Chapter 2

Literature Review

2.1 CO Measurement Methods

Introduction

A large number of methods have been devised for measuring, or estimating, CO. There are differences between methods in the assumptions which underlie the measurement theory; understanding of those differences is important in considering use of a particular technique. It is also important to understand what factors may affect measurements made by a particular technique, so that invalid results can be recognized. Methods also differ in their accuracy and repeatability, as well as degree of invasiveness and risk to the subject. This discussion will begin with the less-used methods and progress to those which are more widely accepted.

A. Direct Measurement

Cardiac output can be measured directly by placing a flow meter around the aorta or pulmonary artery[1], but this has the obvious disadvantage of requiring invasive thoracic surgery. Therefore, indirect methods are usually employed.

B. Pulse Contour Analysis

Numerous algorithms have been developed in an attempt to relate arterial pressure waveforms to stroke volume[2-6]. The primary problem with this method of estimating CO is the fact that pulse wave contours are modified as they are transmitted peripherally[7]. Modification factors include variations in arterial compliance, transmission, and reflection. These factors are in turn influenced by age, heart rate, disease states, and vasoactive drugs. Studies comparing pulse contour analysis vs. TD CO measurements have reported correlation coefficients ranging from 0.43 to 0.98[2, 3, 5, 6], using different algorithms and different patient populations. Each new algorithm has been developed empirically, generally by relying on calibration vs. thermodilution. The algorithms developed tend to apply only to a narrowly defined patient population, and frequent recalibration is necessary[2].

In summary, one could say that pulse contour analysis is flawed by being based on algorithms that are somewhat inaccurate. The very number of different algorithms that have been developed for pulse contour analysis supports the difficulty in correctly modeling the arterial system and thus deriving a reliable estimate of CO from such data.

C. Angiocardiography

Ventricular volume in systole and diastole can be calculated from the area and length of the opacified chamber when it is

visualized with single-plane or bi-plane angiocardiographic images of the left ventricle[1][8-13]. End-diastolic volume minus end-systolic volume equals stroke volume (SV), and SV x HR = CO. The inherent inaccuracies of calculating volumes from two-dimensional angiocardiographic images are similar to those encountered with echocardiography (discussed below). In addition, calibration of radiographic to real-life measurements introduces another source of potential error[14]. Complete immobility of the patient during the injection and imaging period is essential. The need for cineangio-cardiographic imaging limits use of this technique to referral institutions, and the health risks associated with radiation and with the contrast solutions used[15] limit the number of times angio-cardiographic measurements can be repeated[16]. Davidson et al[14] stated that angiocardiographic measurements of CO are frequently unreliable, although other investigators report good correlation with other measurement techniques[8-13].

While angiocardiographic measurements could be made on foals with the above limitations in mind, the size of adult horses introduces a number of practical problems[17] which have precluded the use of this technique. Bolus injection of 500 ml or more of contrast material (required to properly opacify the heart) would be extremely difficult. Image intensifying screens would have to be used due to the thickness of the adult equine thorax; finding screens large enough to project the entire cardiac silhouette could

[1] After correction for x-ray distortion.

pose a problem. X-ray scatter as the beam traverses the thorax could also lead to relatively poor quality images. Rapidly repeated exposures of a magnitude sufficient to penetrate the thorax would also be likely to overheat the x-ray machine.

D. Radionuclide Ventriculography

Radionuclide ventriculography (RVG) has largely replaced angiocardiography as a radiological method for CO measurement. A radioisotope such as ^{99m}Tc pertechnetate is injected intravenously; a scintillation camera is then used to visualize the heart, great vessels, and pulmonary vasculature in rapid sequence[18, 19]. Data can either be acquired in a "first pass" study or via a technique known as gated equilibrium radionuclide ventriculography[18-22]. A first pass study acquires radioactive count data from the time of isotope injection until the marker is cleared from the heart, usually about 30 seconds in horses[17]. Because of the limited number of beats available for analysis, very high count rates must be used (ideally > 200,000 counts/sec) in order to obtain as much data as possible[20]. Achieving such high count rates without losing too much spatial resolution requires a fairly sophisticated camera[19, 20].

Gated equilibrium studies divide each cardiac cycle into sequential periods. Data is collected for 200-800 beats[18]; the individual data acquisition periods for each cycle are then synchronized and averaged so that no individual beat information is

retained at the end of the study[20]. One advantage of this technique is that data can be obtained repeatedly over 4-6 hours[19]. However, since an extended period of immobility is required, use of gated equilibrium studies is limited to anesthetized horses[17].

Regardless of which method is used to acquire data, ventricular volumes can be calculated by either geometric or count-proportional methods[20, 21]. Geometric methods are similar to those employed in standard contrast angiocardiography, as described above, and depend on the accuracy of edge detection[21, 22]. Since spatial resolution is lower with first pass studies, use of geometric approaches with those studies are prone to error[20]. When geometric methods are used, interfacing with computerized tomography improves volume estimates over those obtained by planar methods[22]; however, this technology is rarely available for equine research. Some authors report that geometric methods are not well suited for use with gated equilibrium studies because those studies employ the left anterior oblique projection for quantitative measurements[19], which does not allow accurate detection of the long axis length of the LV in humans[21]. A further drawback to geometric methods is that they have to rely on assumptions of the ventricular area-length relationship and mathematical modeling of the shape of the ventricular chamber[21] – weaknesses of these assumptions will be discussed in the section addressing echocardio-graphy.

Count proportional methods are based on the sound theory that the number of radioisotope counts in a chamber is proportional to the chamber volume[20]. However, determining which counts truly originate from the left ventricle is problematic, due to difficulty in defining the correct region of interest, attenuation, background activity, and scattered activity[19, 20]. Scattered activity is affected by camera spatial resolution, the energy discrimination window setting, and patient size[22]. Measurement of attentuation presents the greatest source of error in count-based RVG[19]. Numerous formulas have been devised to try to account for this, but the "constant of proportionality" seems to differ between individual patients[20].

As with most methods, both proponents and detractors of RVG are easy to find. Gerson[22] reports an excellent correlation ($r=0.978$, $p<0.001$) between first pass RVG and conventional invasive methods, but Harbert et al[21] cite a standard error for count-based methods of 10-35 ml and conclude that "since radionuclide measurements of LV dimensions are imprecise, echocardiography better estimates ventricular volume."

Regardless of which method is used for data acquisition and volume calculation, accuracy measurements published for one lab may not apply in another, due to differences in imaging systems as well as methodology. Validation of volumes obtained by RVG against more standard methods therefore appears to be necessary within each individual laboratory[22].

Although radionuclide ventriculography could conceivably be used to measure CO in the horse, no reports of such use have yet been published, to this author's knowledge.

E. Bioimpedance

Use of the bioimpedance method to determine CO has not been reported in horses, but is an interesting approach in humans. Four electrodes are placed on the neck and thorax. The outer two electrodes deliver a small alternating current (1-4 mA at 50-100 kHz)[23] across the thorax. The others measure resulting changes in voltage. According to Ohm's Law, voltage/current = impedance. There is a baseline impedance (termed Z_o) present, as well as a time-varying impedance due to the respiratory and cardiac cycles. Signal processing can filter out the respiratory variation and any motion artifacts, leaving the impedance changes which are due to the cardiac cycle. These changes are primarily due to the volume of blood ejected, with some portion due to reorientation of red blood cells which takes place as a result of high velocity flow within the aorta. The volume of blood ejected (SV) is calculated from the equation[24]:

$$SV = VEPT \times \frac{dZ/dt}{Z_o} \times T$$

Where VEPT = volume of electrically participating tissue (i.e. the thorax), dZ/dt = the first derivative of the change in impedance (delta Z) curve, and T = ventricular ejection time.

