Pharmacology. In: F.G. Estafanous, P.G. Barash, and J.G. Reeves, eds. *Cardiac Anesthesia: Principles and Clinical Practice*. Philadelphia: Lippincott Williams & Wilkins, 2002; p. 1035.
18. Plumb, D.C., *Veterinary Drug Handbook*. 4 ed. 2002, Ames: Iowa State University Press. 960.
19. Comparisons, F.a., *Drug Facts and Comparisons*. 2002, St. Louis: Facts and Comparisons. 2205.
20. MacDonald, E., and Virtanen, R. Review of the pharmacology of medetomidine and detomidine: two chemically similar alpha-2 adrenoreceptor agonists used as veterinary sedatives. In: C.E. Short, ed. *Animal Pain*. New York: Churchill Livingstone181-200, 1992; p. 181-191, 198-199.
21. Sarazan, R.D., *et al*. Cardiovascular effects of detomidine, a new alpha 2-adrenoceptor agonist, in the conscious pony. *J Vet Pharmacol Ther* 1989; 12(4): p. 378-88.

22. Wagner, A.E., Muir, W. W., and Hinchcliff, K. W. Cardiovascular effects of xylazine and detomidine in horses. *Am J Vet Res* 1991; 52(5): p. 651-7.
23. Muir, W.W., Wagner, A.E., and Hinchcliff, K. W. Cardiorespiratory and MAC-reducing effects of alpha-2 adrenoreceptor agonists in horses. In: C.E. Short, ed. *Animal Pain*. New York: Churchill Livingstone, 1992; p. 201-212.
24. Sampson, S.N., Jacobson, R. L., Sande, R. D., Susumi, C. J., Larntz, K. J., Tucker, R. L., and Bayly, W. M. Reproducibility and repeatability of M-mode echocardiographic measurements collected from 25 normal horses. *J Equine Vet Sci* 1999; 19(1): p. 51-57.
25. Young, L.E., and Scott, G. R. Measurement of cardiac function by transthoracic echocardiography: day to day variability and repeatability in normal Thoroughbred horses. *Equine Vet J* 1998; 30(2): p. 117-22.
26. Patteson, M.W., Gibbs, C., Wotton, P.R., and Cripps, P.J. Echocardiographic measurements of cardiac dimensions and indices of cardiac function in normal adult Thoroughbred horses. *Equine Vet J Suppl 19* 1995: p. 18-27.
27. Patteson, M.W., Gibbs, C., Wotton, P.R., and Cripps, P.J. Effects of sedation with detomidine hydrochloride on echocardiographic measurements of cardiac dimensions and indices of cardiac function in horses. *Equine Vet J Suppl 19* 1995: p. 33-37.
28. Marr, C.M., Bright, J. M., Marlin, D.J., Harris, P.A., and Roberts, C.A. Pre- and post-exercise echocardiography in horses performing treadmill exercise in cool and hot/humid conditions, in *Fifth International Conference on Eqine Exercise Physiology*. 1998;
29. Young, L.E. Cardiac responses to training in 2-year-old thoroughbreds: an echocardiographic study. *Equine Vet J Suppl* 1999; 30(10): p. 195-8.
30. Stetz, C.W., Miller, R.G., Kelly, G.E., and Raffin, T.A. Reliability of the thermodilution method in the determination of cardiac output in clinical practice. *Am Rev Respir Dis* 1982; 126: p. 1001-1004.
31. Mantin, R., and Ramsay, J.G. Cardiac output technologies. *Int Anesthesiol Clin* 1996; 34(3): p. 79-107.

32. Davidson, C.J., R.F. Fishman, and R.O. Bonow. Cardiac Catheterization. In: E. Braunwald, ed. *Heart Disease*. Philadelphia: W.B. Saunders Co., 1997; p. 1996.
33. Kriz, N.G. and R.J. Rose. Repeatability of standard transthoracic echocardiographic measurements in horses. *Aust Vet J* 2002; 80(6): p. 362-370.
34. Corley, K.T.T. *Validation of a new method of determining cardiac output in neonatal foals.*, in *Veterinary Medical Sciences*. 2001, Virginia Polytechnic Institute and State University: Leesburg. p. 75.