Cardiac Power Output during Dobutamine Stress Test in Horses

Charlotte Sandersen, DVM, PhD,[a] Kathleen McEntee, DVM, PhD,[a] Stefan Deleuze, DVM, MSc,[a] Johanne Detilleux, DVM, PhD,[b] and Hélène Amory, DVM, PhD[a]

ABSTRACT

Although echocardiography has greatly improved the diagnostic possibilities in equine medicine, determining the prognosis remains a difficult task. In humans, maximal cardiac power output (CPO) has been described as a powerful indicator of exercise capability and outcome in heart disease. The aim of the study is to describe the measurement of CPO by echocardiography and by thermodilution in healthy horses. Six healthy horses were studied. Cardiac output (CO) was measured by thermodilution and Doppler echocardiography at rest and during a pharmacologic stress test consisting of 35 μg/kg atropine followed by incremental steps 2, 4, 6, and 8 μg/kg/min of dobutamine infusion. Mean arterial pressure (MAP) was measured invasively by a catheter introduced into the transverse facial artery. CPO was calculated as the product of CO and MAP. Baseline CPO measured by thermodilution and by Doppler echocardiography was 10.7 ± 3.3 and 13.7 ± 4.5 watts, respectively. CPO increased significantly with pharmacologic stimulation and reached maximal CPO of 66.4 ± 3.6 and 60.4 ± 5.1 watts when measured by thermodilution and Doppler echocardiography, respectively. This study describes an estimation of CPO in horses. Further studies should demonstrate the usefulness of CPO as a predictive indicator in horses suffering from cardiac disease.

Keywords: Horse; Heart disease; Stress echocardiography; Thermodilution; Dobutamine; Atropine

INTRODUCTION

Commonly, when cardiac function is assessed in exercise physiology or medical research, indexes of either blood flow (eg, cardiac output) or pressure (eg, pulmonary wedge pressure) are used. Unfortunately, these variables correlate poorly with exercise capacity[1,2] or prognosis in human patients.[3] Cardiac power output (CPO) as an alternative measure of cardiac performance has been proposed by Tan.[4] Cardiac power output is the product of cardiac output (CO) and mean systemic arterial pressure (MAP), and is, from the point of view of fluid dynamics, the most logical variable to represent cardiac performance. The heart generates both blood pressure and flow, and therefore both components need to be determined if a comprehensive measure of overall cardiac function is to be obtained.[4-6] Maximal CPO, achieved either by exercise or by pharmacologic stimulation, has been described as a powerful indicator of exercise capability and outcome in heart disease in humans.[7-9] Until now, CPO has not been measured in horses, although other forms of cardiac stress testing based on echocardiography after exercise or during or after pharmacologic stimulation have recently been described in horses. The use of echocardiography has revolutionized equine cardiology by providing an excellent diagnostic and prognostic tool, especially in cases of advanced heart disease. However, diagnosing subtle or occult cardiac disease that limits exercise capacity remains a challenging task for the equine cardiologist. Therefore, it seems desirable to investigate the equine heart under conditions that simulate exercise. Stress echocardiography has been proposed for this purpose; however, its clinical utility still needs to be proved.

The aim of the current study was (1) to measure resting and maximal CPO in healthy horses undergoing pharmacologic stress testing and (2) to compare CPO measured by thermodilution and by Doppler echocardiography, to establish a minimally invasive method of CPO measurement in horses.

MATERIALS AND METHODS

Six healthy horses (age 11.5 ± 5.5 years; body weight 421 ± 71 kg [mean ± SD]) were studied. All procedures were approved by the Ethical Committee for Animal Use of the Faculty of Veterinary Medicine.

