USE OF THE CARDIOPULMONARY FLOW INDEX TO EVALUATE CARDIAC FUNCTION IN THOROUGHBRED HORSES

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ABSTRACT

The ratio of the cardiopulmonary blood volume to stroke volume is called the cardiopulmonary flow index (CPFI). The CPFI can be determined indirectly from the simultaneous recording of a radiocardiogram and an electrocardiogram. The CPFI and cardiac output were measured simultaneously in horses (n = 10) that were diagnosed as having cardiac disease. The diseased subjects were probably all exposed to feed contaminated with the ionophore, salinomycin, and all showed clinical signs indicative of chronic toxic myocarditis. The results obtained from these subjects were compared with those from control animals and significant differences ($P < 0,05$) were found between the mean CPFI of the control horses and those with macroscopically visible myocardial fibrosis on post mortem examination. No significant differences were found between the means of the cardiac output measured in either of the groups of horses. The effect of pharmacological acceleration of the heart rate on the CPFI was also studied. Significant differences ($P < 0,05$) were found between the mean CPFI and the slopes of the regression lines of CPFI on heart rate of the control and principal groups of horses. These differences were greatest at heart rates near to the resting heart rates of the individuals. The CPFI was found to be a more sensitive measure of cardiac function than cardiac output, in the horses.

Key words: Equine, cardiopulmonary flow index, cardiac function.

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INTRODUCTION

In recent years, toxic myocarditis, particularly ionophore intoxication, has become an important clinical entity in horses. Cases of monensin[1 2 6 7 9 16], salinomycin[13] and naracin (R.H. Katzwinkel 1986 Private Practitioner, Gillitts, Natal, RSA, personal communication) poisoning have been reported in various countries. Horses with chronic monensin toxicity present with a history of poor performance and unthriftiness and on necropsy have been shown to have cardiac myopathy and replacement fibrosis[9].

Many diagnostic procedures have been adapted for use in horses and are now used as an aid to diagnose conditions that affect the function of the equine cardiovascular system. The cardiac output is used as a measure of cardiac function in many species, including the horse[3 5]. Horses with mild cardiac disease show a mild to severe drop in performance, although they show no signs which can be detected using existing non-invasive diagnostic methods[4]. A diagnostic technique that is sufficiently sensitive to detect a mild reduction in cardiac function could thus prove valuable in research and clinical practice.

The ratio of the cardiopulmonary blood volume to stroke volume can be determined indirectly from the simultaneous recording of a radiocardiogram (RCG) and an electrocardiogram (ECG). The indirect measurement of the ratio of the cardiopulmonary blood volume (CPBV) to stroke volume (V_s) is called the cardiopulmonary flow index (CPFI)[12 14 15]. This technique has been used in normal sheep, dogs, baboons, humans and horses, as well as in sheep, humans and horses with heart disease and sheep with pulmonary emboli[12 14 15]. From the data obtained in these studies, it was concluded that the CPFI is a sensitive and reliable index to describe the efficiency of the pumping function of the heart, within different models of heart disease in experimental subjects[12 14 15].

The purpose of the present study was to evaluate the CPFI as an index of cardiac function relative to the cardiac output in cardiovascularly sound Thoroughbreds and in Thoroughbreds exposed to feed probably contaminated with toxic levels of salinomycin; to evaluate the effects of changes in heart rate on the CPFI in these normal and diseased subjects; and to evaluate the sensitivity of the CPFI for the differentiation of healthy Thoroughbred horses from Thoroughbred horses with cardiovascular disease.

MATERIALS AND METHODS

Thoroughbred horses (n = 10) with a history of probable exposure to feed contaminated with toxic levels of salinomycin and that showed clinical signs indicative of cardiac disease, were donated for use as the principal subjects in this study. In general, the clinical signs were mild, but included reports of poor racing performance, electrocardiographic abnormalities, including arrhythmias (atrial fibrillation, intraventricular block, premature ventricular concentrations) and elevated serum enzyme activities following exercise. Three clinically normal Thoroughbred horses with no previous history or current signs of cardiac disease were used as control subjects in these investigations. All subjects were maintained under identical conditions of management and feeding during a 3-week adaption period prior to this study and for the entire duration of the investigations. All subjects had a portion of the left common

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carotid artery subcutaneously relocated prior to the commencement of the adaptation period. To reduce psychophysiological influences associated with the experimental protocol, animals were exposed to the laboratory environment on at least 3 occasions prior to data collection. Laboratory exposure included all parts of the experimental protocol and the laboratory personnel.

