Cardiac output measured by lithium dilution, thermodilution, and transesophageal Doppler echocardiography in anesthetized horses

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Objective—To assess the suitability of lithium dilution as a method for measuring cardiac output in anesthetized horses, compared with thermodilution and transesophageal Doppler echocardiography.

Animals—6 horses (3 Thoroughbreds, 3 crossbreeds).

Procedure—Cardiac output was measured in 6 anesthetized horses as lithium dilution cardiac output (LiDCO), thermodilution cardiac output (TDCO), and transesophageal Doppler echocardiographic cardiac output (DopplerCO). For the LiDCO measurements, lithium chloride was administered IV, and cardiac output was derived from the arterial plasma lithium concentration versus time curve, which is measured with a sensor that we have developed.

Halothane anesthesia in horses results in myocardial depression and hypotension,14 which have been implicated in the high incidence of perioperative morbidity12 and mortality13 in this species. Cardiovascular monitoring during equine anesthesia is usually restricted to EKG recording and measurement of arterial pressure.9,10 Cardiac output is rarely measured despite the obvious need, because available techniques such as thermodilution or dye dilution11-13,14 are complex, expensive, or give rise to complications. Transesophageal Doppler echocardiography has been used successfully to measure cardiac output in anesthetized horses,14 but the equipment is expensive and not generally available so that its use is restricted to research applications. Lithium dilution is safe and simple to perform. It avoids having to use a pulmonary artery catheter, because it requires only arterial and venous catheters, which would be routinely inserted in a horse undergoing anesthesia. The purpose of the study presented here was to compare cardiac output measurements obtained by use of lithium dilution with those obtained by use of conventional thermodilution and transesophageal Doppler echocardiography in anesthetized horses.

Materials and Methods

The study conformed to the UK Animals Act (Scientific Procedures, 1986, Home Office Licence No. PPL 80/1017) and was approved by the Animal Health Trust Ethics Committee. Six horses, 3 to 18 years old and weighing 486 to 620 kg, were studied. At least 6 months prior to the study, each horse had a portion of the right carotid artery surgically transposed to lie subcutaneously. Food, but not water, was withheld from the evening before the study. On the morning of the study, the skin overlying the left jugular vein was anesthetized by surface application of an emulsion of 2.5% lidocaine and 2.5% prilocaine hydrochloride15 followed 40 minutes later by SC administration of a 2% solution, which is administered as a bolus via a central venous catheter. Cardiac output is derived from the arterial plasma lithium concentration versus time curve, which is measured with a sensor that we have developed.

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horses were transported to a padded operating table, and ventilation was controlled by use of intermittent positive pressure with horses positioned in left lateral recumbency. End-tidal halothane and carbon dioxide concentrations were monitored, and ventilation was controlled to maintain end-tidal partial pressure of carbon dioxide (Paco2) in the range 45 to 55 mm Hg. The vaporizer was adjusted throughout the study to maintain an end-tidal halothane concentration of 0.9 to 1.0%. Two 8-F percutaneous introducer sheaths were inserted into the right jugular vein and a third into the right carotid artery, using a Seldinger technique. An 8-F 150-cm woven polyethylene terephthalate fiber catheter (with several side holes near the tip) was inserted via the right jugular vein so that its tip lay in the right atrium. Its position was confirmed by pressure measurements as it was withdrawn from the right ventricle into the atrium. This catheter was used for injection of both indicators (LiCl or cold saline [0.9% NaCl] solution). A 150-cm thermodilution catheter (outside diameter, 2.31 mm) was inserted via the other venous sheath until pressure recordings from its distal port indicated that it was in the pulmonary artery. A micromanometer catheter was inserted into the aorta via the carotid sheath, and a lithium sensor was connected with a 3-way tap to the sidearm of this sheath.

**Protocol**—For each horse, the experiment was divided into 4 periods. During each period, there were 3 lithium dilution cardiac output (LiDCO) measurements, 3 transesophageal Doppler echocardiographic cardiac output (DopplerCO) measurements, and 3 sets of 3 thermodilution cardiac output (TDCO) measurements. The LiDCO and DopplerCO measurements were simultaneous, with the TDCO measurements obtained as soon after as possible. All LiDCO measurements were made at intervals of at least 5 minutes to allow the plasma lithium concentration to return to baseline. The ventilator was switched off just prior to the TDCO measurements to reduce variability caused by ventilation. The same period of apnea was produced at the start of the LiDCO and DopplerCO measurements so that the hemodynamic conditions were similar.