Two 8.5-French catheter-introducers (Percutaneous Sheath Introducer Set, Arrow, Reading, PA) were placed in the left jugular vein. A 7.5-French-wide and 130-cm-long thermistor catheter (Swan-Ganz catheter, Baxter, Lessines, Belgium) was inserted into the pulmonary artery

From the Department of Clinical Sciences[a]; and Department of Animal Production[b]; Faculty of Veterinary Medicine, University of Liege, Liege, Belgium.
Reprint requests: Charlotte Sandersen, University of Liège Faculty of Veterinary Medicine, Department of Clinical Sciences—Equine Clinic, Boulevard de Colonster 20, B41, B-4000 Liege, Belgium.
0737-0806/$ - see front matter

doi:10.1016/j.jevs.2009.02.005

via the lower introducer. A multi-opening catheter (Tempo5, Cordis, Waterloo, Belgium) was passed into the right atrium via the upper introducer. A 20-gauge catheter (Intraflon2, Vygon, Ecouen, France) was placed into the transverse facial artery and connected via a fluid-filled pressure transducer to a monitoring system (Series 7010, Marquette Electronics Inc., Milwaukee, WI) to measure MAP throughout the protocol. Correct placement of all the catheters was confirmed by characteristic pressure tracings.

Echocardiographic examinations were performed with a 2.5-MHz phased-array transducer (System Five, GE Ultrasound, Zaventem, Belgium) and recorded for later analyses. The left ventricular outflow tract was viewed from a right parasternal long axis view. The end-diastolic aortic diameter was measured at the largest perpendicular diameter of the sinus of valsalva using the leading edge method. Echocardiographic recordings of a left parasternal left outflow tract view served for the Doppler measurement of the aortic flow as previously described.[10] The velocity time integral (VTI) was obtained by tracking the black/white interface of the pulsed-wave Doppler signal of the aortic flow.

The echocardiographic recordings of the aortic flow tracings were performed at rest and 3 minutes after the onset of each step of the pharmacologic stress test, which consisted of a single intravenous injection of 35 μg/kg of atropine (crystalline powder in 1% aqueous solution, Sigma-Aldrich, Bornem, Belgium) followed by incremental steps of dobutamine infusion (Dobutrex, Eli Lilly, Brussels, Belgium) at rates of 2, 4, 6, and 8 μg/kg/min (Model 960, Imed Coperation, San Diego, CA). Criteria to interrupt the procedure included excessive restlessness of the horse, persistent ventricular arrhythmias, or less than 5% increase of heart rate (HR) in comparison with the preceding step. Simultaneously to the Doppler recordings of the aortic flow, thermodilution-derived cardiac output (CO_{TD}) was determined by three injections of 35 mL ice-cold saline solution and automatically computed by a cardiac output computer (Cardiomax II, Columbus Instruments, Columbus, OH). The mean of the three measurements was calculated to estimate the cardiac output in each of the steps of the pharmacologic challenge. Simultaneously, an apex-base echocardiogram was recorded for later calculation of HR.

The mean of three measurements of the aortic diameter (d) was used to calculate the aortic cross-sectional area (CSA), assuming a circular and constant orifice, by the following formula: $CSA = [d/2]^2 * \pi$. The mean of three VTI was used to calculate stroke volume (SV) using the following formula: CSA* VTI. Doppler-derived cardiac output (CO_{DO}) was calculated as the product of SV and HR. Cardiac power output was calculated for the two methods of CO measurement according to Chantler and co-workers[11] as follows: CPO = (CO * MAP) * k, where k is a conversion factor ($2.22*10^{-3}$) into watts. To compare SV of the two methods, the thermodilution-derived SV was calculated by dividing thermodilution-derived CO by the HR.

Each variable was analyzed separately with a repeated measures model with an auto-regressive variance-covariance matrix for the repeated measures (Proc mixed, SAS/STAT software, SAS Institute Inc., Cary, NC). Least-square means were computed for each step of the protocol. Differences were considered significant at $P < .05$. Comparison between CPO_{DO} and CPO_{TD} was done by Bland-Altman analysis, which is considered the method of choice for comparing two clinical measurement techniques[12] (Medcalc Software, Mariakerke, Belgium).