Precision of the bioimpedance method appears to be excellent, but when compared with TD, results have only been within 15-20% at best[25]. Some human cardiologists find the technique useful for monitoring trends in CO, while relying on other methods when an accurate quantitative measurement is needed[7].

A review of bioimpedance by the U.S. Office of Health Technology Assessment[23] states that "most investigators have concluded that electrical bioimpedance cannot be regarded as a reliable method for providing absolute values of CO, but that changes in CO can be adequately monitored by EB compared with invasive methods." However, conflicting reports of the accuracy of bioimpedance continue to be published, and its use remains controversial. The American College of Cardiology published an opinion in 1991[23] stating that bioimpedance offered "a very promising method for the noninvasive evaluation of cardiac patients, provided the limitations of the system are fully understood." One year later the National Institutes of Health published their conclusion[23] that bioimpedance "as currently used is not clinically acceptable . . . in specific abnormal populations the discrepancies between bioimpedance and direct methods of CO determinations occur frequently and unpredictably."

F. Fick Method:

One of the earliest methods employed to estimate CO was the Fick method[26]. This is based on the principle that the oxygen consumption of a tissue must equal the blood flow through the tissue times the arterial-venous O_2 difference. Simultaneous measurements are made of: (a) oxygen consumption (by measuring O_2 content of inspired and expired gases over the course of a few minutes), (b) O_2 content of arterial blood, and (c) O_2 content of mixed venous blood. CO is then calculated from the equation:

$$CO = \frac{O_2 \text{ consumption (ml/min)}}{\text{Arterial } O_2 \text{ conc - Venous } O_2 \text{ conc (ml/liter)}}.$$

The reasoning behind this calculation can be illustrated by an example. If the blood leaving the right side of the heart had an O_2 concentration of, for example, 150 ml /liter, and the blood leaving the left side of the heart had an O_2 concentration of 200 ml /liter, one can see that each liter of blood passing through the lungs picks up 50 ml O_2. If 2000 ml O_2 are absorbed into the pulmonary blood each minute, there must be 40 one-liter aliquots of blood passing through the pulmonary circulation each minute; thus a CO of 40 l/min.

The Fick method has the advantage of being relatively non-invasive, but the need for analysis of inspiratory and expiratory gases usually limits its application to situations involving inhalant anesthesia. It is inaccurate at high CO values due to the small arterio-venous O2 difference, and it requires the assumption of

negligible pulmonary shunting. It also requires steady-state hemodynamics during the period of gas collection/analysis[7, 27-30].

CO calculated by the Fick method may vary by up to 10% from direct measurements made with electromagnetic flow meters[14].

G. Dye Dilution Method:

Cardiac output has been successfully measured in horses by dye dilution[31-35]. In this method, a dye such as indocyanine green is injected into the right atrium or a peripheral vein[36]. The dye concentration in the arterial system is then continuously measured by a photodensitometer as it passes through a peripheral artery. The dye concentration rises rapidly to a peak, then declines until recirculation brings about a second rise in concentration. The down-slope of the curve for the dye concentration without recirculation is extrapolated[30, 36]. The average dye concentration integrated over the time taken for first passage equals the area under the curve. If the amount of dye injected is then divided by the area under the curve, it gives the volume of dye-containing blood that must have passed the sampling site per unit time, which equals CO[7, 28].

$$CO = \frac{\text{Amount of indicator injected}}{\int [(\text{Mean dye conc.}) \times (\text{Time taken for first circulation})]}$$

Primary disadvantages of this technique include the need to continuously withdraw arterial blood, and difficulties involved in

preparation and handling of the dye solution[14, 30, 36]. In addition, if washout of the indicator from the injection site is prolonged, such as in a low CO state or with valvular regurgitation, it may result in erroneous extrapolation of the downslope of the curve and thus an incorrect measurement[14, 30]. After several measurements have been made, the baseline level of dye in the circulation begins to increase, making accurate measurements more difficult to obtain with each succeeding injection[28].

The thermodilution technique is based on the same principles as dye dilution and has largely replaced it.

H. Lithium Dilution

Lithium dilution was first described as an indicator dilution method in humans in 1993[37] and in horses in 2000[38]. It is based on the same principles as dye dilution, above, but uses an isotonic solution of lithium chloride (LiCl) as the indicator. A sensor containing a lithium-sensitive electrode is connected to an arterial line, with a small amount of blood (4 ml/min) pumped through it by a peristaltic pump. Voltage across the lithium-selective membrane in the sensor is measured as a bolus of LiCl is injected intravenously. The voltage is related to plasma lithium concentration by the Nernst equation.

Lithium dilution has the advantage of being relatively non-invasive, requiring only arterial and venous catheterization. The small dose of LiCl used has no known pharmacologic effect[39], and

the amount of blood required for sampling is negligible. The equipment needed for this measurement method is less expensive and more portable than that required for other indicator dilution methods[39]. Comparisons of lithium dilution with thermodilution in horses have revealed a strong correlation between the two methods[38, 39]. This appears to be a promising new technique.

I. Doppler Echocardiography

Doppler echocardiography can measure the velocity of blood flow in the aorta, pulmonary artery, or across the aortic or mitral valves. The integrated area under the velocity vs. time curve equals what is known as the stroke distance. Stroke distance times the cross-sectional area of the valve or vessel gives the stroke volume, which can then be multiplied by heart rate to give CO. Thus $CO = \int [d_v d_t \text{ x Area x HR}]$.

The weakest link in the calculation of CO from Doppler velocity data is the measurement of the cross-sectional area of the vessel[40, 41]. Mapping of cross-sectional areas with 2D echocardiography has not been sufficiently reliable[42], so areas are generally obtained by measuring vessel diameter via M-mode or 2D echocardiography, then converting to area by the formula $A = \pi r^2$. Any small errors in diameter measurement are thus squared, and this can lead to significant errors. Another difficulty arises from the fact that the cross-sectional measurement needs to be made in precisely the same location where the Doppler velocity will

be measured. This is very difficult to achieve, leading to another source of potential error.

In spite of these limitations, Doppler echocardiography has become a popular method for measuring CO because of its non-invasive nature and the capability of repeated measurements which it offers. Beat to beat changes in stroke volume can be measured. In man, the technique is considered as accurate as conventional invasive methods[43, 44]. However, application of the technique in the horse presents some special challenges. The aorta has been shown to be the most reliable site for making Doppler measurements of CO in the horse[45-48]. However, the ultrasound beam must be aligned parallel to blood flow in order to obtain accurate measurements[42], and this is difficult to accomplish in horses due to anatomical constraints[41, 45, 49]. For this reason Doppler measurement of CO in the horse is better accomplished through a trans-esophageal window, although to date this has only been achieved in anesthetized horses in a research setting[38, 40, 50-54]. While trans-thoracic measurement can be accomplished in the standing horse, it is technically difficult, requiring several years of practice for experienced clinicians to become proficient at it[2]. The high values for aortic flow velocity in horses may also be beyond the software capabilities of ultrasound machines that have

[2] Luis-Fuentes, V. Personal Communication. College of Veterinary Medicine, University of Missouri, Columbia, Missouri, USA, 1997.

not been specially adapted for this measurement[3][4] . Research by Young and coworkers[55] has shown better repeatability within individual horses for M-mode or 2-D echocardiography than for Doppler measurements.

[3] Young, L.E. Personal Communication. Animal Health Trust, Newmarket, Suffolk, U.K., 1997.

[4] Blissitt, K.J. Personal Communication. Department of Veterinary Clinical Studies, University of Edinburgh, Scotland, 1997.