For 4 of 6 horses (horses A, B, C, E), experimental periods were as follows: 1) control; 2) phenylephrine hydrochloride (2 µg/kg IV bolus, followed by 1 µg/kg/min IV infusion for 25 minutes) to cause vasoconstriction and reduce cardiac output; 3) sodium nitroprusside (0.75 µg/kg/min IV infusion for 25 minutes) to cause vasodilation to allow cardiac output to return to control values; and 4) sodium nitroprusside (0.75 µg/kg/min IV infusion) and dobutamine hydrochloride (2 µg/kg/min IV infusion) to induce an increase in cardiac output above control values.

In 2 horses (horses D and F), phenylephrine infusions were not administered, because the cardiac outputs were already low as a result of halothane anesthesia. In horse D, there were 3 sets of measurements obtained during the control period, and the sodium nitroprusside and dobutamine infusion was started prior to obtaining the remainder of the measurements. In horse F, there were 4 sets of measurements obtained during the control and sodium nitroprusside periods and 3 sets during the final period of sodium nitroprusside and dobutamine infusion.

**LiDCO measurements**—The sensor, which is disposable and sterilized by gamma radiation, consists of a poly-carbonate flow-through cell housing a lithium-selective electrode. When the lithium-selective membrane is in contact with blood, the voltage across it is related to plasma lithium concentration by the Nernst equation. This voltage is measured by use of an isolated amplifier, digitized on-line, and analyzed and stored on a portable computer. When a measurement was made, arterial blood passed through the sensor at a flow (4 ml/min) controlled by a small-powered peristaltic pump. When the baseline voltage recorded from the lithium electrode was stable (usually within 0.5 minutes), 18 ml of 150 mM LiCl solution was administered as a bolus via the right atrial catheter. Dead space in this catheter was 3 ml, and so the dose reaching the right atrium was 15 ml (2.25 mmol). The 3 ml of LiCl solution that remained in the catheter was aspirated before the next TDCO measurement was made. Ampoules of sterile 150 mM LiCl were produced by the pharmacy at St. Thomas’ Hospital, London.

**DopplerCO measurements**—Immediately after induction of anesthesia, a 3.75-MHz transesophageal echocardiographic probe was inserted into the esophagus via the right ventral nasal meatus. The probe was made specifically for use in horses and constructed from a 150-cm human colonoscope. The probe was used in conjunction with an echocardiograph. The maximal depth for color-flow mapping and spectral DopplerCO studies was 20 cm. Pulsed wave Doppler echocardiography was performed with ultrasound waves emitted at a frequency of 2.5 MHz.

The probe was advanced into the esophagus through the external nares until a long axis view of the left ventricular outflow tract and aorta was obtained by two-dimensional echocardiography. The Doppler sample volume was guided to the center of the vessel above the aortic valve in the area where color-flow Doppler echocardiography demonstrated...
the fastest flowing blood. Adequate alignment with aortic blood flow was assumed from the clarity of the audible signal and when a complete velocity envelope was obtained.

Data from aortic blood flow velocity spectra were measured by a single observer (KJB) from images that were digitized and stored on optical disk. Cardiac output was calculated, using the following equation:

\[ \text{Cardiac output} = \text{VTI} \times \text{aortic cross-sectional area} \times \text{heart rate} \]

where VTI (velocity time integral) = area under the velocity-spectrum envelope.

Velocity time integrals were measured, using the echocardiograph software. Modal velocities, delineated by the brightest line in velocity envelopes, were used to derive areas beneath spectra. Doppler signals from 8 consecutive cardiac cycles were measured for each cardiac output estimation, and mean VTI and heart rate for the group of 8 cycles were calculated. Cross-sectional area of the aorta was calculated from the aortic diameter measured from a two-dimensional, long-axis image of the aorta at the level of the sinotubular junction. To obtain each diameter, 3 measurements were made during systole from 3 consecutive cardiac cycles, and a mean value was obtained. Two-dimensional images needed for measurements were recorded on optical disk immediately before each set of cardiac output measurements.

Data analysis—Each estimate of cardiac output obtained by lithium dilution was compared with the corresponding DopplerCO measurement and mean value of the corresponding 3 TDCO measurements. Values reported in results are means (± SD). X-Y plots, linear regression analysis, and Bland Altman plots were used to compare data.

Results

Representative LiDCO and TDCO curves are shown for 2 horses (Fig 1), and data for the 6 horses are presented (Fig 2). In horses D and F, cardiac output was low initially (10 to 15 L/min, using lithium dilution) as a result of myocardial depression and, therefore, phenylephrine was not administered. In the 4 horses given phenylephrine, mean whole blood hemoglobin concentration increased from 11.4 to 18.8 g/dl as a result of splenic contraction.