RESULTS

Results of measured (HR, MAP, CO_{TD}, SV_{DO}) and calculated variables (SV_{TD}, CO_{DO}, CPO_{TD}, CPO_{DO}) before and during pharmacologic stimulation are given in Table 1. Bland-Altman analysis (Fig. 1) demonstrated a mean bias between the two methods of CPO estimation of 4.19 watts with a 95% confidence interval for the mean bias 1.79 to 6.85 watts. The limits of agreement were −9.24 watts and 17.62 watts. The 95% confidence interval for the upper limit of agreement was 13.49 to 21.75 watts; the 95% confidence interval for the lower limit of agreement was −13.37 to −5.11 watts.

DISCUSSION

All horses tolerated the procedure without incident. In two horses, the protocol was interrupted after a dobutamine infusion rate of 6 μg/kg/min, because maximal cardiac stimulation had been reached. The pharmacologic stress test of the current study induced a 4.4- to 6.2-fold increase in CPO at maximal stimulation, which is comparable to the results obtained in humans[7] and higher than those obtained in dogs[13] and calves.[14] The observed increase in CPO was mediated by an increase in MAP and HR, whereas SV slightly decreased with increasing cardiac stimulation. Decreased SV during pharmacologic stimulation has already been demonstrated in previous studies in ponies[15] and humans[16] and is probably the result of decreased venous return, lowering preload. In contrast, SV is maintained during exercise because of the muscular pump function. Therefore, CPO obtained during pharmacologic stress test in the current study is probably lower than the maximal CPO that could be achieved during maximal exercise. However, maximal CPO for this pharmacologic protocol was achieved, because there was no more significant increase of MAP and HR between the two final steps of pharmacologic stimulation. Other determinants of cardiac performance such as contractility and afterload have not been investigated in detail, but increasing fractional shortening demonstrated in horses undergoing the same

Table 1. Mean values of heart rate, mean systemic arterial pressure, cardiac output, and cardiac power output measured by thermodilution and by Doppler echocardiography in six horses undergoing pharmacological stress test

Dose (n = 6)	HR (bpm)	MAP (mmHg)	CO TD (L/min)	CO DO (L/min)	CPO TD (W)	CPO DO (W)
Baseline (n = 6)	43.4 ± 5.1	135.9 ± 8.7	35.3 ± 5.5	45.3 ± 7.2	10.7 ± 3.3	13.7 ± 4.5
Atropine 35 µg/kg (n = 6)	69.7 ± 5.2 0	162.1 ± 8.8 0	45.7 ± 5.56	64.4 ± 7.3 0	16.1 ± 3.3 0	22.3 ± 4.5 0
2 µg/kg/min dobutamine (n = 6)	98.8 ± 5.1 0, A	189.3 ± 8.7 0, A	63.4 ± 5.5 0, A	82.8 ± 7.2 0	26.9 ± 3.3 0, A	35.2 ± 4.5 0, A
4 µg/kg/min dobutamine (n = 6)	123.2 ± 5.1 0, A, 2	213.9 ± 8.7 0, A	87.6 ± 5.5 0, A, 2	101.4 ± 7.2 0, A, 2	41.8 ± 3.3 0, A, 2	48.3 ± 4.5 0, A, 2
6 µg/kg/min dobutamine (n = 6)	140.2 ± 5.1 0, A, 2, 4	234.6 ± 8.7 0, A, 2	102.1 ± 5.5 0, A, 2, 4	116.7 ± 7.2 0, A, 2	53.4 ± 3.3 0, A, 2, 4	55.1 ± 4.5 0, A, 2, 4
8 µg/kg/min dobutamine (n = 4)	146.5 ± 5.5 0, A, 2, 4	233.8 ± 10.0 0, A, 2	120.2 ± 5.7 0, A, 2, 4, 6	119.6 ± 7.6 0, A, 2, 4	66.4 ± 3.6 0, A, 2, 4, 6	60.4 ± 5.1 0, A, 2, 4

All values expressed as least square means ± S.E.; $p < 0.05$. 0= significantly different from baseline, A = significantly different from atropine, 2 = significantly different from 2 µg/kg/min of dobutamine infusion, significantly different form 4 µg/kg/min of dobutamine infusion, significantly different from 6 µg/kg/min of dobutamine infusion. HR = heart rate, MAP = mean systemic arterial pressure, CO = cardiac output, CPO = cardiac power output, TD = thermodilution, DO = Doppler echocardiography.