The cardiac output was measured using the Fick principle, with oxygen as the indicator substance. Mixed expired gas was collected by placing an airtight facemark over the horse's muzzle and allowing the subject to exhale via flow-directed valves into a meteorological balloon. The facemask was held in place by attaching it to the head-piece of a bridle. The airtight seal on the mask consisted of a thin rubber shroud over a piece of expanded foam rubber. The facemask was connected to the flow-directed valves by a 10 cm length of 5 cm-diameter flexible plastic tubing. The inspiratory side of the valves was open to the environment. The expiratory side was connected to the 200 ℓ meteorological balloon. A separate balloon was used to collect the gas during each of 3 one-minute sampling periods. The volume of gas in each balloon was measured, using a spirometer (Warren E. Collins, Braintree, MA). A 50 ml sample of the gas from each balloon was analysed for O_2 and CO_2 content using a semi-automated gas analyser (ABL3, Radiometer A/S, Copenhagen). Arterial and mixed venous blood samples were collected anaerobically into heparinised syringes during each of the one-minute sampling periods. Arterial blood was sampled via a previously-placed 18 G cannula, using aseptic technique, into the transposed portion of the carotid artery. Mixed venous blood was sampled, using a catheter, fashioned from polyethylene tubing (Clay Adams, New Jersey, NJ) introduced aseptically into the jugular vein via a 15 G hypodermic needle and then passed into the pulmonary artery. Correct positioning of the pulmonary artery catheter was confirmed both prior to and following sample collection by recording the intravascular pressure, and observation of the characteristic pulmonary artery waveform. Blood samples were sealed and placed in an iced water bath until they were analysed. Blood gas analyses were performed on these samples within an hour of collection, using a semi-automated blood gas analyser (ABL3, Radiometer A/S, Copenhagen). The haemoglobin concentration of these samples was measured, using a photometer and associated dual diluter (Coulter Electronics Inc., Hialeah, FL).

The oxygen consumption was calculated from the true oxyen fraction of the mixed expired gas and the gas volume. Oxygen content of arterial and venous blood samples was calculated from the haemoglobin concentration and saturation (calculated from oxygen tension) of the blood samples. Cardiac output was calculated by dividing the oxygen consumption by the arterio-venous oxygen content difference. These calculations were performed using a personal computer (International Business Machines, Boca Raton, FL) and dedicated software.

The radiocardiogram (RCG) was recorded by injecting a bolus of 185-370 MBq of 99m-Technitium (^{99m}Tc) into the left jugular vein via a catheter and then recording the gamma ray activity, with a gamma ray probe, as the isotope passed through the right and subsequently the left ventricles. The catheter used for the introduction of the isotope into the jugular vein, was made from polyethylene tubing and was approximately 30 cm long. It was introduced aseptically into the vein through a 15 G hypodermic needle. The gamma ray probe consisted of a collimated scintillation crystal and a discriminator, producing a signal that was recorded on a multichannel physiological recorder (Mingograf 62, Siemens-Elema AB, Solna, Sweden). The probe was supported by a stand which could be adjusted for height and which allowed variable positioning of the probe in both the horizontal and vertical planes. For recording of the RCGs, the probe was positioned on the left side of the horse with the collimator approximately one cm away from the chest wall at a point overlying the 6th intercostal space at the costochondral junction. The collimator was directed upwards at an angle of approximately 20° and forward at an angle of approximately 30°, thus pointing toward the point of the right shoulder. When the collimator is positioned correctly, the RCG is characterised by a left ventricular peak that is between 50 and 100% that of the right ventricular peak[12]. A simultaneous recording of the ECG was made on the multichannel physiological recorder using the semi-orthogonal Y lead. The CPFI was calculated by dividing the time between the two peaks of gamma activity on the RCG (CPTT) by the average duration of the R-R interval for the 10 heart beats that included the entire passage of the isotope through both ventricles. All procedures were carried out and all radioactive material was handled according to local statutes.

The cardiac output and CPFI were measured simultaneously. This was achieved by starting the mixed expired gas and blood sample collection and then injecting the bolus of ^{99m}Tc approximately 10s after the beginning of sample collection. Gas and blood samples were collected over a period of one minute, after which the meteorological balloon and heparinised blood samples for blood gas analysis were sealed and the latter placed in a bath of ice-water. This procedure was repeated 3 times on each individual during each experimental period, with approximately a one minute delay between each procedure. This entire experimental procedure was repeated on 3 separate occasions, with at least 7d between each procedure.