J. Thermodilution

Thermodilution is an indicator dilution technique, based on the same principles as dye dilution or lithium dilution, discussed above. Cold 5% dextrose or saline is used as the indicator, and the downstream concentration of "cold" is measured by a thermistor-tipped pulmonary artery catheter as the change in temperature over time. CO is calculated from the Stewart-Hamilton equation:

$$CO = \frac{Vol. \times (T_b - T_i)}{\int T\,dt} \times \frac{C_i \times S_i}{C_b \times S_b} \times K$$

where Vol. = volume of injectate, T = temperature, subscripts b and i denote blood and injectate, $\int T\,dt$ = integral of the time x temperature curve, S = specific gravity, C = specific heat, and K = a computation constant that adjusts for the heat gained by the injectate during injection. The computation constant is a function of catheter length, composition, dead space, and injection speed. Weisel et al[56]reported that the computation constant is valid over a wide range of injection speeds, patient temperatures, and catheter insertion distances.

The time-temperature curve needs to correspond to a gamma-variate shape[5], with a smooth, rapid rise to peak followed by a smooth exponential decay back to baseline. (See Fig.2.1.) Examples of curves which do not correspond to this shape are shown in Fig.2.2, and can result from imperfect injection technique[6], wedging

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[5] Mayes, D. Personal Communication. Columbus Instruments, Columbus, OH, USA, 1998.

[6] Poor quality curves can result from inconsistent injection flow rate or an injection time that is too long. In humans, manual injections have been reported

of the pulmonary artery catheter against the vessel wall, thermistor obstruction by clotted blood, low curve amplitude, or other factors[7, 57, 58]. Because the CO computer extrapolates the downslope of the curve based on its expectation of exponential decay, any deviation of the curve from its expected shape will result in significant errors. Each curve must therefore be scrutinized to determine if it meets the criteria for a valid measurement. The Cardiomax CO computer automatically compares each curve with an ideal gamma variate curve and gives an R^2 value to indicate how strongly each curve corresponds to the ideal.

While thermodilution was first proposed in 1954[59], it was seventeen years before its widespread acceptance was made possible by the development of a flow-directed, balloon-tipped, multiple lumen pulmonary artery catheter by Ganz and co-workers[60]. Fegler's early work comparing TD measurements to direct flow measurements[59] found the mean difference between the two techniques to be 4.2% (range 0.2-8.9%), with a correlation coefficient of 0.993. Other flowmeter studies reported correlations of 0.97-1.0[61-63]. Weisel et al[56] found TD to be significantly less variable (mean +/- SD% difference of replicate measurements -3.96 +/- 3.17) than dye dilution (7.03 +/- 6.05). Based on a review of 43

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to be satisfactory as long as they are completed in four seconds or less[102, 87, 61, 77]. Some authors have obtained satisfactory curves from manual injections in horses[86]; however, the larger volumes required in this species make smooth rapid injections difficult to obtain. In addition, manual injection leads to problems with heat gain from handling of the syringes. We were unable to consistently obtain satisfactory curves until we used a gas-powered injector.

studies of CO determination by TD, dye dilution, and the Fick method, Nishikawa and Dohi[64] concluded that TD is more reproducible than dye dilution or Fick, particularly with high or low flows, and that it is "simple, rapid, safe, and accurate." It has the advantage of providing immediate results, and can be repeated numerous times with no need for blood withdrawal. These advantages have combined to make it the industry standard against which new measurement techniques are compared[7, 65, 66]. However, TD can not truly be considered a gold standard[29, 66-71], since it is itself an imperfect indicator of the true CO, and not a direct measurement.

The variability of thermodilution measurements has been widely reported. A review of six reports by Mantin and Ramsay[7] revealed coefficients of variability (CVs) from 3-8%, and in 16 reports reviewed by Nishikawa and Dohi[64], CVs ranged from 4-7.5%. Stetz et al[66]reviewed nine studies which evaluated reproducibility of thermodilution determination. (They define a "determination" as the average of a variable number of thermodilution "measurements".) They found that the SEM% (SEM/avg CO) ranged from 2-5% when three measurements were used per determination, and from 3.5-8.7% when determinations were based on a single measurement. This is the statistical basis for the widely accepted recommendation to use the mean of three measurements for a single CO determination.

When three measurements are used per determination, determinations may need to be different by 6-15% in order to be 95% confident that the determinations indicate a significant change[66].

Sources of Error in Thermodilution Measurements

i. Injectate Volume :

If the actual volume injected does not correspond to what is entered into the CO computer, the computer will use incorrect values in the equation used to calculate CO. Small errors in syringe filling, or small leaks, will produce a larger percent error when smaller volume doses are used. Levett and Replogle[72] showed an average error of 1.4% in filling a 5 ml plastic syringe, when compared by weight of the syringe.

Another potential source of volume error is the dead space within the injection catheter. This is equal to 0.86 ml for a commercial 7.5 French catheter[7]. This amount of dead space is a known variable and is adjusted for in the computation constant. There is thus no need to pre-fill the injection catheter with iced solution immediately before an injection, unless a custom CO computer is used which does not adjust for this dead space. Jansen[65] cited four studies[73-76] that found no significant difference when alternate catheter lumens (including a separate injection catheter in the RA) were used for injection.

Assuming that the actual volume injected does correspond to the amount used in the computer calculation, we also have to assume that the injection of the indicator does not affect the measured flow. Early studies by Fronek and Ganz[77] did find increased flow with injection in the region of the thermistor, but Levett and Replogle[72] reported that the 10 ml dose most commonly used in humans is not believed to alter flow. Alteration of flow is less of a concern in horses, as a 60 ml injectate dose in the average horse represents only half the proportion of SV as does a 10 ml dose in the average human (0.06 SV vs 0.125 SV).

ii. Injectate Temperature :

As with volume, if the actual temperature of the injectate does not match the temperature entered into the CO computer, incorrect values will be used to calculate CO. This may occur if there is a difference between what the temperature probe measures in the ice bath and the actual temperature of the injectate as it enters the horse. This can occur due to failure of the solution in the syringes to fully equilibrate to the ice bath temperature, warming of the injectate in the syringes after they are removed from the ice bath, or heat gained as the injectate travels between the injector and the animal.

Failure of solution in syringes to fully equilibrate: Dunlop et al[78] found that ice bath and injectate reservoir (injectate prior to being loaded into syringes) differed by $1^{0}C$ or less after a 12 hour

equilibration period. Filling of syringes from the reservoir resulted in a 1-1.5^{o}C heat gain in spite of putting the syringes back into the ice bath for an additional 30-60 minutes.

Warming of injectate in syringes after removal from ice bath: Nishikawa and Dohi[64] reported that syringes of iced injectate held in a warm hand gained 1^{o}C in 13 seconds. Dunlop et al[78] found that loading of syringes into the injector and waiting 45 seconds or less before injection resulted in a 1^{o}C temperature gain. Despite these concerns, Woods et al[79] reported that injectate warming was probably not significant if the time between removal from the ice bath and injection was less than 30 seconds[80, 81].

Heat gain as injectate travels between injector and animal: Each 1^{o}C of heat gain could result in a 2.86% overestimation of C.O.[64]. For this reason, some authors recommend the use of a second thermistor placed to measure injectate temperature as it enters the subject[38, 64, 82-84], although Taylor and Sheffler[28] found that this did not make any significant difference in the amount of error when TD measurements were compared to directly measured flows in vitro. Forrester et al[61] reported that the computation constant was just as effective as a second thermistor for determining the degree of injectate warming. Some studies have minimized temperature gain by pre-filling the RV catheter with iced solution[85], but this partially confounds the effect of the computation constant. Muir et al[86] reported that with the large injectate volumes used in horses, the volume of warmed fluid

between injector and thermistor is relatively small and introduces minimal error.