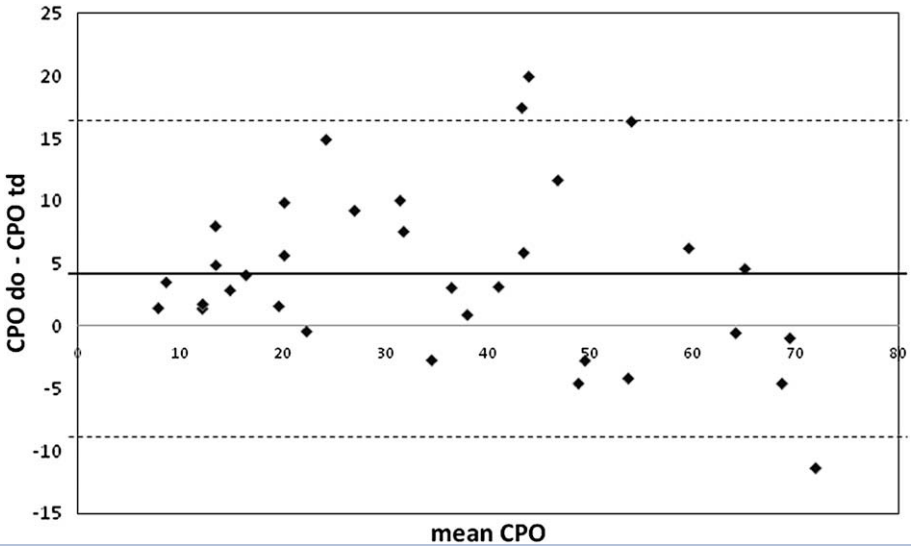

Fig. 1. Bland-Altman plot of cardiac power output (CPO) measurements by thermodilution (TD) and Doppler echocardiography in six horses during a pharmacological stress test. — mean bias, ---- upper and lower limit of agreement

protocol of pharmacologic stimulation might indicate an increasing contractility.[17] Afterload, often estimated by systemic vascular resistance and calculated as MAP divided by CO, is decreasing during this form of stress test. These data indicate that pharmacologic stimulation mimics exercise only incompletely. However, the success of CPO as an estimate of cardiac performance depends primarily on its capacity to reach maximal stimulation for a given test.[7-9] This criterion seemed to be fulfilled by the given test, because there was no observable increase in HR, CO_{TD}, or MAP in two of the six

horses at a dobutamine infusion rate of 6 μg/kg/min; in the remaining four horses, no further stimulation was observed in the final two steps of pharmacologic stimulation.

An earlier study by Blissit and co-workers[18] has demonstrated a mean bias of 4.01 ± 12.26 L/min CO measured by thermodilution and Doppler echocardiography, which is comparable to the current study. Thermodilution, although often considered as the gold standard, is subject to measurement errors caused by preheating of the thermal indicator, errors in injectate volumes, and injection time.[19] The advantage of Doppler echocardiography as a means of CO estimation is its noninvasiveness. However, during stress echocardiography, an increased dispersion of the signal is observed, which makes it difficult to identify modal velocity envelopes accurately.[14,18] These findings are also reflected in the Bland-Altman analysis, which showed a considerable lack of agreement between the two methods and indicated that variation in at least one method depends on magnitude of measurements. However, both techniques were capable of demonstrating a gradual increase of CPO with increasing stimulation.