Response of CPFI to pharmacological acceleration of heart rate was studied in the cardiovascularly sound horses and

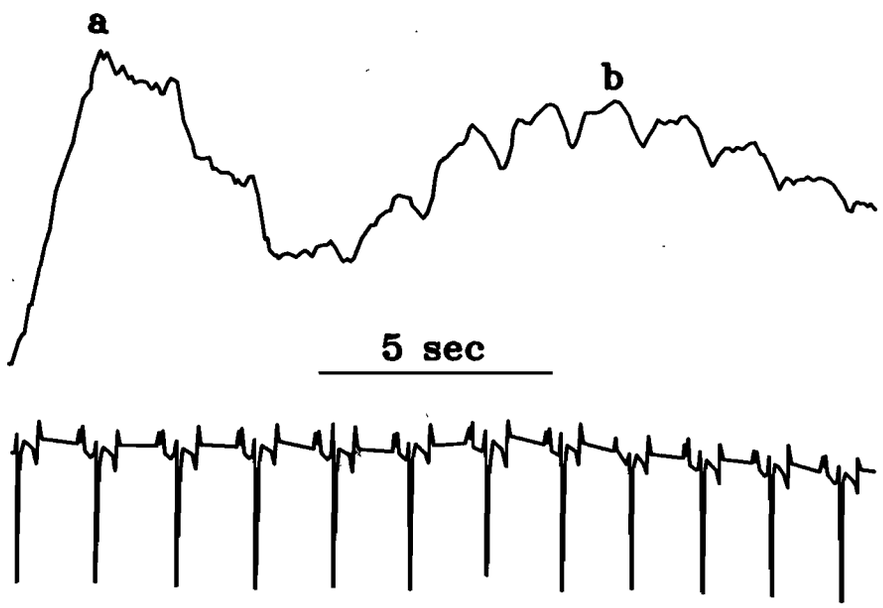

Fig. 1: **A typical tracing of the RCG (above) and ECG from a cardiovascularly sound subject. a and b - right and left ventricular peaks of gamma activity. Cardiopulmonary transit time (CPTT) was measured between a and b**

diseased subjects. This study was performed approximately one month after the initial study described above was completed. In these subjects a dose of 0,1 mg of isoproterenol (Isuprel, Sterling Drug (SA) (Pty) Ltd., Durban) was injected intravenously and the CPFI was measured one, 3 and 5 min after administration of the drug. This procedure was repeated 3 times in all subjects with at least 7 d between recordings.

Following these studies, all principal subjects were euthanased and autopsies performed. Subjects with and without macroscopically visible foci of myocardial replacement fibrosis were assigned to different groups. Principal subjects without macroscopically visible myocardial fibrosis, were assigned to Group 2 and those with such lesions were assigned to Group 3.

All statistical analyses were performed using the SAS (SAS Institue Inc., Cary, NC) package of computer programmes. The cardiovascularly sound horses were treated as a separate group (Group 1). CPFI data and cardiac output data from the 3 groups of horses were separately analysed, using an analysis of variance procedure with group, and the animals within each group, as factors and the heart rate as a covariate. Between-animal variation was used when group means were compared.

CPFI data from the horses with pharmacologically elevated heart rates (Groups 1 and 3) were analysed, using a regression analysis between the heart rate and CPFI with the group acting as a covariate. The interaction between the group and the heart rate was included in the model to test whether the slopes of the regression lines of the CPFI on the heart rate differed between the 2 groups.

Table 1: **Mean (±SD) and number of observations (n) for age, mass, cardiac output, cardiac index, cardiopulmonary flow index, heart rate, stroke volume and cardiopulmonary blood volume in control horses and horses probably exposed to feed contaminated with toxic levels of salinomycin**

Variable	Group 1	Group 2	Group 3
Age (yr)	8,3 ± 2,3 (3)	4,7 ± 0,5 (7)	5,3 ± 0,6 (3)
M_b (kg)	530 ± 4 (3)	468 ± 11 (7)	489 ± 23 (3)
$\dot{Q}$ (ℓ min^{-1})	26,01 ± 13,31 (20)	24,27 ± 5,89 (27)	24,34 ± 6,20 (12)
CI (ml min^{-1} kg^{-1})	49,18 ± 25,23 (20)	51,71 ± 12,50 (27)	49,37 ± 11,20 (12)
CPFI	5,94* ± 0,51 (28)	6,31 ± 0,55 (50)	8,09* ± 0,51 (21)
HR (beats min^{-1})	42,59 ± 8,89 (34)	37,89 ± 12,03 (53)	38,67 ± 6,34 (24)
V_s (ml)	628 ± 167 (20)	677 ± 120 (27)	650 ± 116 (12)
CPBV (ℓ)	3,97 ± 1,09 (17)	4,20 ± 0,81 (24)	4,99 ± 0,71 (24)