Iced vs room-temperature injectate: Greater changes in temperature during preparation for injection can be expected with iced versus room-temperature injectate, which has led many investigators to use the latter[66, 87-92]. There are several other drawbacks to iced injectate which shed a favorable light on such a choice. Iced solutions may affect the heart and other cardiopulmonary variables[88]. Numerous authors have found transient slowing of the heart rate and decreased right ventricular output after injection of iced solution[93-98]. The magnitude of these changes was shown to be dependent on the temperature and volume of the cold injectate[95]. The prime advantage of iced injectate over room-temperature solutions is that it delivers a larger negative caloric dose, thus improving the signal to noise ratio[99]. This is especially important in the horse, with its relatively greater blood flow. Muir et al[86] found that room-temperature injectate gave unacceptably variable results in horses, presumably because of an inadequate signal-to-noise ratio. Even in humans, room-temperature injectate is reported to not perform well at flows in excess of 9 l/min[28]. Woog and McWilliam[100] suggest that the use of room-temperature injectate may necessitate the use of larger volumes of indicator, which would be difficult to accomplish in horses. However, Blissitt et al[45] and Young et al[40] both

achieved satisfactory results in horses with 45 ml of room-temperature injectate.

Review of studies by several authors[81, 87, 101-103] suggests that the improved signal-to-noise ratio may outweigh the disadvantages of iced injectate. These studies found that CO determinations were generally more reproducible with iced rather than room temperature injectate, and with larger volumes. Accuracy appeared to be improved by increased injectate volume, while the effects of temperature on accuracy were not clear.

iii. Computation :

Inaccuracies in any of the variables entered into the Stewart-Hamilton equation will result in errors. Two possible sources of error which have not yet been addressed are the specific heat and gravity of the injectate solution and of the blood. Before beginning thermodilution measurements, one needs to know which injectate characteristics (5% dextrose or saline) are programmed into the CO computer's computation. Substitution of one fluid for the other will result in an error of approximately 2%[72].

The specific gravity and specific heat of blood, which also enter into the computation, are somewhat dependent on hematocrit. According to Nishikawa and Dohi[64], a change in hematocrit from 42% to 30% introduces an error of 1.5% (all other factors being equal).

iv. Innacurate Time x Temperature Curves :

As previously mentioned, accurate computation of the area under the time x temperature curve is dependent on the curve conforming to the characteristic gamma variate shape. However, even when this requirement is fulfilled, there are other factors which can introduce errors in the curve measurement. The primary source of concern is drift in the baseline pulmonary artery temperature. Blood temperature in the pulmonary artery is known to vary cyclically with respiration. Variations are reported to be on the order of .01-.1°C[7, 56, 64, 104][[83]. Since the temperature change induced from a bolus of iced injectate may only be on the order of .05°C[7], this creates a significant amount of background noise. Possible causes of this cyclic variation include cooling of the right ventricle by overlying lung[7], changes in the amount of relative venous return from the superior versus inferior vena cava, and changes in total venous return with respiration[7, 57, 64, 72]. Woods et al[79]have shown that ignoring the phase of respiration with respect to timing of thermodilution measurements can potentially introduce significant error - they found that successive CO measurements made at the same phase of the respiratory cycle were within 6.7% of each other, while measurements taken a half-cycle out of phase varied by as much as 14%. The problem of PA temperature fluctuations has been resolved by programming most

[7]The degree of this cooling may depend on the temperature and humidity of the inspired air.[57, 105]

commercial CO computers to average the blood temperature for a short period before injection[57, 105]. While this does not improve accuracy, it does improve reproducibility[57].

However, because respiration causes real changes in venous return which affect CO, the following question still has to be addressed: Which phase of the respiratory cycle will yield measurements that most closely approximate the average CO? Unfortunately the answer to this question varies between patients, as well as within individuals, depending on volume status, mode of ventilation, respiratory rate, tidal volume, and the use of positive end-expiratory pressure[65]. For this reason some authors recommend basing each CO determination on the average of measurements spaced equally throughout the respiratory cycle[64, 106-110]. Others recommend making all measurements at the same phase of respiration[66, 72, 79, 106, 111-113], although this will result in under or over-estimation of the average, depending on which phase of the respiratory cycle is selected. Jansen et al[109] found that always measuring at end-expiration caused CO to be over-estimated by 1.05-1.5 times the average value.

Inaccurate time-temperature curves can also result from insufficient signal strength. This is a particular problem in horses, with their relatively greater blood flow. Muir et al[86] reported that injectate volumes of less than 30 ml in the horse gave highly variable results, presumably due to insufficient signal strength.

Most reports in horses have used injectate volumes of 35-50 ml[38, 40, 45, 78, 85, 86, 114].

Another potential source of inaccuracy in the time-temperature curve is an inappropriate time interval between sequential measurements. The interval must be long enough for the injection catheter and its fluid to have re-warmed to pre-injection temperature, and short enough to hopefully avoid any real change in average CO. Intervals ranging from 20 to 180 seconds have been reported to be acceptable in people[59, 60, 115].

v. Low Flow States :

With low flow states, time to appearance of the TD curve is delayed, and its decay is prolonged. This may result in excessive heat loss between the RA injection site and the thermistor, leading to over-estimation of CO. In addition, "recirculation"[8] of indicator may occur before the computer acquisition of data is completed. These factors may cause CO values obtained during low flow states to be more variable[57], but TD has still been shown to be accurate at COs of less than 1-2 liters/minute both in vitro[116, 117] and in animal studies[116, 118].

[8]This is not true recirculation of indicator, but continued cooling of the PA due to residual injectate remaining in the lumen of the RA catheter[7, 105].

vi. Inadequate Mixing of Injectate in the Bloodstream :

Inadequate mixing of injectate in the bloodstream will result in erroneous measurements[105]. It was established in early studies[119, 120]that adequate mixing does normally occur, provided that injection is made rapidly. Muir et al[86] found that injection of 50 ml or more in horses yielded highly variable results, presumably due to the inability of manual injection to deliver the entire bolus fast enough to obtain complete mixing. Inadequate mixing might also be a concern in the case of shunts, as discussed below.

vii. Intra or Extra-Cardiac Shunts :

True recirculation of indicator will occur with left-to-right intracardiac shunts, interrupting the exponential downslope of the TD curve. Provided that adequate mixing of injectate with the bloodstream occurs prior to shunting, mathematical techniques can be used to calculate the portion of the measured CO which is due to the shunt[121, 122]. Right-to-left shunts will result in some indicator reaching the left side of the heart prior to passing the thermistor; this results in over-estimation of CO[123]. A different set of mathematical techniques can be applied to again calculate the portion of the measured CO which is due to the shunt[124, 125].

viii. Valvular Regurgitation :

Tricuspid or pulmonic regurgitation are generally recognized as being incompatible with accurate TD determinations[64, 65].

ix. Rapid Infusions of IV Fluids :

Rapid infusions of IV fluids can alter the baseline PA temperature. If this is occurring at the same time that TD measurements are being made, errors can result. Rapid infusions need to be discontinued at least 30 seconds prior to TD measurement or else maintained at a constant rate[126].

Continuous Thermodilution

A variation of the TD technique has been developed in which the RA portion of the TD catheter contains a small heating filament. The filament cycles on and off, thereby delivering repeated small doses of heat which are detected by the PA thermistor. Whereas bolus TD creates a temperature change on the order of .05°C in the PA, the heat delivered by such a modified PA catheter creates temperature changes on the order of .007°C[7]. Such a small thermal signal is easily overwhelmed by the baseline noise of cyclic PA temperature changes. Yelderman [127-129] solved this problem with the following stochastic system identification technique: the heating filament is cycled on and off in a pseudo-random pattern. The on-off sequence is recorded as well as the PA temperature fluctuations. A computer then cross-correlates a time x temperature

curve similar to that for bolus TD. The nature of the calculations necessitates approximately five minutes of computer data acquisition before a cardiac output can be calculated. After the initial five minutes, the CO measurement is updated every thirty seconds, but the displayed CO value actually represents an average over the preceding 3-7 minutes[7]. Both in vitro[129] and in vivo[128, 130] studies have shown continuous CO by this technique to be highly accurate, and several studies have also reported good reproducibility[129, 130]. Further refinements to the software continue to be developed[131]. This seems like a promising technique; however, to date the necessary equipment has not been modified for equine use.