In conclusion, the results of the current study indicate that CPO measurement during pharmacologic stimulation is feasible in horses and can be performed noninvasively using Doppler echocardiography. Further studies are needed to show the usefulness of CPO measurement as a prognostic indicator of cardiac disease in horses.

REFERENCES

1. Benge W, Litchfield RL, Marcus ML. Exercise capacity in patients with severe left ventricular dysfunction. Circulation 1980;60: 955–959.
2. Franciosa JA, Park M, Levine TB. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol 1981;47:33–39.
3. Tan LB. Cardiac pumping capability and prognosis in heart failure. Lancet 1986;ii:1360–1363.
4. Tan LB. Clinical and research implications of new concepts in the assessment of cardiac pumping performance in heart failure. Cardiovasc Res 1987;21:615–622.
5. Cooke GA, Marshall P, Al-Tilman JK, Wright DJ, Riley R, Hainsworth R, et al. Physiological cardiac reserve: development of a non-invasive method and first-estimates in man. Heart 1998;79: 289–294.
6. Williams SG, Cooke GA, Wright DJ, Parsons WJ, Riley RL, Marshall P, et al. Peak exercise cardiac power output: a direct indicator of cardiac function strongly predictive of prognosis in chronic heart failure. Eur Heart J 2001;22:1496–1503.
7. Tan LB, Bain RJ, Littler WA. Assessing cardiac pumping capability by exercise testing and inotropic stimulation. Br Heart J 1989;62: 20–25.
8. Williams SG, Jackson M, Cooke GA, Barker D, Patwala A, Wright DJ, et al. How do different indicators of cardiac pump function impact on the long-term prognosis of patients with chronic heart failure? Am Heart J 2005;150: 983e1-983e6.
9. Otasevic P, Popovic ZB, Vasiljevic JD, Pratali L, Vlahovic-Stipac A, Boskovic SD, et al. Head-to-head comparison of indices of left ventricular contractile reserve assessed by high-dose dobutamine stress echocardiography in idiopathic dilated cardiomyopathy: five-year follow up. Heart 2006;92:1253–1258.
10. Long KJ, Bonagura JD, Darke PG. Standardised imaging technique for guided M-mode and Doppler echocardiography in the horse. Equine Vet J 1992;24:226–235.
11. Chantler PD, Clements RE, Sharp L, George KP, Tan LB, Goldspink DF. The influence of body size on measurements of overall cardiac function. Am J Physiol Heart 2005;289:2059–2065.
12. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;8476: 307–310.
13. Amory H, McEntee K, Linden AS, Desmecht DJ, Beduin JM, D'Orio V, et al. Comparison of the cardiac pumping capability and cardiac pumping reserve in double-muscled and conventional calves. Can J Physiol Pharmacol 1993;71:946–951.
14. McEntee K, Clercx C, Pypendop B, Peeters D, Balligand M, D'Orio V, et al. Cardiac performance in conscious healthy dogs during dobutamine infusion. Res Vet Sci 1996;61:234–239.
15. Sandersen CF, Detilleux J, Delguste C, Pierard L, van Loon G, Amory H. Atropine reduces dobutamine-induced side effects in ponies undergoing a pharmacological stress protocol. Equine Vet J 2005;37:128–132.
16. Cnota JF, Mays WA, Knecht SK, Kopser S, Michelfelder EC, Knilans TK, et al. Cardiovascular physiology during supine cycle ergometry and dobutamine stress. Med Sci Sports Exerc 2003;35: 1503–1510.
17. Sandersen C, Detilleux J, Art T, Amory H. Exercise and pharmacological stress echocardiography in healthy horses. Equine Vet J 2006;36(Suppl):159–162.
18. Blissitt KJ, Young LE, Jones RS, Darke PG, Utting J. Measurement of cardiac output in standing horses by Doppler echocardiography and thermodilution. Equine Vet J 1997;29:18–25.
19. Corley KT, Donaldson LL, Durando MM, Birks EK. Cardiac output technologies with special reference to the horse. J Vet Intern Med 1981;17:262–272.