Group 1 - cardiovascularly sound horses, Group 2 - horses probably exposed to toxic levels of salinomycin without macroscopically-visible myocardial fibrosis and Group 3 - diseased horses with macroscopically-visible myocardial fibrosis
M_b = Body mass, $\dot{Q}$ = Cardiac output, CI = Cardac index, CPFI = Cardiopulmonary flow index, HR = Heart rate, V_s = Stroke volume, CPBV = Cardiopulmonary blood volume
*- signifies that the means are significantly different at $P < 0,05$

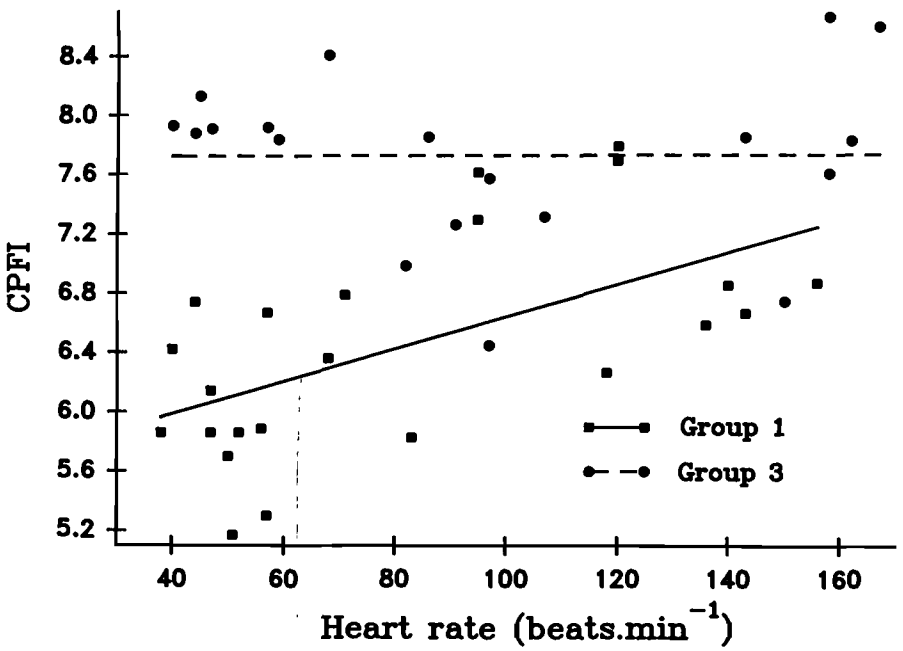

Fig. 2: **Linear regression of cardiopulmonary flow index (CPFI) on heart rate for controls (Group 1) and horses with macroscopically-visible myocardial lesions (Group 3) following intravenous injection of 0,1 mg of isoproterenol**

RESULTS

An example of the simultaneous recording of the radiocardiogram (RCG) and the electrocardiogram (ECG) is shown in Fig. 1. The first peak of activity was observed as the radioisotope passed through the right ventricle and the second peak was observed as the blood containing the isotope passed through the left ventricle. In this specific recording, the cardiopulmonary transit time was 9,80 s and the mean R-R interval of the 10 heart beats that included the entire RCG was 1,685 s. The CPFI was therefore 5,82.

The means, standard deviations and number of observations of the measured variables are tabulated in Table 1 for the sound group of horses (Group 1) and for the 2 groups of horses that were probably exposed to toxic levels of salinomycin (Groups 2 and 3). The mean CPFI of the horses in Group 1 was significantly different from that of the horses in Group 3 at the 95% confidence level. The coefficient of variation of repeated CPFI measurements on the same subject, ranged from 5,1 to 9,1% in the control subjects (Group 1), between 0,0 and 8,7% in Group 2 subjects and between 1,6 and 3,3% in Group 3 subjects.

Fig. 2 depicts the effects of pharmacological acceleration of heart rate on the CPFI in control (Group 1) and principal subjects (Group 3). The descriptive statistics for linear regressions of CPFI on heart rate for these groups of horses are shown in Table 2. The slopes of the 2 regression lines and the mean CPFI values from the 2 groups of horses were significantly different at the 95% confidence level.