Risks Associated With Cardiac Catheterization and Thermodilution Measurements

Determination of CO by TD is generally regarded as a safe, although invasive, procedure. The registry of the Society for Cardiac Angiography reported[132] that among 58,332 patients catheterized in 1990, procedure-related mortality was 0.08%, with major complications occurring in 1.5%. The incidence of major complications could be further subdivided into 0.3% for patients without high-risk factors (congestive heart failure, multi-vessel coronary artery disease, renal insufficiency), and 2.5% for the high-risk group [133]. Major complications which occurred in a study of

1609 cases [134] included stroke (0.1%), cardiac perforation (0.05%), arrhythmias requiring countershock or temporary pacemaker (0.3%), anaphylaxis (0.1%), and death(0.12%). Minor complications included transient neurologic events (0.1%), local vascular problems (1.6%), vasovagal reactions (2.1%), and hives (2.0%). These complication rates apply to people with sub-optimal cardiac function exposed to irritating contrast agents and undergoing procedures more invasive than simple right heart catheterization. Healthy individuals undergoing right-sided catheterization for TD should experience less risk.

Of 25 reports of TD and cardiac catheterization in large animals which were reviewed[38, 40, 45, 46, 78, 85, 86, 114, 135-151]], only four mentioned complications[138, 139, 145, 151]. Bueno et al[138] reported transient weakness, ataxia, and recumbency associated with right heart catheterization in 3/19 horses. Amory et al[145] experienced adverse reactions to right heart catheterization in 7/21 young calves, and Reeves and Leathers[139] reported weakness and pulmonary hypertension in 25% of neonatal calves, although older calves were unaffected. Schlipf et al[151] performed repeated thermodilution measurements on 9 horses which were anesthetized for a separate experiment. The horses were necropsied within one hour after the end of anesthesia. They observed lesions in the right atrium in 8 horses, right ventricle in 7, pulmonic valve in 8, and pumonary artery in 3. Lesions were described as flat fibrinous deposits attached to the endocardial/

endothelial surface. In the right atrium, they also observed circular areas of endocardial ulceration and areas of sub-endocardial hemorrhage. A single thrombus was also observed in the pulmonary artery of one horse. Since similar lesions were not observed in the left side of the heart, they concluded that the traumatic lesions resulted from cardiac catheterization and cardiac output determination.

K. M-Mode and Two-Dimensional Echocardiography

Calculation of ventricular volumes from two-dimensional or one-dimensional (M-mode) echocardiographic images depends on (1) the accuracy of the original measurements (chamber diameter, area, and/or length) and (2) how closely the true shape of the ventricular cavity conforms to the mathematical formulas used to represent it.

Measurement Accuracy:

Early work with echocardiography in patients with normal left ventricular volume (LVV) showed significant correlations between angiographically-measured LVV and echocardiographic measurements of left ventricular internal diameter (LVID) [16, 152]. This inspired numerous efforts to model a mathematical relationship by which LVID or another echocardiographic dimension could predict LVV. Before considering the validity of such mathematical models, however, we should consider the accuracy of the echocardiographic measurements themselves. Bhatt et al[152] concluded that "end-diastolic dimensions can be determined accurately (by echocardiography) in patients with normal LVV." Voros et al[153] showed that in vivo two-dimensional echocardiographic (2DE) measurements in horses corresponded to in vitro measurements on the same hearts and to direct post-mortem measurements. However, numerous authors have noted that

scrupulous technique must be adhered to in order for echocardiographic measurements to be accurate.

The specific details of technique which must be attended to vary somewhat with the echocardiographic measurement being made (2DE vs M-mode, diameter vs area, etc.); our discussion will address M-mode measure-ment of LVID. A standard 2DE right parasternal short axis view at the level of the chordae tendinae is obtained. The mitral valve and papillary muscles should not be visible when the correct view is obtained. When the LV appears as close to circular as possible (indicating that the image plane is perpendicular to the long axis of the ventricle), the M-mode cursor is directed across the major axis of the ventricle and the image is switched to M-mode. Ensuring that the ultrasound beam strikes the tissues at right angles will produce the strongest artifact-free echoes. Septal echoes are normally easy to identify, but correct discernment of the endocardial echoes of the left ventricular free wall (LVFW) requires careful adjustment of the gain and reject controls in addition to proper beam alignment[154].

Measurements of LVID should be made from the leading edge of the IVS echoes to leading edge of the LVFW echoes, according to the recommendations of the American Society of Echocardio-graphy[155]. This enhances accuracy because the width of the echoes may vary from one instrument to another, and may even vary with the gain settings. The American Society of Echocardio-graphy also recommends that M-mode systolic measurements be

taken at the moment of peak downward excursion of the interventricular septum (IVS), and diastolic measurements be made coincident with the Q wave[155]. Some authors have used onset of the downward motions of the IVS as the moment for diastolic measurements, and have reported this method to be satisfactory[154, 156-160]. In fact, O'Callaghan[154] reported that in horses, atrial contraction resulted in obvious wall movement prior to the Q wave, which would make measurement at the onset of IVS motion more representative of true end-diastole. This method may also be useful when a simultaneous ECG recording can not be obtained, as in the case of a standing horse which resists restraint.

Oblique alignment of the ultrasound beam can cause a false appearance of exaggerated wall thickness. Apparent wall thickness can also be increased if the beam passes through the papillary muscle as a result of vertical misalignment or poor angulation. If the cursor is placed too close to the base of the IVS, the M-mode image will show very little movement of the septal wall[161].

Uehara et al[158] found that the most significant causes of error in echocardiographic measurements were (1) failure to obtain the most circular depiction of the left ventricular (LV) cross-section, and (2) improper identification of the endocardial borders. The subjectivity inherent in proper identification of the endocardial borders is supported by the analysis of Felner et al[162]. Felner and coworkers also found that subject position systematically influenced the measurement of RVID. It is unknown how variations in subject

position affect measurements in horses (this could be especially important in standing horses due to movement).

Mathematical Models of Ventricular Volume:

2DE Models :

2DE measurements of LV long and short axes and/or cross-sectional areas can be combined in various ways in order to estimate ventricular volume. The simplest method is a single short-axis measurement of chamber diameter, which is then converted to a volume by any of a number of different mathematical models. Accuracy can be increased by also measuring the long axis when possible. Alternatively, the minor axis can be calculated from a measurement of cross-sectional area (the "area-length method"). However, in the horse, the long axis length of the LV is often impossible to measure accurately[163] because the cardiac apex is covered by the sternum[153, 164]. Voros et al[164] used chordae tendinae length as an index of total anatomical length in necropsied equine hearts; however, application of their techniques by this author in the living horse failed to produce believable volume estimates[9]. Lord and Croft[163] derived the average ratio of long axis length to cross-sectional external diameter in 30 necropsied equine hearts and applied this to various mathematical models. They found that modeling the LV as an ellipse yielded an R^2 value equal to that of more complicated formulas (R^2 = 94.3) without any

[9] Moore, D.P. Unpublished research, 1997.

increase in the variability of measurements, when the volume of the ellipse was calculated from cross-sectional area. Such a measurement was superior to volume calculation from chamber diameter in their study

2DE vs M-Mode :

In spite of Lord and Croft's findings, M-mode continues to be popular for volume determination for several reasons. It is easier to determine the proper moment when systolic and diastolic measurements should be made with M-mode. It is also more convenient, as measurements can be made directly on-line without needing to use cine-recall or video recordings. M-mode also offers superior resolution of endocardial surfaces[42, 154, 165, 166]. Since improper identification of the borders of the ventricular walls has been identified as one of the two most significant factors leading to measurement errors[158], this advantage is highly significant. Woythaler et al[167] found M-mode estimates of LV mass to be superior to 2DE methods, and other studies have suggested that clinical results with M-mode may be more satisfactory than with 2DE[165, 166].