X-Y plots and regression equations of LiDCO versus TDCO, LiDCO versus DopplerCO and DopplerCO versus TDCO are presented (Fig 3) together with the corresponding Bland Altman analyses (Fig 4).

Percentage changes (compared with control values) in mean aortic cross-sectional area caused by the drug infusions were as follows: phenylephrine, + 0.3%; sodium nitroprusside, −1.2%; and sodium nitroprusside and dobutamine, −1.6%. Correlations of the product of VTI and heart rate with TDCO or LiDCO measurements \((r = 0.91\) and \(0.92\), respectively) were similar to the correlation between DopplerCO and TDCO measurements.
Figure 2—Plots of cardiac output values versus time in 6 horses (horses A-F) obtained by use of lithium dilution (LiDCO; ▲), thermodilution (TDCO; ○) and transesophageal Doppler echocardiography (DopplerCO; ▼). Time 0 is the time of the first LiDCO measurement. In horses D and F the cardiac output was so low initially (LiDCO = 10 to 15 L/min) as a result of myocardial depression that phenylephrine was not administered. In horse D, there were 3 sets of measurements during the control period and the sodium nitroprusside and dobutamine infusions were started prior to the remainder of the measurements. In horse F, there were 4 sets of measurements during the control and sodium nitroprusside periods and 3 sets during the final period of sodium nitroprusside and dobutamine infusion.

Figure 3—X-Y plots of cardiac output measurements in horses. In each panel there are 70 data points. The regression equations are as follows: LiDCO vs TDCO, LiDCO = –1.90 + 1.05 TDCO (r = 0.94); LiDCO vs DopplerCO, LiDCO = –2.53 + 0.99 DopplerCO (r = 0.93); and DopplerCO vs TDCO, DopplerCO = 2.36 + 0.98 TDCO (r = 0.94).

Figure 4—Bland Altman plots of cardiac output measurements in horses. In each panel there are 70 data points. The mean bias ± SD in L/min for each comparison are as follows: LiDCO – TDCO, –0.86 ± 2.80; LiDCO – DopplerCO, –2.68 ± 3.01; and DopplerCO – TDCO, 1.82 ± 2.6.
Discussion

On the basis of all measurements, mean LiDCO (20.9 L/min) and mean DopplerCO (23.6 L/min) values were within 4 and 9%, respectively, of mean TDCO (21.8 L/min). It is not possible to be certain which method gave the most accurate estimate of cardiac output. The bias (LiDCO – TDCO) in our study (~0.86 L/min) was similar to the bias of 1 L/min reported by Dunlop et al., who compared a dye dilution method with thermodilution in 8 anesthetized horses that had a mean cardiac output of 20 L/min. Mizuno et al. also studied anesthetized horses and found that thermodilution gave higher values of cardiac output than dye dilution.

In our study, discrepancies between LiDCO and TDCO measurements may have been caused by a change in cardiac output that developed during the interval between LiDCO and the corresponding TDCO measurement, an error in the TDCO measurements, or an error in the LiDCO measurements. We decided not to add the LiCl to the cold injectant used for thermodilution, because such dilution would not normally be used, and we wanted to compare LiDCO values obtained with the standard technique (bolus injection by hand of 150 mM LiCl) with TDCO values. The greatest discrepancy between a LiDCO measurement and mean TDCO measurement was 12.0 L/min. This data point represented the comparison of the penultimate LiDCO value obtained in horse C (Fig 2) with the mean of the 3 TDCO values obtained just after the LiDCO measurement. The LiDCO value (41.9 L/min) agreed closely (within 6%) with the immediately preceding single TDCO measurement (39.7 L/min). The final LiDCO value in this horse (36.2 L/min) was within 6% of the immediately succeeding single TDCO value (34.3 L/min). It seems likely, therefore, that the 12.0 L/min discrepancy was the result of a true decrease in cardiac output just after the LiDCO measurement but before the TDCO measurements with which it was compared. The corresponding simultaneous DopplerCO measurements also agreed better with those obtained by lithium dilution than with those obtained by thermodilution.

Errors in TDCO measurements, which are known to have a large variability in humans, could have been caused by error in the dose of indicator, loss of indicator in its passage through the heart, error in recording pulmonary arterial blood temperature, and irregularity of the recorded thermodilution curve. Error in the dose of indicator would have been small. Volumes of injectant were measured accurately by weighing the syringes before and after use, and the temperature of the injectant was measured with the in-line thermistor. There would have been some increase in temperature (loss of cold) as the solution passed through the heart, although this is impossible to quantify. The effect of this would have been to make the curves smaller and, therefore, the cardiac output estimates higher. Irregularities of the curve may be the result of heart rate variation or fluctuations in pulmonary artery temperature, which we attempted to minimize by making the measurements during apnea. Overestimation of cardiac output by thermodilution may also result from a short-term increase in stroke volume caused by the volume of injectant.