Table 2: **Descriptive statistics of linear regressions of CPFI on heart rate for control horses (Group 1) and horses exposed to salinomycin (Group 3) after intravenous administration of 0,1 mg of isoproterenol**

Group	Y intercept	Gradient	n	r	P
Control	5,548	0,011*	23	0,58	<0,05
Group 3	7,717	0,00018*	20	0,02	>0,05

*-signifies that the slopes are significantly different at $P<0,05$

DISCUSSION

Recording of the data necessary for calculation of the CPFI was a simple procedure. The procedure was well-tolerated by all subjects and no adverse reactions were observed in any of the subjects. At least 3 measurements could be made in succession before the RCG became affected by background activity. Calculation of the CPFI from raw data was simple. Recording and analysis of data could be accomplished in a very short time. On the other hand, the collection of samples, analysis of samples and calculation of cardiac output was a difficult and time-consuming task.

The mean cardiac indexes in the 3 groups of horses studied, were very similar and ranged from 49,18 to 51,71 ml min^{-1} kg^{-1}. These results compare favourably with that of 63 ml min^{-1} kg^{-1} reported for resting horses using similar techniques[11]. These results are less than cardiac indices measured using thermodilution (72,61 ml min^{-1} kg^{-1})[8] and dye dilution techniques (80 ml min^{-1} kg^{-1})[10].

The mean CPFI of the cardiovascularly sound horses used in the present study was 5,94, whereas that of the control group of horses in the studies of Van Aarde and co-workers, was 6,75[12]. These differences could have been due to differences in methodology. In the present study, the ^{99m}Tc solution was introduced into the jugular vein using a 30 cm catheter, whereas the previous studies were performed using a hypodermic injection needle. The RCG can be affected by differences in collimator positioning[12]. In both studies, RCGs were only analysed if the left ventricular peak was between 50 and 100% the amplitude of the right ventricular peak. Thus differences between the results from this study and those of previous studies due to differences in collimator positioning, should have been minimised. The differences between the results could also be due to the fact that the horses used in the present study had a known history of being free from any signs of cardiac disease, whereas the horses used by Van Aarde and co-workers[12] were from a more heterogeneous population and had less well-documented histories.

Significant differences ($P<0,05$) were found to exist between the mean CPFI of cardiovascularly sound horses and principal subjects with macroscopically visible myocardial replacement fibrosis. Means of cardiac output for all 3 groups were similar and no significant differences were found to exist between any of the groups, even after standardisation of the cardiac output for body mass (cardiac index) and for heart rate. These results suggest that the CPFI is a more sensitive cardiac function test than measurements of the cardiac output or cardiac index.

In studies of the influence of exogenously-induced tachycardia on CPFI, significant differences were found to exist between the mean CPFIs and the slopes of the regression lines of CPFI on heart rate from the 2 groups of horses studied (at $P<0,05$). In the cardiovascularly sound group of horses, CPFI and heart rate increased concurrently. Van Aarde et al. showed similar findings in a group of 12 sound horses[12]. In this study, the linear regression equation of CPFI on heart rate was, $CPFI=4,16+0,0686 \times HR$, $r=0,3647$[12]. This equation is comparable with that of the control animals in the present study. In similar studies in diseased subjects, Van Aarde et al. found that the gradients of regression lines of CPFI on heart rate were steeper than those of control horses[12]. These authors ascribed these differences to increases of CPBV and concurrent decreases of V_s in the subjects with cardiovascular disease[12]. In the present study, the slope of the regression line of CPFI on heart rate of diseased subjects was less steep than that of control subjects. Furthermore, stroke volume was very similar in all groups of animals studied, while mean CPBV was increased, although not significantly, in the affected animals. This suggests that the cardiac changes associated with toxic myocarditis result in increases of CPBV without a reduction in stroke volume.

These data show that in the diseased subjects used in these studies, CPFI deviated more at a heart rate that was close to the resting heart rate of the individual. Increase of CPBV without concurrent increases in V_s suggest that toxic myocarditis associated with salinomycin intoxication may result in more severe reduction of left ventricular than right ventricular function. These data also suggest that the CPFI is a sensitive index of cardiac function in resting Thoroughbred horses. The CPFI may thus provide a reproducible and practical diagnostic technique for detecting mild cardiac pathology in Thoroughbred horses.

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