M-Mode Models :

M-mode dimensions can be incorporated into various mathematical formulas in order to estimate volume. All of the formulas assume that the measured LVID approximates the true

short axis, and that the LV wall contracts uniformly. The assumption of uniform contraction of the LV wall is often difficult to satisfy in humans, but is rarely a problem in the horse. The greatest difficulty with M-mode measurements is that the path of the M-mode cursor across the LV rarely corresponds to the true minor axis[42], although it does approximate it [168, 169]. Furthermore, the relationship between the M-mode diameter measurement and the true minor dimension varies from patient to patient, due to differences in the 'view' through the available echocardiographic windows[42]. This source of variability in echocardiographic measurements has been studied in humans[42]: Among 50 adults, the 2DE LV minor axis and the M-mode dimension were within 3mm of each other in 30% of the subjects. The two measurements differed by 4-6mm in another 30%, and in 40% the difference was greater than 6 mm. (With an average human LVID of 4.6cm[42] this represents significant variability.) Although the position of the M-mode cursor is routinely oriented using the 2DE image, this does not overcome the difficulty, as the proper acoustic window for obtaining a true minor axis measurement may simply be unavailable in a given individual.

Another obstacle to accurate M-mode measurements is that as the base of the heart moves toward the apex during systole, the position of the minor axis changes, and the M-mode beam actually transects a different portion of the IVS and LVFW[42, 152]. This

explains the greater variability of systolic vs diastolic measurements which has been reported very consistently.

In spite of these limitations, success with use of M-mode dimensions in calculations of LVV has been reported in humans.

i. Cube Formula : Early attempts to correlate M-mode echocardiographic measurements of LV diameter with angiographically-determined LV volumes found the relationship was strongest when the diameter was cubed[16, 168-170]. The use of such a mathematical formula ($LVV = LVID^3$) assumes that the ventricular cavity is shaped like a prolate ellipse, with two equal short axes which are also equal to one half of the long axis. The assumption about the geometrical shape of the LV cavity is usually correct in normal humans[11-13, 42, 171], but is not as accurate in the horse, in whom the chamber assumes a more conical shape[172][10].

The majority of reports of M-mode derived LV volumes in horses have utilized the cube formula[173-177], although its accuracy in the horse has not been validated against established methods[55].

ii. Teichholz Formula : Teichholz et al[178] investigated the relationship between the long (L) and short axes (D) of the LV, which had been assumed to be L = 2D. They found that while this

[10] All the mathematical models of LV shape discussed here are less accurate in the enlarged heart, in which the geometric shape is altered.

relationship held for normal-sized ventricles, in small ventricles L approached 3D, while in large ventricles L was closer to 0.77D. Thus while use of the cube formula gave good correlation between echocardiographic and angiographic volume measurements, the measurements were not equal and needed to be related by use of an empirically determined regression equation. By substituting the relationship they found between L and D ($1/(L/D) = 0.075D + 0.18$) in the standard angiographic volume formula $V = \pi/6D^2L$, they derived a "corrected" formula of $V = (7.0 / 2.4 + D) (D^3)$ which gave a linear relationship which was not significantly different from the line of identity of volumes.

Inspection of the above formula reveals that if $D > 4.6$ cm, the volume calculated by Teichholz's "corrected" formula will be less than that calculated by the cube formula, while if $D < 4.6$ cm the opposite will be true. While this satisfied Teichholz's objective of correcting for the different L/D ratios in hearts which were larger or smaller than normal, it is not surprising when it underestimates volumes in the equine heart, in which the average normal D (mean of systoic and diastolic measurements) is approximately 9.25 cm[161]. It is also worth noting that the numerical value of 7.0 / 2.4 in the Teichholz formula was determined empirically by comparison to angiographically-determined volumes in patients with various cardiac diagnoses. A different numerical value might be more appropriate in the normal population. It would also be

interesting to derive formulas for systole and diastole separately and see if that improved accuracy.

Some reports of M-mode derived LV volumes in horses have utilized the Teichholz formula[173, 177].

iii. *Other Formulas* : Because of the drawbacks of the cube and Teichholz formulas, numerous investigators have sought to determine more accurate mathematical models of the LV cavity. Kronik et al[160] compared M-mode derived LV volumes determined by 8 different mathematical formulas[178,][168, 170, 179-182] [183]with subsequent TD and angiographic measurements. They found the strongest correlation between measurements using the Teichholz formula (r = 0.86 with TD, 0.74 with angiography); the cube formula was the next best with r = 0.75 for TD and 0.64 for angiography. These authors reported good correlation and no significant systematic difference between M-mode derived SV and SV as measured by TD, although the standard errors were relatively high. When compared with SV determined by single-plane cineangiography, use of echocardiographic measurements in the Teichholz formula gave comparable accuracy.

Summary

Many indirect methods of measuring (estimating) CO have been devised because direct measurement is extremely invasive. Thermodilution remains the standard method in human medicine.

A search continues, however, for a non-invasive substitute for TD, because (1) the invasiveness of the TD procedure exposes subjects to some degree of risk and also imposes practical limits on its use, and (2) it is time-consuming, technically demanding, and requires specialized equipment. Doppler echocardiography has become increasingly popular in human medicine, but its use in the horse is more difficult, and Doppler measurements have been shown to be more variable than measurements made with M-mode or 2-D echocardiography in horses. Echocardiography would be an attractive alternative to TD if it could be shown to have adequate reliability, because CO can be estimated from 2-D or M-mode images relatively quickly, easily, and noninvasively. M-mode is easier to use for volume determinations, and has better temporal resolution and visual resolution of the endocardial borders. However, to this author's knowledge, comparisons of CO values determined by M-mode echocardiography have not been compared with values obtained by a standard method.

2.2 Pharmacology of Drugs Used in This Experiment

Introduction

Various drugs can be used to alter cardiac output, via a combination of inotropic and chronotropic effects or changes in preload or afterload. Investigators have used several different pharmacological protocols to induce a range of cardiac outputs in animals for the purpose of experimental studies[38, 40, 45, 137, 184, 185]. Human stress tests also employ pharmacologic agents to alter CO when exercise is inadvisable[186]. This study sought to utilize the pharmacological protocol of Blissitt et al[45], since its use had proved sufficient for comparison of CO between the methods of TD and Doppler echocardiography. This analysis addresses the pharmacology of the drugs used in this experiment and reviews the effects others have reported from their use.

A. Dopamine

Dopamine is an endogenous catecholamine which is the immediate precursor to norepinephrine[187]. It is a direct agonist of α_1, α_2, pre and post-synaptic dopaminergic, and B_1 and B_2 receptors[187-189]; relative activity at the different receptor sites varies with dose (Table 2.1)[189]. It also exerts indirect effects via increasing levels of norepinephrine[187, 189-191]. Norepinephrine is increased via (1) hydroxylation of dopamine to form more norepinephrine[187, 188], (2) release of norepinephrine from presynaptic storage vesicles, and (3)inhibition of norepinephrine

reuptake at nerve terminals[187]. The beta receptor activity causes a direct positive inotropic effect[192] and increased automaticity within the heart muscle, with little increase in heart rate[191]. Activation of dopamine receptors causes visceral vasodilation and increased renal blood flow[191]. Dopamine is also active as a neurotransmitter within the central nervous system, but, as intravenously administered dopamine can not cross the blood-brain barrier, no CNS effects are seen[187].