Error in the LiDCO measurements could have been caused by loss of LiCl from the pulmonary circulation, error in measurement of whole blood hemoglobin concentration, or irregular LiCl dilution curves. By recording LiCl dilution curves following right or left atrial injection of LiCl in humans, we showed that the pulmonary loss of LiCl is less than 4%. Similar measurements have not been made in horses, but it is unlikely that such loss is important, because its effect would be to give falsely high estimates of cardiac output and, in our study, the mean of all LiDCO measurements was less than the mean of all TDCO measurements.

Only 1 LiDCO curve was rejected (because of an interruption resulting from a loose connection), and the shape of the other 70 curves was as expected. One cause of abnormal shape is variation in blood flow through the sensor; should this happen, the distortion is recognized by the software, and the curve is rejected. This problem did not occur during our study.

The mean difference between DopplerCO and TDCO values (DopplerCO – TDCO) of 1.82 ± 2.67 L/min was greater than that found in an earlier study in 8 anesthetized horses in which the mean difference was 0.7 ± 4.2 L/min" and another study in 9 conscious horses in which the mean difference was 0.43 ± 6.26 L/min, but the variance was less. Transesophageal Doppler echocardiography has been found to be an inaccurate method of determining cardiac output in humans but is more reliable in horses probably because of better parallel alignment between the ultrasound beam and aortic blood flow. Any error in measurement of the aortic diameter will of course be squared in deriving the cross-sectional area. Because the correlations of the product of VTI and heart rate (VTI × HR) with TDCO or LiDCO measurements were similar to the correlation between DopplerCO and TDCO measurements, we could have used (VTI × HR) to follow changes in cardiac output, although calculation of absolute cardiac output requires measurement of aortic cross-sectional area. Transesophageal Doppler echocardiography is relatively noninvasive and appears reliable in horses, but the equipment is expensive and considerable operator expertise is required. For this reason, the use of the technique is likely to remain restricted to research institutions.

Horses were anesthetized with halothane, which is known to reduce cardiac output. The effect of this varied considerably from horse to horse. In horse F, the initial control value of cardiac output was less than half the normal value for an awake horse of this size, and, thereafter it continued to decline, despite administration of sodium nitroprusside and dobutamine, to such an extent that the phenylephrine could not be used. If vasoconstriction had been used to increase blood pressure, the further reduction in cardiac output that this would have caused might have had disastrous consequences. Dobutamine was chosen as the inotropic drug, because epinephrine and isoproterenol hydrochloride cause dysrhythmias, especially in association with halothane, and doxepamine caus-
es pronounced sweating and stormy recovery with excitement, violent shivering, and colic. There are several advantages in the use of lithium dilution, compared with thermodilution and transesophageal Doppler echocardiography. It is much quicker to set up. The sensor needs to be soaked for 5 minutes in heparinized saline solution, and then it is ready for connection to the arterial line. In contrast, insertion of a Swan-Ganz catheter in our anesthetized horses usually took about 30 minutes, although in 1 horse (horse F) it took 1.5 hours. Placement of the transesophageal probe is also time consuming. Horses have to be adequately anesthetized and need to be extubated for insertion of the probe and reintubated. Transesophageal probes for horses to have to be custom made. The probe diameter (18 mm) is too large for use in ponies and small horses and even in larger horses may cause hemorrhage and sinusitis. Especially in horses, it is important to avoid any prolongation of anesthetic time because of related deterioration in cardiovascular state and gas exchange. Numerous complications arising from Swan-Ganz catheters have been described in humans; these include perforation of the heart, rupture of the pulmonary artery, catheter knotting, damage to the tricuspid and pulmonary valves, dysrhythmias, and infection. Several authors have expressed concern about these hazards, many of which could also develop in horses. In 8 of 9 horses examined at necropsy after having had pulmonary artery catheters inserted for between 5 and 6 hours, there were lesions in the right atrium, right ventricle, and on the pulmonary valve.

Risks of using lithium dilution to determine cardiac output are negligible. The jugular venous and arterial catheters are usually already in place in anesthetized horses in which case no further cannulation is necessary. The amount of blood required (sampling at 4 ml/min) is small, and the LiCl has no known pharmacologic effect at this low dose. This study shows that the LiDICO method is suitable for measuring cardiac output in horses. As well as being accurate, it has the advantage of avoiding pulmonary artery catheterization. In view of the low values of cardiac output measured in some of the horses in this series during the control periods, it may be expected that cardiac output monitoring could help reduce the mortality associated with anesthesia in horses.

References