At the doses used in this experiment, dopamine acts primarily as a beta adrenergic agonist with action at both B_1 and B_2 receptors[187, 189] Dopaminergic effects predominate at very low doses of 0.5-2 ug/kg/min[187]. At high doses (>10 ug/kg/min), the dopaminergic effects are over-ridden by alpha-adrenergic agonist activity, causing increased peripheral resistance and decreased renal blood flow[187, 189].

Onset of action is reported to be within 5 minutes of IV administration. Due to a short half-life (approximately 2 min.), drug activity ceases within 10 minutes after IV infusion has stopped[191]. It is rapidly metabolized to inactive compounds by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) in the kidney, liver, and plasma[187].

Expected effects at dose rates between 2 and 10 ug/kg/min, as reported in the pharmacological literature, include increased CO, no change or slight increase in systolic blood pressure (BP), decreased diastolic BP, and no change or slight decrease in mean BP[191].

These effects correspond with those reported for halothane-anesthetized horses by Swanson et al[188] with the exception of diastolic pressure, which was unchanged at 5 ug/kg/min and increased at 10 ug/kg/min in their report.

Possible adverse effects include ectopic beats, tachycardia, hypo- or hypertension, dyspnea, and vasoconstriction[191]. Dopamine is contraindicated in patients with pheochromocytoma, ventricular fibrillation, and tachyarrhythmias[191]. Halothane has been reported to sensitize the myocardium to the effects of catecholamines, making ventricular arrhythmias more likely when dopamine is administered to halothane-anesthetized animals[191]. Robertson et al[190] reported that, in halothane-anesthetized horses, 1/6 developed arrhythmia at a dose rate of 5 ug/kg/min; at 10 ug/kg/min 4/7 developed arrhythmias. In the event of adverse effects, treatment consists of discontinuance of the drug; due to the short half-life of dopamine, detrimental effects are usually abolished quickly[192].

Reports on the effects of dopamine in conscious horses have not been found. Dopamine infusions of 5 ug/kg/min in halothane-anesthetized horses in lateral recumbency have produced CO increases of approximately 50-58%[184, 188]. A similar dose resulted in an approximate 17% increase in CO in halothane-anesthetized ponies in dorsal recumbency[135]. These results may have been affected by previous administration of lower doses of dopamine in each experiment.

Responses to the administration of dopamine depend on the relative contribution of its actions at the various adrenergic receptors, which have differing and sometimes counteracting effects (Table 2.2). Both Robertson et al[190] and Swanson et al[188] 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. Swanson et al[188] found that its inotropic effects were less potent than those of dobutamine, possibly because responses to it are more variable. In human cardiovascular anesthesia, the primary benefit of dopamine is believed to be its low-dose dopaminergic effects, while other, more potent agents are relied upon for inotropic effects[189].

B. Dobutamine

Dobutamine is a synthetic B agonist which is structurally related to dopamine[187]. Its activity is primarily directed at B_1 receptors, although at therapeutic doses it also has mild B_2 and α_1 effects (Table 2.1)[188, 192]. Unlike dopamine, it does not cause increases in norepinephrine levels[192]. Dobutamine's activity results primarily in increased myocardial contractility, although it also has mild chronotropic effects[187, 191, 192]. It also produces mild vasodilation and a mildly increased propensity for arrhythmias[191].

Onset of action occurs within 2 minutes of IV administration and peaks after 10 minutes[191, 192]. Dobutamine's half-life is

approximately 2 minutes, as it is rapidly metabolized by glucuronic acid in the liver and other tissues[187, 192].

Expected effects at dose rates between 2 and 10 ug/kg/min, as reported in the pharmacological literature[191], include increased CO, and no change or slight increase in BP and heart rate. Swanson et al[188] found significant increases in systolic, diastolic, and mean arterial pressure and decreased HR at dose rates of 3 and 5 ug/kg/min in halothane-anesthetized horses. The decreased HR was believed to be a result of increased parasympathetic tone in response to the increased arterial pressure, which over-rode the positive chronotropic effects of B_1 receptor activation.

Possible adverse effects reported in the pharmacological literature [191]include ectopic beats and increases in HR and BP. Rarely, dyspnea might be observed. Because it can increase A-V conduction, it should not be used in patients with atrial fibrillation without prior digitalization[191]. Use of halothane with dobutamine may result in increased incidence of ventricular arrhythmias[192]. Swanson et al[188] noted arrhythmias in 1/7 halothane-anesthetized horses receiving 3 ug/kg/min dobutamine, and 1/7 at a dose rate of 5 ug/kg/min. When dose rates exceeded 10 ug/kg/min, supraventricular and ventricular arrhythmias were "frequently" observed[11]. If adverse effects do occur, they are

[11] Muir, W.W., Ohio State University, College of Veterinary Medicine, Unpublished observations, 1983.

usually relieved quickly by discontinuation of the drug, since its half life is so short[192].

Reported CO responses to dobutamine infusions of 4-5 ug/kg/min in halothane-anesthetized horses have been variable, ranging from none (until after 40 min. of continuous infusion)[52] to increases of 151% [184] and 203%[135] over baseline. Increases in the range of 50%[188] seem to be what is usually expected. In standing horses, Hinchcliff et al[137] reported a 6% increase in CO in response to dobutamine at 5 ug/kg/min.

C. Detomidine

Detomidine is an α_2 adrenergic agonist which acts primarily as a sedative/analgesic[191]. It also causes skeletal muscle relaxation through centrally-mediated mechanisms[191]. Expected effects reported in the pharmacological literature[191], include initial (within 15 seconds)[193] increases in blood pressure and total peripheral resistance, followed by a longer period of hypotension[191]. Duration of the hypertensive response is dose-dependent[193]. There is a negative chronotropic effect, with decreased A-V conduction which results in 2nd degree A-V bock in some animals. Cardiac output may be decreased by up to 40%. At high doses, respiratory depression with decreased tidal volume and respiratory rates can occur. Thermoregulation is depressed by detomidine, and hypo- or hyperthermia can occur, depending on the ambient temperature. Clinically insignificant reponses which

may be seen include sweating, salivation, muscle tremors, piloerection, increased blood glucose, and polyuria.

Within the recommended dose range, the primary adverse effects of detomidine are bradycardia and heart block[191]. The degree of bradycardia is dose dependent[193]. Bradycardia appears to be mediated primarily by a baroreceptor reflex to hypertension [193], which results from activation of post-synaptic α_1 adrenergic receptors. Numerous authors have also suggested that decreased sympathetic output from the central nervous system plays a supplemental role in the development of bradycardia[194, 195].

Half-life of intravenously administered detomidine is 72 minutes; elimination is primarily by hepatic hydroxylation[194].

Effects of a 10 ug/kg dose of detomidine in conscious horses have been reported by several authors. Cardiac output was decreased by 35.6% from baseline at 5 min. and by 34.1% at 15 min[196]. By 30 min. the decrease had lessened to 21.0%. Peak ventricular pressure was increased in a dose-dependent manner for 10 minutes, with an increase of 55% in response to 10 ug/kg[193]. Left ventricular end-diastolic pressure was also increased (within 1 minute of administration of 10 ug/kg); increased pressure persisted for 1-60 minutes depending on the dose[193]. Systemic vascular resistance was increased by 75.5% within 5 minutes; the increase persisted for 30 minutes[196]. DP/dt_{max} was decreased by approximately 24% for periods ranging from 30[196] to 90 minutes[197]. Nollett et al[197] noted that the decrease in DP/dt_{max} persisted for

longer than the bradycardia. Bradycardia was greatest at 1 minute after a dose of 10 ug/kg in conscious ponies (18-25 bpm)[193, 197], and had recovered to approximately 60% of baseline values by 5 minutes[193]. Significant bradycardia persisted for 45-120 minutes[193, 196]. Wagner et al[196] reported that 24% of conscious horses developed 2nd-degree AV block in response to a 10 ug/kg dose.

Effects of constant-dose detomidine infusion in halothane-anesthetized horses have been reported by several investigators [198, 199]. Effects of a bolus dose of 80 ug/kg in halothane-anesthetized horses have also been reported [194, 200]. Unfortunately there is not enough published information about plasma detomidine levels in response to varying bolus doses to directly compare these results to those obtained with bolus doses. Muir et al [195] 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%, right atrial pressure increased by 16 and 15%, and mean arterial pressure decreased by 12 and 9%. All hemodynamic variables had returned to baseline levels by 60 minutes.

D. Butorphanol

Butorphanol is a synthetic opiate with agonist-antagonist activity[201]. It acts primarily at kappa and sigma receptors and in the limbic system. In addition to its analgesic effects, butorphanol has significant anti-tussive properties in some species[202]. It can cause CNS excitation in horses, though usually only at high doses[202]. It is reported[191] to cause mild decreases in BP; hypotension together with the increased parasympathetic tone elicited by butorphanol can result in decreased HR. Sedation and ataxia are common side effects in horses, although excitement may be exhibited at higher doses[191, 202].

Onset of action occurs within 3 minutes after IV administration, and effects may last up to 4 hours[191]. Butorphanol is metabolized primarily by hydroxylation in the liver, although N-dealkylation and conjugation are also significant[191]. The metabolites are excreted primarily through the urine (86-89%), with the remainder excreted into the bile[191].

Butorphanol in conscious horses at 5, 10, and 20 times the dose used in this experiment produced no alterations in CO, HR, or MAP[202]. 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 [201], and decreases of 20.8% in another[203]. Administration of butorphanol after xylazine produced no further alterations in

hemodynamic variables beyond those produced by xylazine alone[203]. In halothane anesthetized horses, administration of 40 ug/kg butorphanol produced no changes in hemodynamic variables or blood gases[195].

E. Halothane

Halothane is an inhalant general anesthetic agent. Key pharmacologic effects include CNS depression, respiratory and myocardial depression, vasodilation, hypotension, increased cerebral blood flow, and decreased thermoregulation[191]. It is rapidly absorbed through the lungs. Approximately 12% of the absorbed dose is metabolized by the liver and excreted in the urine[191]. The majority of the drug is eliminated through the lungs along with expired air[191].

Halothane sensitizes the myocardium to the effects of catecholamines, which can result in ventricular arrythmias[191].

Although halothane is known to be a myocardial depressant, its effects on hemodynamic variables can be difficult to separate from those of induction agents, mechanical ventilation, body position, time, and other factors. Steffey et al[204] studied mechanically ventilated horses in left lateral recumbency which were induced and maintained by halothane. Mean alveolar concentration (MAC) of halothane was increased in a stepwise manner over 4 hours. They found that CO decreased 26.7% between MAC 1 and MAC 2 as a result of a significant decrease in

SV. When mechanical ventilation was discontinued at a steady MAC, CO increased by 71%. Steffey et al[205] induced and maintained spontaneously breathing horses on halothane in left lateral recumbency at 1.2 MAC for 12 hours. Cardiac output increased between hours 3 and 8, reaching 155% of baseline by the end of the study. The increased CO was initially due to increased SV, but after 5 hours HR began to increase as well. In another study by Steffey and coworkers[206], CO and SV increased throughout an extended period of anesthesia induced and maintained by halothane in spontaneously breathing laterally recumbent horses.

Grosenbaugh et al[207] induced horses with xylazine, guiafenesin, and ketamine, and placed them in right lateral recumbency under halothane. Thermodilution COs were measured every 15 minutes for 1 hour. Measured decreases from baseline (40 l/min) over time were 17%, 37%, 44%, and 42%. Studies using other induction agents have reported CO decreases of 58%[208] and 40%[33] after 15 minutes of halothane anesthesia. In the study by Hillidge et al[33], CO gradually increased over the ensuing 105 minutes, reaching 80% of baseline values by 120 minutes.

Summary

Dopamine and dobutamine are both positive inotropes which can be used to increase cardiac output. Dobutamine may have a more potent inotropic effect and may give more consistent results. Detomidine decreases CO primarily through a reflex-mediated

bradycardia. Administration of butorphanol along with detomidine is not expected to produce any further alterations in hemodynamic variables. Halothane induces myocardial depression and decreased CO, but its effects should be relatively consistent across subjects and thus should not interfere with a method comparison study.

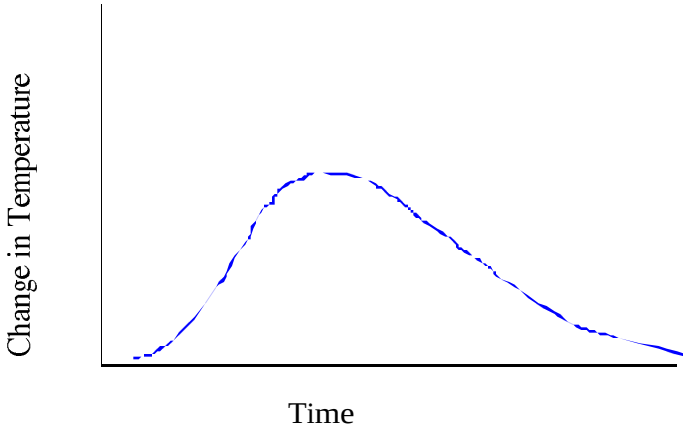

Fig. 2.1 Ideal thermodilution curve

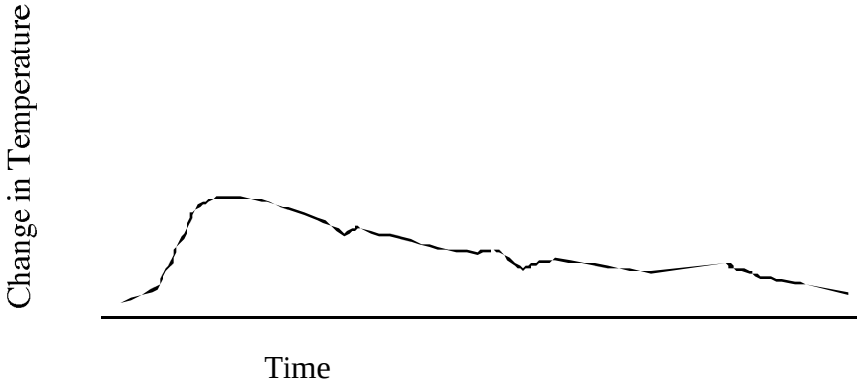

Fig. 2.2a Unsatisfactory thermodilution curve, typical of the thermistor being against the vessel wall.

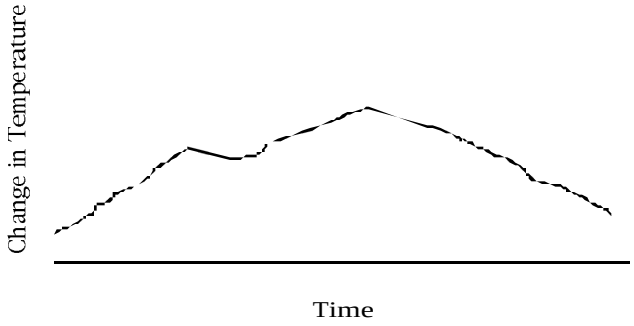

Fig. 2.2b Unsatisfactory thermodilution curve, typical of the injection period being too long.